Yanze Liu · Zhimin Wang
Junzeng Zhang *Editors*

Dietary Chinese Herbs

Chemistry, Pharmacology and Clinical Evidence

Springer

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Editors
Yanze Liu
Institute of Medicinal Plant Development
Chinese Academy of Medical Sciences
and Peking Union Medical College
Beijing
China

Junzeng Zhang
Aquatic and Crop Resource Development
National Research Council of Canada
Halifax
Canada

Zhimin Wang
Institute of Chinese Materia Medica
China Academy of Chinese Medical
Sciences
Beijing
China

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Foreword I

"We are what we eat." This old saying rings true as an increasingly large body of scientific evidence has revealed the close relationship between food and health. In China, we say "disease comes through the mouth," meaning that bad food choice leads to illness. Indeed, human life relies on three basic resources: the air we breathe, the water we drink, and the food we eat. Human health is thus the outcome of constant interplay among genetic background, environmental condition, and food choice.

In traditional Chinese medicine (TCM), illness means imbalance and the focus is always to adjust and restore the balance. Over 2,000 years, TCM has used herbs and other approaches such as acupuncture, for treatment and prevention of diseases. The prevention approach or health conservation has been an important part of TCM. The oldest herbal "Shen Nong Ben Cao Jing" (Shen Nong Materia Medica) has 120 nontoxic herbs categorized as a superior group, and most of them are tonics and used for health preservation. This forms the basis of using medicated foods and dietary herbs in health maintenance—"food is medicine."

This book, "Dietary Chinese Herbs: Chemistry, Pharmacology and Clinical Evidence," edited by Drs. Liu, Wang, and Zhang brings to readers concise reviews of the history of dietary herbs in China, the perspective of natural health products and nutraceutical application relevant to dietary Chinese herbs and ingredients, and focuses on 86 selected herbs that are commonly used and regulated as food or heath food raw materials in China. The editors are well-established researchers, all with background in traditional Chinese medicine and phytochemistry, natural products chemistry, or medicinal chemistry. My colleague Dr. Liu had worked on Chinese herbal research in leading institutions in the United States for many years, while Dr. Wang is an expert in China on TCM quality and standardization, a member of the Chinese Pharmacopoeia Commission. Dr. Zhang currently leads the functional ingredients chemistry R&D of a national program on natural health products and functional foods in Canada. They are all passionate about the health benefits of dietary herbs, the bioactive components, mechanisms of actions, and new health food products development.

I have been working in the field of medicinal plant research for more than 60 years, but the love and understanding for medicinal plants never ceases. I am glad to see the book Dietary Chinese Herbs edited by Drs. Liu, Wang, and Zhang. Among the books that have touched on TCM for its dietary application, this one is unique as it provides a collection of high-level scientific literature reviews on the most commonly used dietary Chinese herbs. It will be a good reference book for researchers, graduate students, and R&D managers from industry of natural health products, dietary supplements, and functional foods.

Peigen Xiao
Academician, Chinese Academy of Engineering
and Honorary Director, Institute of Medicinal Plant Development
Chinese Academy of Medical Sciences
and Peking Union Medical College
Beijing, China

Foreword II

Traditional Chinese medicine (TCM) and Chinese materia medica (CMM) have thousands of years of history and are important elements of Chinese culture. Most CMM are derived from botanical materials or plants, so they are called Chinese herbal medicines. Historically, decoctions and herbal teas have been the most popular and effective forms; however, tablets, pills, capsules, lozenges, and injections have become the mainstream of modern CMM. Throughout the history of clinical practice, people have recognized and recorded properties such as taste, function, therapeutic effect, dosage, administration, side effects, and toxicity of various herbs. People also understand that some herbs are mainly used for therapeutic purpose, while others are used for their health-maintaining properties. Also, some herbs are mainly consumed as foods, although they show certain biological function and health benefits.

Drs. Liu, Wang, and Zhang have each been working on CMM and natural health products for more than 30 years. With similar research experience and interests, they selected 86 herbs with health-maintaining properties and invited a group of experienced researchers from China, USA, and Canada who worked in this area to contribute to the book shown here.

The book is composed of 88 chapters, including two introductory chapters and 86 chapters on specific dietary herbs, such as renshen (*Panax ginseng*), danggui (*Angelica sinensis*), shanyao (*Dioscorea opposita*), bajitian (*Morinda officinalis*), gegen (*Pueraria lobata*), baiguo (*Ginkgo biloba*), gouqi (*Lycium barbarum*), luhui (*Aloe barbadensis*), jinyinhua (*Lonicera japonica*), juju (*Cichorium glandulosum*), lingzhi (*Ganoderma lucidum*), and yangqicai (*Sargassum fusiforme*). Each herb is described based on botanical identity, chemical constituents, pharmacological studies, TCM application and dietary usage, clinical evidence, safety evaluation and toxicity data. In the botanical identity section, color photos of plants showing typical plant morphology give readers clear information on the sources. Main components, bioactive compounds, and marker compounds with updated references are included in the chemical constituents section. In the pharmacological studies section, traditional, confirmed, and newly discovered pharmacological activities are summarized. In the TCM application and dietary usage section, examples of dietary

usage are included. As one of the current foci on safety and toxicity, authors also included relevant data published for readers' reference.

I have been working in this area, especially pharmacological research, for more than three decades and have traveled to Japan, USA, Korea, Malaysia, and other countries for research and academic exchanges on herbal medicine. It is my honor to have this opportunity to introduce the book. I am sure that readers who are interested in herbal medicine can find what they are looking for.

Xiaobo Sun
Professor and Director
Institute of Medicinal Plant Development
Chinese Academy of Medical Sciences
and Peking Union Medical College
Beijing, China

Preface

The concept of "food is medicine" can be dated back to 2,000 years ago in the earliest traditional Chinese medicine (TCM) literature "Huang Di Nei Jing" ("黄帝内经", or "Emperor's Inner Canon," 475 BCE–220 CE), where it emphasized the importance of maintenance or preservation of wellness and health and the prevention of illness and diseases, with the old but still valid notion "the best doctor prevents, not treats illness." As such, maintaining system balance with the use of food, herbal medicine, and other complementary approaches in an integrated manner is the essence of TCM for disease prevention and treatment.

Over thousands of years, food materials have been continuously studied for their health benefits, while a wide range of TCM herbs have also been investigated and incorporated into the daily diet for maintaining general wellness or prevention of certain diseases in China. In the West, the convergence of food and medicine driven by market force has led to increasing demand for dietary supplements, natural health products, nutraceuticals, or functional foods. This trend has also stimulated interest in the West to look at many natural materials that could be used as sources for developing new, effective, and safe ingredients to capture the rapidly expanding opportunity in the global market place.

The book idea came out a few years ago when the three of us, working in China, Canada, and the United States at that time, were all involved in studying or reviewing the bioactive components of dietary herbs. We realized that, although there is a large and rapidly growing body of scientific information in the literature for various Chinese herbs, it is somewhat scattered and not specific toward dietary applications. The book Dietary Chinese Herbs is our first attempt to bring together selected TCM herbs and highlight the plant source, traditional use, main chemical components, biological and pharmacological activities, and clinical and dietary uses. It is not meant to cover all the available information, but rather to introduce these selected herbs with some of the research findings and relevant information on TCM and dietary uses in China. We hope it can be a useful reference for researchers and students in academia, R&D, and business managers in dietary supplement, natural health products, and the functional food industry.

The contents are arranged by starting with a brief chronological review of Chinese literatures on dietary herbs, overview of food and nutraceutical applications, and followed by chapters dedicated to each selected dietary herb. For each dietary herb or group of similar herbs, the plant source, processing method, TCM, and dietary uses will be introduced, and then followed by up-to-date literature reviews of some key chemical, pharmacological, and clinical studies.

In the preparation of this book, we are grateful to the dedication of all contributors for their rich knowledge and diverse perspectives in organizing the chapter contents. We also appreciate the time and efforts of the following students from the Applied Human Nutrition program, Mount Saint Vincent University, Halifax, Canada for language editing assistance: Laura Bellussi, Elizabeth Dickson, Shelby MacGregor, Esther Adsett, Kennedy Bennicke, Gillian Blundon, Ashleigh Cassell, Sarah Creelman, Hayley Ewing, Susan Gillespie, Michelle Higgins, Liza Hooper, Tika Jakobsen, Joseph Legere, Molly McLaughlin, Megan Phillips, Katrina Ross, Katie Tanner, Amanda Worth, Erada Alghamdi, Kim Allen, Melissa Church, Angela Crouquet, Virginia De Silva, Sarah Hallett, Mallory Harvie, Katie Inkpen, Kristen Lutes, Sarah McKay, Janie Nelson-Isenor, Olivia Newton, Leila Shaw, Clarissa Smith, and Mylene Whynot.

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Last but not least, we would like to thank the publisher Springer and its publishing editors Stephen Soehlen and Annelies Kersbergen for all the patience and support over the years to bring this from an idea to reality.

Yanze Liu
Zhimin Wang
Junzeng Zhang

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Editors and Contributors

About the Editors

Dr. Yanze Liu graduated from Henan University of Traditional Chinese Medicine (HUTCM) and received his Ph.D. in Organic Chemistry from Zhengzhou University (ZZU), China. He was a visiting scholar at the Institute of Materia Medica, Chinese Academy of Medical Science (CAMC 1985), Beijing, and Okayama University, Japan (1988–1992), who focused on the isolation and structure determination of botanical tannins and polyphenols. He was promoted to associate professor (1991) and full professor (1995), and served as associate director and director in the Department of Organic and Natural Product Chemistry since 1992 at HUTCM. In 1999 Dr. Liu went to the Department of Chemistry, The Pennsylvania State University for his visiting research, and then was transferred to Bio-organic and Natural Product Lab, McLean Hospital/Harvard Medical School, working as postdoc fellow and then as instructor.

Since 2010, Dr. Liu was invited to take the position in charge of *Chinese Herbal Medicines*, a newly founded journal published in English as a senior editor and serve as a full professor in Beijing Union Medical College/CAMC. Dr. Liu as a principal investigator took charge of three national projects of National Natural Science Foundation of China (NSFC) since 1991, one Key Project of National Scientific Research of 9th Five-Year Plan, and one Project of Henan Provincial Foundation for Excellent Young Scientist.

Dr. Liu is a guest speaker of New England School of Acupuncture, Boston, and adjunct professor of ZZU, Beifang University of Nationality, Harbin University of Commerce, and Nanyang Medical College. He was a member of experts of National Toxicology Program under NIH to evaluate 12th Report on Carcinogens. Dr. Liu received a dozen awards and honorary titles including Excellent Young Scientist of Henan Province given by Henan provincial government; published more than 120 papers on national and international journals; invented and patented flash extractor and concentrator for herbal medicine research; and licensed and patented a number of new herbal health products.

Dr. Liu's research was highlighted in the Progress Report of NSFC (1996) as the only one in the area of chemistry and also in the cover of *Chinese Herbal Medicines* (April, 2014). His research interests include natural product chemistry, R&D of healthy food and herbal products, quality control and standardization of herbal products, analysis and characterization of tannin and polyphenol, and crystallization of organic compounds.

Dr. Zhimin Wang is the Chief Professor of China Academy of Chinese Medical Sciences (CACMS), Director of National Engineering Laboratory for Quality Control Technology of Chinese Herbal Medicine, and Deputy Director of State Key Laboratory for New Technology in Manufacture Process of Chinese Medicines, from Institute of Chinese Materia Medica (ICMM), CACMS. Dr. Wang obtained his B.Sc. (1984) in Pharmacy from Henan University of Traditional Chinese Medicine, M.Sc. (1991) in Phytochemistry from China Pharmaceutical University, and Ph.D. (1994) in Medicinal Chemistry from Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, China.

Prof. Wang mainly engages in phytochemistry, quality standard, and quality evaluation of Chinese herbal medicines, and antitumor new drug development. As a principal investigator, he was involved in over 55 research projects related to basic research (National 973 Project) and R&D of new medicines and quality control of Chinese medicines since he joined ICMM. Dr. Wang received over fifteen scientific awards, published more than 300 research papers, and 16 books, including four books in which he served as editor-in-chief. As a senior expert for authoritative evaluation of novel food in China, he is responsible for reviewing the chemistry, quality, and production process of novel food from botanical resources or folk medicines.

Dr. Junzeng Zhang is a research officer from the Aquatic and Crop Resource Development, National Research Council of Canada (NRC). He is the current board member of the Canadian Institute of Chinese Medicinal Research (CICMR) and the Natural Health Products Research Society of Canada (NHPRS). Dr. Zhang obtained his B.Sc. (1984) in Pharmacy from Henan University of Traditional Chinese Medicine, and M.Sc. (1991) and Ph.D. (1994) in natural products chemistry from Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, China. He then did his postdoctoral research in Peking University, China; Rutgers, the State University of New Jersey, USA, and INRS-Institut Armand-Frappier, Canada, on natural products-based drug discovery and nutraceutical ingredients characterization.

Dr. Zhang then joined Ocean Nutrition Canada Ltd. (ONC, now a division of DSM) as a senior research scientist in the year 2000 to work on a marine-based natural health products and functional food discovery and development, later assumed the role of group leader and principal research scientist in natural products chemistry, and then the manager of licensing and research collaborations at ONC by focusing on potential product licensing opportunities and coordinating R&D collaborations in 2005. While working at ONC, he also took a part-time program at

the Sobey School of Business, Saint Mary's University, and received his MBA in 2006.

Dr. Zhang joined the National Research Council of Canada as a research officer in April 2006, at the Institute for Nutrisciences and Health and now the Aquatic and Crop Resource Development portfolio, the Division of Life Sciences at NRC. He is currently a pillar lead for NRC's Natural Health Products and Functional Ingredients (NHP/FI) program. His research expertise includes natural products-based drug/nutraceutical discovery from bioresources, including dietary Chinese herbs; microbial or enzymatic transformation of natural products; in vitro and in vivo metabolism of bioactive natural products; and the application of metabolomics tools in natural health products research and development, including quality assessment.

Contributors

Haji Akber Aisa Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi, Xinjiang, China

Yin-Ching Chan Department of Food and Nutrition, Providence University, Taichung, Taiwan

Sue-Joan Chang Department of Life Sciences, National Cheng Kung University, Tainan, Taiwan

Hubiao Chen School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China

Ping Ding School of Chinese Materia Medica, Guangzhou University of Chinese Medicine, Guangzhou, China

Caixia Dong School of Chinese Medicine, Hong Kong Baptist University, Kowloon, Hong Kong

Tingting Feng College of Pharmacy, Guizhou University, Guiyang, Guizhou, China; Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guiyang, Guizhou, China

Min Fu McGill University, Montreal, QC, Canada

Hui-Min Gao Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Muxin Gong School of Traditional Chinese Medicine, Capital Medical University, Beijing, China

Xiao-jun Gou Key Laboratory of Medicinal and Edible Plants Resources Development of Sichuan Education Department, Chengdu University, Chengdu, Sichuan, China

Li-hua Gu Shanghai University of Traditional Chinese Medicine, Shanghai, China

Tao Guo School of Life and Engineering, Lanzhou University of Technology, Lanzhou, China

Xiao-qiang Guo Key Laboratory of Medicinal and Edible Plants Resources Development of Sichuan Education Department, Chengdu University, Chengdu, Sichuan, China

Quanbin Han School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China

Chunnian He Institute of Medicinal Plant Development, Chinese Academy of Medical Science, Beijing, China

Gang He Key Laboratory of Medicinal and Edible Plants Resources Development of Sichuan Education Department, Chengdu University, Chengdu, Sichuan, China

Chun Hu Nutrilite Health Institute, Buena Park, CA, USA

Shengyu Hua Tianjin University of Traditional Chinese Medicine, Tianjin, China

Chun-Yung Huang Department of Seafood Science, National Kaohsiung Marine University, Kaohsiung, Taiwan

Guangling Jiao Aquatic and Crop Resource Development, National Research Council of Canada, Halifax, NS, Canada; Coastal Zones Research Institute Inc., Shippagan, NB, Canada

Phillip Joy Department of Applied Human Nutrition, Mount Saint Vincent University, Halifax, NS, Canada

Priya Kathirvel Department of Applied Human Nutrition, Mount Saint Vincent University, Halifax, NS, Canada

Chun Li China Academy of Chinese Medical Sciences, Institute of Chinese Materia Medica, Beijing, China

Haixia Li School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China

Minhui Li Baotou Medical College, Baotou, Inner Mongolia, China

Pengfei Li Science and Technology Department, Henan University of Traditional Chinese Medicine, Zhengzhou, Henan, China

Raorao Li Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Yazhuo Li State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, Tianjin Institute of Pharmaceutical Research, Tianjin, China

Yingqin Li Nutrilite Health Institute, Buena Park, CA, USA

Bing Lin College of Pharmacy, Guizhou University, Guiyang, Guizhou, China; Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guiyang, Guizhou, China

Li-mei Lin School of Pharmacy, Hunan University of Chinese Medicine, Changsha, China

Changxiao Liu State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, Tianjin Institute of Pharmaceutical Research, Tianjin, China

Fan Liu China-ASEAN Traditional Medicine Exchange and Cooperation Center, Guangxi Botanical Garden of Medicinal Plant, Nan'ning, China

Jianhui Liu College of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing, China; Chongqing Technology and Business University, Chongqing, China

Ta-si Liu Hunan University of Traditional Chinese Medicine, Changsha, China

Tongxiang Liu Institute of Chinese Minority Traditional Medicine, Minzu University of China, Beijing, China

Xiongli Liu College of Pharmacy, Guizhou University, Guiyang, Guizhou, China; Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guiyang, Guizhou, China

Yanze Liu Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Ying-Jiao Liu Hunan University of Traditional Chinese Medicine, Changsha, China

Fei Long School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Chunbo Lu School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China

Guanghua Lu School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Xuran Lu School of Traditional Chinese Medicine, Capital Medical University, Beijing, China

Yin Lu Department of Pharmacology, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

Bohdan L. Luhovyy Department of Applied Human Nutrition, Mount Saint Vincent University, Halifax, NS, Canada

Mingsan Miao Science and Technology Department, Henan University of Traditional Chinese Medicine, Zhengzhou, Henan, China

Zifan Pei Department of Pharmacology, College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

Wenhui Qian Department of Pharmacology, College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

Panbo Qiu Science and Technology Department, Henan University of Traditional Chinese Medicine, Zhengzhou, Henan, China

Caifang Wang Capital Medical University, Beijing, China

Ling Wang College of Pharmacy, Henan University of Traditional Chinese Medicine, Zhengzhou, China

Yulan Wang Dalian Institute for Drug Control, Dalian, China

Zhengtao Wang Shanghai University of Traditional Chinese Medicine, Shanghai, China

Zhimin Wang Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Zhuju Wang Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Zongwei Wang Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Hua Wei Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China; Key Laboratory of Plant Resources Conservation and Utilization, College of Biology and Environmemtal Science, Jishou University, Jishou, China

Yingfang Wei School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Jiandong Wu Key Laboratory of Marine Drugs, Ministry of Education, Shandong Provincial Key Laboratory of Glycoscience and Glycotechnology, School of Medicine and Pharmacy, Ocean University of China, Qingdao, Shandong, China

Lihong Wu Shanghai R&D Centre for Standardization of Chinese Medicines, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Xuelei Xin Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi, Xinjiang, China

Bei Xu Hunan University of Traditional Chinese Medicine, Changsha, China

Hong Xu Shanghai University of Traditional Chinese Medicine, Shanghai, China

Jun Xu School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China

Jie Yan School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Li-hua Yan Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Jin Yang Beifang University of Nationalities, Ningxia, China

Li Yang Shanghai University of Traditional Chinese Medicine, Shanghai, China

Yang Yi College of Food Science and Engineering, Wuhan Polytechnic University, Wuhan, China

Fei Yin College of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing, China

Fei Yu Tianjin Key Laboratory on Technologies Enabling Development of Clinical Therapeutics and Diagnostics, School of Pharmacy, Tianjin Medical University, Tianjin, China

Guangli Yu Key Laboratory of Marine Drugs, Ministry of Education, Shandong Provincial Key Laboratory of Glycoscience and Glycotechnology, School of Medicine and Pharmacy, Ocean University of China, Qingdao, Shandong, China

Wen-Jen Yu Department of Biotechnology, Hung Kuang University, Taichung, Taiwan

Feng Zhang Department of Pharmacology, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

Jun Zhang Tianjin Key Laboratory on Technologies Enabling Development of Clinical Therapeutics and Diagnostics, School of Pharmacy, Tianjin Medical University, Tianjin, China

Junzeng Zhang Aquatic and Crop Resource Development, National Research Council of Canada, Halifax, Canada

Ming-wei Zhang Sericultural and Agri-Food Research Institute, Guangdong Academy of Agricultural Sciences, Guangzhou, China

Qi-wei Zhang China Academy of Chinese Medical Sciences, Institute of Chinese Materia Medica, Beijing, China

Xiaozhe Zhang Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China

Xiao-liang Zhao Experimental Research Center, China Academy of Chinese Medical Sciences, Beijing, China

Xiaoliang Zhao Key Laboratory of Marine Drugs, Ministry of Education, Shandong Provincial Key Laboratory of Glycoscience and Glycotechnology, School of Medicine and Pharmacy, Ocean University of China, Qingdao, Shandong, China

Yang Zhao Key Laboratory for Information System of Mountainous Areas and Protection of Ecological Environment, Guizhou Normal University, Guiyang, China; The Research Center for Quality Control of Natural Medicine, Guizhou Normal University, Guiyang, China

Yuqing Zhao School of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang, China

Xidan Zhou Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Xin Zhou Key Laboratory for Information System of Mountainous Areas and Protection of Ecological Environment, Guizhou Normal University, Guiyang, China; The Research Center for Quality Control of Natural Medicine, Guizhou Normal University, Guiyang, China

Ying Zhou College of Pharmacy, Guizhou University, Guiyang, Guizhou, China; Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guiyang, Guizhou, China

En-yuan Zhu Shanghai University of Traditional Chinese Medicine, Shanghai, China

Jing-jing Zhu Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

Part I
Introduction

Chapter 1
A Brief History of Dietary Chinese Herbs

Junzeng Zhang, Zhimin Wang and Yanze Liu

Diet is important to health, not just for the nourishment of the body but also for maintaining optimal balance and thus preventing illness. In traditional Chinese medicine (TCM), food is an essential component for the prevention and treatment of many diseases. A combination of diet, herbal medicine, acupuncture and physical exercise techniques such as "Tai Ji" ("太极", Tai Chi), has been an important aspect of Chinese culture related to health and wellbeing from ancient times to the present day.

To introduce the topic, the major literature is discussed in chronological order to provide an overview of the origin and development of dietary therapy or medicated food in Chinese history. The discussion of the major literature on TCM is based mainly on the studies of Chen [1], Liu [2], and Xi [3].

The concept of food as medicine had already been mentioned in the earliest TCM literature "Huangdi Neijing" ("黄帝内经", or "Emperor's Inner Canon", generally accepted as having been written between 475 BCE—220 CE). It was not written by a single author, although author names are unknown. It is the fundamental piece of theoretical work in Chinese medicine and includes the introduction of the principles of "Yin-Yang" ("阴阳"), "Qi" ("气", or "Chi", life energy) and the Five Elements ("五行"), as well as the importance of balance in health. In addition,

J. Zhang (✉)
Aquatic and Crop Resource Development,
National Research Council of Canada, Halifax, Canada
e-mail: junzeng.zhang@nrc-cnrc.gc.ca

Z. Wang
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences,
Beijing, China

Y. Liu
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences
and Peking Union Medical College, Beijing, China

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the interior of the body as well as the environment are both important considerations for this balance for health. Disease prevention was regarded as the preferred approach of health management, with the famous statement of "the best doctor is the one who prevents diseases."

As early as in the Zhou Dynasty (c. 1122 BCE–256 BCE), dietitians appeared and shared the official title of healthcare professional along with physicians, surgeons, and veterinarians. Health preservation with food ("食养") has since become an important aspect of Chinese culture and healthy living.

The earliest TCM herbal drug book, "Shennong Bencao Jing" ("神农本草经", or Shennong's Classic of Materia Medica, authors unknown), was compiled between 221 BCE–220 CE. It describes 365 items (minerals, herbs, and animals) across 3 categories, the top-, middle-, and low-grades based on medicinal and safety properties. More than a hundred materials are listed in the top-grade group. The list includes recommendations on the consumption of many non-toxic items which yield a variety of health benefits.

The concept of dietary therapy ("食疗" or "食治") was first explicitly introduced by the prominent doctor, also known as the "King of Medicine", Simiao Sun, in his book "Beiji Qianjin Yaofang" ("备急千金要方", or Essential Formulas for Emergencies Worth a Thousand Pieces of Gold, 652 CE). This work contains 30 volumes, and Vol. 26 was dedicated to dietary therapy ("食治"). In the introduction section of this volume, he wrote: "As a doctor, you must first check into the root of illness and understand all the affected. Treatment should start with foods, if dietary therapy not working, then medicine". It included 154 food items, such as 29 fruits, 58 vegetables, 27 grains, and 40 animal materials as well as detailed discussion on the relations of foods, internal organs and their functions, compatibility, and seasonal considerations.

In Tang Dynasty, the first book on dietary herbs, "Shiliao Bencao" ("食疗本草", or Materia Medica for Dietary Therapy by Shen Meng and Ding Zhang), was compiled in the early 8th century. It included 227 items of herbs and various foods. For each item, the health benefit property, applicability or precaution, proper harvesting time, and processing and cooking methods were discussed. The work laid the foundation for the application of dietary Chinese herbs. There was another book, "Shixing Bencao" ("食性本草", or Edible Materia Medica, by Shiliang Chen, 937–957) which also appeared around this time as an important contribution to this field.

During the Yuan Dynasty, dietary therapy and dietary herb application were further developed, as revealed in several books; two are worth mentioning. "Riyong Bencao" ("日用本草", or Materia Medica for Daily Use, by Rui Wu, 1329), is a collection of 540 food or herb materials. It expands on the particular use of the different parts of plants. The other book, "Yinshan Zhengyao" ("饮膳正要", or Principles of Correct Diet, by Sihui Hu, 1330), includes 230 food items and describes details on their properties, such as the basic cold, hot, warm, cool and moderate nature of food. For the first time, food items from northern ethnic groups, including Mongolian food materials are introduced.

Food and dietary therapy prospered in the Ming Dynasty, with the publication of a long list of important books in history. “Jiuhuang Bencao” (“救荒本草”, or Materia Medica for the Relief of Famine, by Su Zhu, 1406) recorded 414 wild edible plants, including 245 whole herbs, 80 wood materials, 20 grains, 23 fruits, and 46 vegetables. Most of the plants were also grown by the author and have very detailed pictures drawn by professional painter, so it is also an important piece of literature in botany, agriculture and Chinese medicine. “Shiwu Bencao” (“食物本草”, or Food Materia Medica) published in 7–8 different versions by various authors within a century (1500–1620), contains similar contents (386 food materials, and one version with 492 color pictures of plants and plant parts). One later version of a book with the same name was compiled by Kecheng Yao (based on the work of Li Gao, Yuan Dynasty and assisted by Shizhen Li, the greatest doctor and herbalist in Chinese history). It was published in 1621 which contains 22 volumes, recorded 1679 items of water (refers to water from various sources and geographic sites or origins) and food items with 750 dedicated to water. Most of the food and herb items are based on Shizhen Li’s “Bencao Guangmu” (“本草纲目”, Compendium of Materia Medica, 1596), with the exception of the items related to water.

The Compendium of Materia Medica, with a description of 1892 items became the most complete and comprehensive medical book and one of the most important pieces of literature in the history of TCM. In addition to a number of dietary herbs, it contains 43 items of water for medical use, 73 grains, 105 vegetables, 127 fruits, and 444 animal related materials most of which are edible and nutritious. The work also listed more than 50 medicated porridges and about 80 tinctures (medicated liquors), as well as applications to common food cooking practices in medicinal foods or dietary herbal preparations [4].

During the Qing Dynasty, dietary application of herbs in health preservation, disease prevention and treatment continued to expand. Important works include: “Shiwu Bencao Huizuan” (“食物本草会纂”, or Collections of Food Materia Medica, by Lilong Shen, 1691), with 608 entries; “Shiwu Kao” (“食物考”, or Food Records, by Bai Long, 1795), with 1106 entries; and “Tiaoji Yinshi Bian” (“调疾饮食辩”, or Mechanism Analysis on Medicated Food, by Mu Zhang, 1813), with 653 entries and a detailed analysis of properties and healing mechanisms of the food items.

In the past 200 years, research and the practical application of dietary therapy have grown rapidly. Searches into National Library of China for Chinese books related to “食疗” (dietary therapy) and “药膳” (medicated diet/food) ended in 1613 and 934 titles in the collection respectively [5]. In the most comprehensive Chinese scientific research publication database, China National Knowledge Infrastructure (CNKI), the number of hits for the above two search subjects in Chinese scientific journals, dissertations, patent applications are at 5175 and 1601 (the CNKI database covers Chinese publications primarily for the past 30 years, with some dating back to the 1950s) [6].

For more than two thousand years dietary therapy and medicated food or diet, from macro/micro balance health concepts to dietary herb application as well as scholarly research into people’s daily life, have been an integrated part of Chinese

culture. Nowadays, disease prevention and non-medical approaches of management for stress related sub-healthy conditions are becoming increasingly important.

In China, recent economic growth has also led to active commercialization of health food ingredients or products and a growing need of regulation in this area. The Chinese health authorities thus introduced the first regulation in 2002 to define dietary herbs (Chinese herbs allowed as herbal drug or food) and herbs that can be used to produce health food products. The regulation also listed a number of items, including some Chinese herbs that are prohibited from being used in food products. The current lists of dietary herbs and herbs allowed for health food products from China Food and Drug Administration (CFDA) [7] and the proposed updates from China National Health and Family Planning Commission (NHFPC, formally the Ministry of Health) [8] are shown in Tables 1.1 and 1.2.

Currently, there are 12,523 domestic health food products and 700 imported ones that are listed in the licensed health food products database from CFDA [9]. These health food products, in various oral administration formats such as tablets, capsules, pills, soft capsules, liquid, and powder, may include dietary supplements, natural health products, and functional foods that are normally found in global markets. The Chinese health food regulation allows 27 health claims (Table 1.3) for these products, based on a review of safety and health specific functional data, including data from animal and in some cases human trials [10].

For health food products that use plants or other organisms with no history of human consumption in China, novel food application has to be filed first. Based on the *Food Hygiene Act* of the P. R. China, a new regulation was introduced on December 1, 2007 for novel food products. According to this Regulation on Novel Food Products, novel food products include: (1) Animals, plants, or microorganisms with no consumption history in China as food; (2) Food ingredients derived from animals, plants, or microorganisms, which have no consumption history in China; (3) New microorganism strains used for food processing; and (4) Food ingredients with composition or property changes due to new processing methods. Novel food products are regulated under the *Food Hygiene Act*, which stipulates that these products should have neither acute, sub-acute, or chronic toxicity nor other potential safety concerns. As any novel food material for making health food products will need to be registered and attain approval first, this provides companies from outside of China with a market entry point for new and specialty food materials. Another type of novel food that has gained approval from Chinese health authority includes herbs that have not usually been consumed as food widely, but with documented evidence for human dietary use and solid safety profiles. A good example includes the approval of the roots of cultivated Chinese ginseng (*Panax ginseng*) as a novel food by the Chinese health authority [11] in 2012. This changed the regulatory status of Chinese ginseng from a herbal drug material that can be used in health foods (licensed, approval required) to a dietary herb (food material where no approval is required for derived food products if not making no health claims).

Table 1.1 List of dietary herbs under current regulation in China

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Bajiaohuixiang	八角茴香	*Illicium verum* Hook. f.	八角茴香	Dried fruit	[7, 8]
Baibiandou	白扁豆	*Dolichos lablab* L.	扁豆	Dried seed and flower	[7, 8]
Baiguo	白果	*Ginkgo biloba* L.	银杏	Dried seed	[7, 8]
Baihe	百合	*Lilium lancifolium* Thunb.	卷丹	Dried bulb	[7, 8]
		Lilium brownie F. E. Brown var. *viridulum* Baker	百合		
		Lilium pumilum DC.	细叶百合		
Baizhi	白芷	*Angelica dadurica* (Fisch. ex Hoffm.) Benth. et Hook. f.	白芷	Dried root	[7, 8]
		Angelica dahurica (Fisch. ex Hoffm.) Benth. et Hook. f. var. *formosana* (Boiss.) Shan et Yuan	杭白芷		
Bohe	薄荷	*Mentha haplocalyx* Brig.	薄荷	Dried aerial part	[7, 8]
Chixiaodou	赤小豆	*Vigna umbeuata* Ohwi et Ohashi	赤小豆	Dried seed	[7, 8]
		Vigna angularis Ohwi et Ohashi	赤豆		
Daidaihua	代代花	*Citrus aurantium* L. var. *amara* Engl.	代代花	Dried bud and fruit	[7, 8]
Daodou	刀豆	*Canavalia gladiata* (Jacq.) DC.	刀豆	Dried seed	[7, 8]
Dandouchi	淡豆豉	*Glycine max* (L.) Merr.	大豆	Fermented product from seed	[7, 8]
Danzhuye	淡竹叶	*Lophatherum gracile* Brongn.	淡竹叶	Dried stem and leaf	[7, 8]
Dingxiang	丁香	*Eugenia caryophyllata* Thunb.	丁香	Dried flower bud	[7, 8]
Ejiao	阿胶	*Equus asinus* L.	驴	Gelatin produced from skin	[7, 8]

(continued)

Table 1.1 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Feizi	榧子	*Torreya grandis* Fort.	榧	Dried seed	[7, 8]
Fengmi	蜂蜜	*Apis cerana* Fabricius	中华蜜蜂	Honey	[7, 8]
		Apis mellifera Linnaeus	意大利蜂		
Foshou	佛手	*Citrus medica* L. var. *sarcodactylis* Swingle	佛手	Dried fruit	[7, 8]
Fuling	茯苓	*Poria cocos* (Schw.) Wolf	真菌茯苓	Dried stub	[7, 8]
Fupenzi	覆盆子	*Rubus chingii* Hu	华东覆盆子	Dried fruit	[7, 8]
Fushe	蝮蛇	*Agkistrodon acutus* (Guenther)	蝮蛇	Dried body (viscera removed)	[7]
Gancao	甘草	*Glycyrrhiza uralensis* Fisch.	甘草	Dried rhizome and root	[7, 8]
		Glycyrrhiza inflata Bat.	胀果甘草		
		Glycyrrhiza glabra L.	光果甘草		
Gaoliangjiang	高良姜	*Alpinia officinrum* Hance	高良姜	Dried rhizome	[7, 8]
Gegen	葛根	*Pueraria lobata* (Willd.) Ohwi	野葛	Dried root	[7, 8]
		Pueraria thomsonii Benth.	甘葛藤		[8]
Gouqizi	枸杞子	*Lycium barbarum* L.	宁夏枸杞	Dried fruit	[7, 8]
Heye	荷叶	*Nelumbo nucifera* Gaertn.	莲	Dried leaf	[7, 8]
Heihujiao	黑胡椒	*Piper nigrum* L.	胡椒	Dried fruit	[7, 8]
Heizhima	黑芝麻	*Sesamum indicum* L.	脂麻	Dried seed	[7, 8]
Huajiao	花椒	*Zanthoxylum schinifolium* Sieb. Et Zucc.	青椒	Dried pericarp	[7, 8]
		Zanthoxylum bungeanum Maxim.	花椒		
Huaihua or Huaimi	槐花、槐米	*Sophora japonica* L.	槐	Dried flower or flower bud	[7, 8]

(continued)

Table 1.1 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Huangjiezi	黄芥子	*Brassica juncea* (L.) Czern. et Coss. or *B. juncea* (L.) Czern. et Coss. var. *gracilis* Tsen et Lee	芥	Dried seed	[7]
Huangjing	黄精	*Polygonatum kingianum* Coll. et Hemsl.	滇黄精	Dried rhizome, leaf and whole	[7, 8]
		Polygonatum sibiricum Red.	黄精		
		Polygonatum cyrtonema Hua	多花黄精		
Huomaren	火麻仁	*Cannabis sativa* L.	大麻	Dried seed	[7, 8]
Huoxiang	藿香	*Agastache rugosa* (Fisch. et Mey.) O. ktze.	土藿香	Dried aerial part	[7, 8]
		Pogostemon cablin (Blanco) Benth.	广藿香		[8]
Jineijin	鸡内金	*Gallus gallus domesticus* Brisson	家鸡	Dried inner membrane of gizzard	[7, 8]
Jiang (Shengjiang or Ganjiang)	姜(生姜、干姜)	*Zingiber officinale* Rosc.	姜	Fresh or dried rhizome	[7, 8]
Jiegeng	桔梗	*Platycodon grandiflorum* (Jacq.) A. DC.	桔梗	Dried root	[7, 8]
Jinyinhua	金银花	*Lonicera japonica* Thunb.	忍冬	Dried flower bud or new flower	[7, 8]
Juhong	橘红	*Citrus reticulata* Blanco	橘	Dried exocarp	[7, 8]
Juhua	菊花	*Chrysanthemum morifolium* Ramat.	菊	Dried flower	[7, 8]
Juju	菊苣	*Cichorium glandulosum* Bioss. et Huet	毛菊苣	Dried aerial part or whole	[7, 8]
		Cichorium intybus L.	菊苣		
Jupi (or Chenpi)	橘皮(或陈皮)	*Citrus reticulata* Blanco	橘	Dried pericarp	[7, 8]
Juemingzi	决明子	*Cassia obtusifolia* L.	决明	Dried seed	[7, 8]
		Cassia tora L.	小决明		[8]

(continued)

Table 1.1 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Kuxingren	苦杏仁	*Prunus armeniaca* L. var. *ansu* Maxim	山杏	Dried bitter seed	[7, 8]
		Prunus sibirica L.	西伯利亚杏		
		Prunus mandshurica (Maxim.) Koehne	东北杏		
		Prunus armeniaca L.	杏		
Kunbu	昆布	*Laminaria japonica* Aresch.	海带	Dried thallus	[7, 8]
		Ecklonia kurome Okam.	昆布		
Laifuzi	莱菔子	*Raphanus sativus* L.	萝卜	Dried seed	[7, 8]
Lianzi	莲子	*Nelumbo nucifera* Gaertn.	莲	Dried seed	[7, 8]
Longyanrou	龙眼肉	*Dimocarpus longan* Lour.	龙眼	Dried aril	[7, 8]
Luohanguo	罗汉果	*Siraitia grosvenorii* (Swingle.) C. Jeffrey ex A. M. Lu et Z. Y. Zhang	罗汉果	Dried fruit	[7, 8]
Machixian	马齿苋	*Portulaca oleracea* L.	马齿苋	Dried aerial part	[7, 8]
Maiya	麦芽	*Hordeum vulgare* L.	大麦	Dried germinated caryopsis	[7, 8]
Mugua	木瓜	*Chaenomeles speciosa* (Sweet) Nakai	贴梗海棠	Dried fruit	[7, 8]
Muli	牡蛎	*Ostrea gigas* Thunberg or *O. talienwhanensis* Crosse or *O. rivularis* Gould	牡蛎	Dried shell	[7]
Pangdahai	胖大海	*Sterculia lychnophora* Hance	胖大海	Dried seed	[7, 8]
Pugongying	蒲公英	*Taraxacum mongolicum* Hand.-Mazz.	蒲公英	Dried whole plant	[7, 8]
		Taraxacum borealisinense Kitam.	碱地蒲公英		[7, 8]
		Other *Taraxacum* spp.			[8]
Qianshi	芡实	*Euryale ferox* Salisb.	芡	Dried seed	[7, 8]
Qingguo	青果	*Canarium album* Raeusch.	橄榄	Dried fruit	[7, 8]

(continued)

Table 1.1 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Renshen (Cultivated)	人参(人工种植)	*Panax ginseng* C. A. Meyer	人参	Dried rhizome and root	[11]
Roudoukou	肉豆蔻	*Myristica fragrans* Houtt.	肉豆蔻	Dried seed	[7, 8]
Rougui	肉桂	*Cinnamomum cassia* Presl	肉桂	Dried bark	[7, 8]
Sangshen	桑椹	*Morus alba* L.	桑	Dried fruit	[7, 8]
Sangye	桑叶	*Morus alba* L.	桑	Dried leaf	[7, 8]
Shaji	沙棘	*Hippophae rhamnoides* L.	沙棘	Dried fruit	[7, 8]
Sharen	砂仁	*Amomum villosum* Lour.	阳春砂	Dried fruit	[7, 8]
		Amomum villosum Lour. var. *xanthioides* T. L. Wu et Senjen	绿壳砂		
		Amomum longiligulare T. L. Wu	海南砂		
Shanyao	山药	*Dioscorea opposita* Thunb.	薯蓣	Dried rhizome	[7, 8]
				Dried fruit	[8]
Shanyinhua	山银花	*Lonicera confuse* DC.	华南忍冬	Dried flower bud or flower	[8]
		Lonicera hypoglauca Miq.	红腺忍冬		
		Lonicera macranthoides Hand. -Mazz.	灰毡毛忍冬		
		Lonicera fulvotomentosa Hsu et S. C. Cheng	黄歇毛忍冬		
Shanzha	山楂	*Crataegus pinnatifida* Bge. var. *major* N.E.Br.	山里红	Dried fruit	[7, 8]
		Crataegus pinnatifida Bge.	山楂		
Suanzao or Suanzaoren	酸枣、酸枣仁	*Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou	酸枣	Dried fruit and seed	[7, 8]

(continued)

Table 1.1 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Tianxingren	甜杏仁	*Prunus armeniaca* L.	杏	Dried sweet seed from selected cultivated varieties	[8]
		Prunus armeniaca L. var. *ansu* Maxim	山杏		
Taoren	桃仁	*Prunus persica* (L.) Batsch	桃	Dried seed	[7, 8]
		Prunus davidiana (Carr.) Franch.	山桃		
Wumei	乌梅	*Prunus mume* (Sieb.) Sieb. et Zucc.	梅	Dried fruit	[7, 8]
Wu Shao She	乌梢蛇	*Zaocys dhumnades* (Cantor)	乌梢蛇	Dried body	[7]
Xian Baimaogeng	鲜白茅根	*Imperata cylindrica* Beauv. var*major* (Nees) C. E. Hubb.	白茅	Fresh rhizome	[7, 8]
Xian Lugen	鲜芦根	*Phragmites communis* Trin.	芦苇	Fresh rhizome and new shoot	[7, 8]
Xiangru	香薷	*Mosla chinensis* Maxim.	石香薷	Dried aerial part	[7, 8]
		Mosla chinensis 'Jiangxiangru'	江香薷		
Xiangyuan	香橼	*Citrus medica* L.	枸橼	Dried fruit	[7, 8]
		Citrus wilsonii Tanaka	香圆		
Xiaohuixiang	小茴香	*Foeniculum vulgare* Mill.	茴香	Dried fruit	[7, 8]
Xiaoji	小蓟	*Cirsium setosum* (Wild.) MB.	刺儿菜	Dried aerial part	[7, 8]
Xiebai	薤白	*Allium macrostemon* Bge.	小根蒜	Dried bulb	[7, 8]
		Allium chinensis G. Don	薤		

(continued)

Table 1.1 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name (source material)	Name in Chinese (source material)	Part used	References
Yiyiren	薏苡仁	*Coix lacryma-jobi* L. var. *mayuen* (Roman.) Stapf	薏苡	Dried seed	[7, 8]
Yizhiren	益智仁	*Alpinia oxyphylla* Miq.	益智	Dried fruit	[7]
Yuganzi	余甘子	*Phyllanthus emblica* L.	余甘子	Dried fruit	[7, 8]
Yuliren	郁李仁	*Prunus humilis* Bge. or *P. japonica* Thunb. or *P. pedunculata* Maxim.	郁李	Dried seed	[7]
Yuxingcao	鱼腥草	*Houttuynia cordata* Thunb.	蕺菜	Dried aerial part or whole	[7, 8]
Yuzhu	玉竹	*Polygonatum odoratum* (Mill.) Druce	玉竹	Dried rhizome	[7, 8]
Zao (Dazao or Heizao)	枣(大枣、黑枣)	*Ziziphus jujuba* Mill.	枣	Dried fruit	[7, 8]
Zhijuzi	枳椇子	*Hovenia dulcis* Thunb. or *H. acerba* Lindl. or *H. trichocarpa* Chun et Tsiang	枳椇	Dried seed	[7]
Zhizi	栀子	*Gardenia jasminoides* Ellis	栀子	Dried fruit	[7, 8]
Zisu	紫苏	*Perilla frutescens* (L.) Britt.	紫苏	Dried stem and leaf	[7, 8]
Zisuzi	紫苏子	*Perilla frutescens* (L.) Britt.	紫苏	Dried seed	[7, 8]

Table 1.2 List of herbs allowed for use in health food products in China

Herb name in Pin Yin	Herb name in Chinese	Latin name of (source material)	Part used	References
Bajitian	巴戟天	*Morinda officinalis* How	Dried root	[7]
Baidoukou	白豆蔻	*Amomum kravanh* Pierre ex Gagnep. or *A. compactum* Soland ex Maton	Dried fruit	[7]
Baiji	白及	*Bletilla striata* (Thunb.) Reichb. f.	Dried rhizome	[7]
Baishao	白芍	*Paeonia lactiflora* Pall.	Dried root	[7]
Baizhu	白术	*Atractylodes macrocephala* Koidz.	Dried rhizome	[7]
Baiziren	柏子仁	*Platycladus orientalis* (L.) Franco	Dried seed	[7]
Beishashen	北沙参	*Glehnia littoralis* Fr. Schmidt ex Miq.	Dried root	[7]
Bibo	荜茇	*Piper longum* L.	Dried fruit	[7]
Biejia	鳖甲	*Trionyx sinensis* Wiegmann	Dried tergum	[7]
Buguzhi	补骨脂	*Psoralea corylifolia* L.	Dried fruit	[7]
Cangzhu	苍术	*Atractylodes lancea* (Thunb.) DC. or *A. chinensis* (DC.) Koidz.	Dried rhizome	[7]
Cebaiye	侧柏叶	*Platycladus orientalis* (L.) Franco	Dried twigs and leaf	[7]
Cheqiancao	车前草	*Plantago asiatica* L. or *P. depressa* Willd.	Dried whole plant	[7]
Cheqianzi	车前子	*Plantago asiatica* L. or *P. depressa* Willd.	Dried seed	[7]
Chishao	赤芍	*Paeonia lactiflora* Pall. or *P. veitchii* Lynch	Dried root	[7]
Chuanbeimu	川贝母	*Fritillaria cirrhosa* D. Don or *F. unibracteata* Hsiao et K. C. Hsia or *F. przewalskii* Maxim. or *F. delavayi* Franch.	Dried bulb	[7]
Chuanniuxi	川牛膝	*Cyathula officinalis* Kuan	Dried root	[7]
Chuanxiong	川芎	*Ligusticum chuanxiong* Hort.	Dried rhizome	[7]
Cimeiguo	刺玫果	*Rosa davurica* Pall.	Dried fruit	[7]
Ciwujia	刺五加	*Acanthopanax senticosus* (Rupr. Et Maxim.) Harms	Dried root, rhizome, and caulis	[7]
Daji	大蓟	*Cirsium japonicum* Fisch. ex DC.	Dried aerial part	[7]

(continued)

Table 1.2 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name of (source material)	Part used	References
Danshen	丹参	*Salvia miltiorrhiza* Bge.	Dried root and rhizome	[7]
Danggui	当归	*Angelica sinensis* (Oliv.) Diels	Dried root	[7]
Dangshen	党参	*Codonopsis pilosula* (Franch.) Nannf. or *C. pilosula* Nannf. var. *modesta* (Nanf.) L. T. Shen or *C. tangshen* Oliv.	Dried root	[7]
Digupi	地骨皮	*Lycium chinense* Mill. or *L. barbarum* L.	Dried root cortex	[7]
Dongchongxiacao	冬虫夏草	*Cordyceps sinensis* (Berk.) Sacc.	Dried caterpillar fungus	[12]
Duzhong	杜仲	*Eucommia ulmoides* Oliv.	Dried cortex	[7]
Duzhongye	杜仲叶	*Eucommia ulmoides* Oliv.	Dried leaf	[7]
Fanxieye	番泻叶	*Cassia angustifolia* Vahl or *C. acutifolia* Delile	Dried small leaf	[7]
Fengjiao	蜂胶	*Apis mellifera* L.	Dried secretion	[7]
Gusuibu	骨碎补	*Drynaria fortunei* (Kunze) J. Sm.	Dried rhizome	[7]
Guijia	龟甲	*Chinemys reevesii* (Gray)	Dried turtleback	[7]
Honghua	红花	*Carthamus tinctorius* L.	Dried flower	[7]
Hongjingtian	红景天	*Rhodiola crenulata* (Hook. f. et. Thoms.) H. Ohba	Dried root and rhizome	[7]
Houpo	厚朴	*Magnolia officinalis* Rehd. et. Wils. or *M. officinalis* Rehd. et. Wils. var. *biloba* Rehd. et Wils.	Dried bark of trunk, twig, and root	[7]
Houpohua	厚朴花	*Magnolia officinalis* Rehd. et. Wils. or *M. officinalis* Rehd. et. Wils. var. *biloba* Rehd. et Wils.	Dried flower bud	[7]
Hubeibeimu	湖北贝母	*Fritillaria hupehensis* Hsiao et K. C. Hsia	Dried bulb	[7]
Huluba	葫芦巴	*Trigonella foenum-graecum* L.	Dried seed	[7]
Huainiuxi	怀牛膝	*Achyranthes bidentata* Bl.	Dried root	[7]
Huaishi	槐实	*Sophora japonica* L.	Dried fruit	[7]
Huangqi	黄芪	*Astragalus membranaceus* (Fisch.) Bge. var.	Dried root	[7]

(continued)

Table 1.2 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name of (source material)	Part used	References
		mongholicus (Bge.) Hsiao or *A. membranaceus* (Fisch.) Bge.		
Jili	蒺藜	*Tribulus terrestris* L.	Dried fruit	[7]
Jixuecao	积雪草	*Centella asiatica* (L.) Urb.	Dried whole plant	[7]
Jianghuang	姜黄	*Curcuma longa* L.	Dried rhizome	[7]
Jiaogulan	绞股蓝	*Gynostemma pentaphyllum* Thunb. Makino	Dried whole plant	[7]
Jinqiaomai	金荞麦	*Fagopyrum dibotrys* (D. Don) Hara	Dried rhizome	[7]
Jinyingzi	金樱子	*Rosa laevigata* Michx.	Dried fruit	[7]
Jiucaizi	韭菜子	*Allium tuberosum* Rottl.	Dried seed	[7]
Hezi	诃子	*Terminalia chebula* Retz. or *T. chebula* Retz. Var. *tomentella* Kurt.	Dried fruit	[7]
Kudingcha	苦丁茶	*Ilex kudingcha* C. J. Tseng	Dried leaf	[7]
Luhui	芦荟	*Aloe barbadensis* Miller or *A. ferox* Miller	Dried leaf juice	[7]
Luobuma	罗布麻	*Apocynum venetum* L.	Dried leaf	[7]
Malugu	马鹿骨	*Cervus elaphus* Linnaeus or *C. Nippon* Temminck	Dried bone	[7]
Malurong	马鹿茸	*Cervus elaphus* Linnaeus or *C. Nippon* Temminck	Dried unossified antler	[7]
Malutai	马鹿胎	*Cervus elaphus* Linnaeus or *C. Nippon* Temminck	Dried fetus and placenta	[7]
Maidong	麦冬	*Ophiopogon japonicus* (Thunb.) Ker-Gawl.	Dried tuberous root	[7]
Meiguihua	玫瑰花	*Rosa rugosa* Thunb.	Dried flower bud	[7]
Meiguiqie	玫瑰茄	*Hibicus sabdariffa* L.	Dried flower	[7]
Mohanlian	墨旱莲	*Eclipta prostrata* L.	Dried aerial part	[7]
Mudanpi	牡丹皮	*Paeonia suffruticosa* Andr.	Dried root cortex	[7]
Muxiang	木香	*Aucklandia lappa* Decne.	Dried root	[7]
Muzei	木贼	*Equisetum hiemale* L.	Dried aerial part	[7]

(continued)

Table 1.2 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name of (source material)	Part used	References
Niubanggen	牛蒡根	*Arctium lappa* L.	Dried root	[7]
Niubangzi	牛蒡子	*Arctium lappa* L.	Dried fruit	[7]
Nvzhenzi	女贞子	*Ligustrum lucidum* Ait.	Dried fruit	[7]
Peilan	佩兰	*Eupatorium fortunei* Turcz.	Dried aerial part	[7]
Pingbeimu	平贝母	*Fritillaria ussuriensis* Maxim.	Dried bulb	[7]
Puhuang	蒲黄	*Typha angustifolia* L. or *T. orientalis* Presl.	Dried pollen	[7]
Qiancao	茜草	*Rubia cordifolia* L.	Dried root and rhizome	[7]
Qingpi	青皮	*Citrus reticulate* Blanco	Dried pericarp of young and unripe fruit	[7]
Renshenguo	人参果	*Panax ginseng* C. A. Mey.	Dried fruit	[7]
Renshenye	人参叶	*Panax ginseng* C. A. Mey.	Dried leaf	[7]
Sanqi	三七	*Panax notoginseng* (Burk.) F. H. Chen	Dried root and rhizome	[7]
Sangbaipi	桑白皮	*Morus alba* L.	Dried root cortex	[7]
Sangzhi	桑枝	*Morus alba* L.	Dried young twig	[7]
Shayuanzi	沙苑子	*Astragalus complanatus* R. Br.	Dried seed	[7]
Shanzhuyu	山茱萸	*Cornus officinalis* Sieb. et Zucc.	Dried fruit	[7]
Shengdihuang	生地黄	*Rehmannia glutinosa* Libosch.	Dried tuberous root	[7]
Shengheshouwu	生何首乌	*Polygonum multiflorum* Thunb.	Dried tuberous root	[7]
Shengma	升麻	*Cimicifuga heracleifolia* Kom. or C. *dahurica* (Turcz.) Maxim. or *C. foetida* L.	Dried rhizome	[7]
Shihu	石斛	*Dendrobium nobile* Lindl. or *D. candidum* Wall. ex Lindl. or *D. fimbriatum* Hook. var. *oculatum* Hook.	Dried caulis	[7]

(continued)

Table 1.2 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name of (source material)	Part used	References
Shijueming	石决明	*Haliotis diversicolor* Reeve or *H. discus* hannai Ino or *H. ovina* Gmelin or *H. ruber* (Leach) or *H. asinina* Linaeus or *H. laevigata* (Donovan)	Dried shell	[7]
Shouwuteng	首乌藤	*Polygonum multiflorum* Thunb.	Dried caulis	[7]
Shudahuang	熟大黄	*Rheum palmatum* L. or *R. tanguticum* Maxim. ex Balf. or *R. officinale* Baill	Alcohol cooked or streamed root and rhizome	[7]
Shudihuang	熟地黄	*Rehmannia glutinosa* Libosch.	Processed tuberous root	[7]
Suanjiao	酸角	*Tamarindus indica* Linn.	Dried fuit	[7]
Taizishen	太子参	*Pseudostellaria heterophylla* (Miq.) Pax ex Pax et Hoffm.	Dried tuberous root	[7]
Tianma	天麻	*Gastrodia elata* Bl.	Dried tuber	[7]
Tiandong	天冬	*Asparagus cochinchinensis* (Lour.) Merr.	Dried tuberous root	[7]
Tufuling	土茯苓	*Smilas glabra* Roxb.	Dried rhizome	[7]
Tusizi	菟丝子	*Cuscuta chinensis* Lam.	Dried seed	[7]
Wujiapi	五加皮	*Acanthopanax gracilistylus* W. W. Smith	Dried root cortex	[7]
Wuweizi	五味子	*Schisandra chinensis* (Turez.) Baill.	Dried fruit	[7]
Wuzhuyu	吴茱萸	*Evodia rutaecarpa* (Juss.) Benth. or *E. rutaecarpa* (Juss.) Benth. var. *officinalis* (Dode) Huang or *E. rutaecarpa* (Juss.) Benth. var. *bodineri* (Dode) Huang	Dried pre-ripe fruit	[7]
Xiyangshen	西洋参	*Panax quinquefolius* L.	Dried root	[7]
Xiangfu	香附	*Cyperus rotundus* L.	Dried rhizome	[7]
Xuanshen	玄参	*Scrophularia ningpoensis* Hemsl.	Dried root	[7]
Yejuhua	野菊花	*Chrysanthemum indicum* L.	Dried flower	[7]

(continued)

Table 1.2 (continued)

Herb name in Pin Yin	Herb name in Chinese	Latin name of (source material)	Part used	References
Yimucao	益母草	*Leonurus japonicus* Houtt.	Dried aerial part	[7]
Yinxingye	银杏叶	*Ginkgo Biloba* L.	Dried leaf	[7]
Yinyanghuo	淫羊藿	*Epimedium brevicornum* Maxim. or *E. sagittatum* (Sieb. et Zucc.) Maxim. or *E. pubescens* Maxim. or *E. wushanense* T. S. Ying or *E. koreanum* Nakai	Dried aerial part	[7]
Yuanzhi	远志	*Polygala tenuifolia* Willd. or *P. sibirica* L.	Dried root	[7]
Yueju	越橘	*Vaccinium vitis-idaea* Linn.	Fruit or leaf	[7]
Zelan	泽兰	*Lycopus lucidus* Turcz. var. *hirtus* Regel	Dried aerial part	[7]
Zexie	泽泻	*Alisma orientalis* (Sam.) Juzep.	Dried rhizome	[7]
Zhebeimu	浙贝母	*Fritillaria thunbergii* Miq.	Dried bulb	[7]
Zhenzhu	珍珠	*Pteria martensii* (Dunker) or *Hyriopsis cumingii* (Lea) or *Cristaria plicata* (Leach)	Dried pearl	[7]
Zhidahuang	制大黄	*Rheum palmatum* L. or *R. tanguticum* Maxim. ex Balf. or *R. officinale* Baill.	Alcohol processed dry root and rhizome	[7]
Zhiheshouwu	制何首乌	*Polygonum multiflorum* Thunb.	Black bean soup processed dry tuberous root	[7]
Zhimu	知母	*Anemarrhena asphodeloides* Bge.	Dried rhizome	[7]
Zhiqiao	枳壳	*Citrus aurantium* L.	Dried unripe fruit	[7]
Zhishi	枳实	*Citrus aurantium* L. or *C. sinensis* Osbeck	Dried young fruit	[7]
Zhuru	竹茹	*Bambusa tuldoides* Munro or *Sinocalamus beecheyanus* (Munro) McClure var. *pubescens* P. F. Li or *Phyllostachys nigra* (Lodd.) Munro var. *henonis* (Mitf.) Stapf. ex Rendle	Dried inner layer of caulis	[7]

Table 1.3 Health claims allowed for health food products in China

1. Enhances immune function
2. Assists in lowering blood lipid
3. Assists in lowering blood glucose
4. Anti-oxidant
5. Assists in improving memory
6. Relieves vision fatigue
7. Stimulates lead removal
8. Clears throat
9. Assists in lowering blood pressure
10. Improves sleep
11. Stimulates milk production
12. Relieves physical fatigue
13. Increases tolerance of hypoxia
14. Assists in protecting from radiation damage
15. Lowers body weight
16. Improves growth and development
17. Increases bone density
18. Improves nutritional anemia
19. Assists in protecting liver from chemical damage
20. Removes acne
21. Removes melasma
22. Improves in keeping skin moisture
23. Improves in keeping skin lipid content
24. Regulates gut microflora
25. Stimulates digestion
26. Relaxes bowels
27. Assists in protecting from gastric mucosal damage

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Chapter 2
Food and Nutraceutical Applications of Chinese Herbal Products

Priya Kathirvel, Phillip Joy and Bohdan L. Luhovyy

2.1 Introduction

Traditional Chinese medicine (TCM) is undergoing rapid growth and development in China and worldwide. Risks and benefits associated with Chinese herbal products, that are consumed as functional foods or nutraceuticals, requires further understanding before entering new markets including Canada. A recent market report indicates that China exports 240,000 tonnes of Chinese medicine annually, of which 200,000 tonnes are raw herbs that accounts for 20 % of the country's annual harvest [1]. The growth in demand of Chinese herbs can be attributed to the rise in use of complementary and alternative medicine in the U.S., which has increased from 36 % of population in 2002 to 38.3 % in 2007 [2]. Nutritional Business Journal's Supplement Report for 2012 shows that herbs (botanicals) represented 17 % of dietary supplement sales in 2011 and the industry grew by 7 % in the U.S in the same time period [3]. While many Chinese herbal remedies have been used for more than 5000 years [4], their efficacy and safety needs to be evaluated using evidence-based approaches including double-blinded randomized clinical trials and toxicological studies. Another important issue is the lack of uniform regulations for herbal remedies (other terms are *herbal supplements*, *herbal substances*, *botanicals*, and others) which vary significantly between jurisdictions [5].

P. Kathirvel · P. Joy · B.L. Luhovyy (✉)
Department of Applied Human Nutrition, Mount Saint Vincent University, Halifax, NS, Canada
e-mail: bohdan.luhovyy@msvu.ca

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2.2 Regulation of Dietary Use of Herbal Remedies in Canada, USA and European Union

2.2.1 Natural Health Product Regulation in Canada

In Canada, herbal remedies and traditional Chinese medicine products (TCM) are regulated as Natural Health Products (NHP). In 2013, NHP market includes more than 50,000 products authorized for sale by Health Canada [6] including 2000 TCM [7]. According to Ipsos Reid 2010 report, 73 % of Canadians regularly take natural health products. While vitamin, minerals and essential fatty acids represent the most widely consumed NHP (71 %), herbal products are typically used as a tea (11 %), herbal remedies (10 %) and Echinacea (7 %) [8]. There is no distinction between dietary and non-dietary (i.e. medicinal) herbs in Canadian Regulations even though the earlier version of NHP regulation was intended to distinguish between dietary and medicinal herbs [9]. The consumption pattern of NHP in Canada and other countries does not account for the ethic and cultural specifics which influence the choice and type of NHP consumed. The study conducted with Canadians of Chinese and white backgrounds revealed that the responders of Chinese descent were more inclined to use herbal medicine compared to their white counterparts. Furthermore, their motivation to use herbal products was different. Thus, for Chinese responders the main factor to choose herbal medicine was the presence of chronic disease while for white responders it was perceived higher safety of herbal products compared to pharmaceuticals [10]. This indicates the substantial gaps in consumers' knowledge and provides the opportunities for nutritionists and other health care practitioners to translate the available scientific data and promote at least those products with proven safety and clinical efficacy.

While the main purpose of NHP is to: prevent, treat, mitigate a disease, disorders or abnormal physical state or its symptoms, or restore, correct or modify organic functions and overall maintain and promote human health [9], the Food and Drug Act prohibits to advertise and label any food, drug, cosmetic or device as a treatment preventative or cure for any of the diseases listed in Schedule A [11]. This list includes the following conditions: acute alcoholism, acute anxiety state, acute infectious respiratory syndromes, acute, inflammatory and debilitating arthritis, acute psychotic conditions, addiction (except nicotine addiction), appendicitis, arteriosclerosis, asthma, cancer, congestive heart failure, convulsions, dementia, depression, diabetes, gangrene, glaucoma, haematologic bleeding disorders, hepatitis, hypertension, nausea and vomiting of pregnancy, obesity, rheumatic fever, septicemia, sexually transmitted diseases, strangulated hernia, thrombotic and embolic disorders, thyroid disease, and ulcer of the gastro-intestinal tract. In 2007, NHP were exempted from preventative claim prohibition in respect to Schedule A listed diseases, while the previous conditions regarding the treatment and mitigation remain in force [12]. Considering that in Canada TCM are regulated as NHP, these regulations pertain to Chinese herbs as well. In order to better understand the issues related to TCM including traditional and novel TCM products, their sale,

importation and use in Canada, the Advisory Council on Traditional Chinese Medicines represented by stakeholder groups including industry, consumers and patients, health care professionals and academics was established by Health Canada in 2011.

2.2.2 Botanical Products and Their Regulation in the U.S. and European Union

In the U.S., herbal products are regulated under the Federal Food, Drug, and Cosmetic Act either as foods, botanical drugs or dietary supplements. While the herbs consumed as foods primarily due to their taste, aroma or nutritive value are regulated as foods, dietary supplements are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994 and may not claim to: diagnose, mitigate, treat, cure, or prevent a specific diseases. Instead, dietary supplements may claim a benefit related to a classical nutrient deficiency disease, describe the benefits for structure or function of human body and the mechanisms of thereof. If a botanical product is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans, such product is regulated as a drug. Both botanical drug products and herbal dietary supplements can be manufactured in the form of herbal tea and non-food forms such as concentrates, powder, tablet, capsule, elixir and other forms. Another type of products that are not regulated as drugs and do not require prescription are called *medical foods* intended to meet specific nutritional requirements of a disease or condition and must be used under medical supervision. The regulation of botanical products and medical foods in the U.S. is enforced by U.S. Food and Drug Administration [13].

In the European Union, the use of herbal products is regulated under the Directive 2004/24/EC of the European Parliament and of the Council enacted in 2004. Article 31 of the Directive defines *herbal substances* as mainly: whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. This definition also includes certain exudates that have not been subjected to a specific treatment. Article 32 defines *herbal preparations* as preparations obtained by subjecting herbal substances to treatments such as: extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include: comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates [14]. According to the Directive, each Member State has to set up a simplified registration for herbal medicines that have been traditionally used for at least 30 years including 15 years within the EU. In 2004, the Committee on Herbal Medicinal Products (HMPC) was established and aimed to assist the harmonisation of procedures and provisions concerning herbal medicinal products laid down in EU Member States, and further integrating herbal medicinal products in the European regulatory framework. HMPC serves as a scientific body and provides its opinion on herbal medicinal

products to EU Member States, establishes 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products', and Community herbal monographs [15]. In respect to botanicals intended for use in food applications, European Food Safety Authority (EFSA) has issued the "Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements". The Compendium covers about 900 botanicals, their scientific name, common synonyms and safety concerns [16].

2.3 Randomized Clinical Trials Using Dietary Herbs and/or Active Ingredients and Their Limitations

Dietary Chinese herbs have long been used in Traditional Chinese Medicine (TCM) for disease prevention, treatment and to enhance the overall wellbeing of human beings. However in the recent years, an increased focus on clinical and pharmacological-evidence based investigation on the efficacy of herbs and their active ingredients can be noticed. Based on a study published in the Chinese Medical Journal, the four major health categories where the application of Chinese medicine and natural products were more pronounced included: cancer, cardiovascular, oral & gastrointestinal as well as inflammatory/immune disorders [17]. Other categories consisted of neurological disorders, stroke, skin diseases, metabolic disorders, reproductive health, mental health and metabolic or endocrine disorders [17].

A wide range of disparity exists in the use of Chinese herbs for therapeutic purposes in modern medical practice. Traditional Chinese medicine practitioners use herbal combinations rather than single herbs in which each herb plays a specific role in addressing the patterns of symptoms. The inclusion of one herb may enhance the activity of the other or reduce the risk of short-term or long-term side effects of another herb [18, 19]. When herbal combinations/decoctions are subjected to preliminary studies, characterization of the principal component and/or adjuvant phytochemical constituents responsible for the curative action becomes impossible [20]. This is extremely essential when studies are to be applied to human subjects in various clinical trials. However, such an approach is not compatible with the basic theories of TCM including 'treating the patient as a whole' where the interaction of forces and energies both within and outside the individual is given importance [21].

Conducting randomized, controlled clinical trials in human subjects using dietary herbs becomes difficult due to: various factors including herb quality issues, improper processing and manufacturing practices, variations in active herbal components and interactions between herbs as well as with administered drugs [22]. The chemical composition of TCM and natural products are mostly governed by growing conditions such as rainfall, length of cultivation, soil nutrients and geography. A change in any one of these factors inevitably affects the content of chemical constituents present in herbal products. Even though the products are

standardized for content of their known active ingredients, there could be differences in the content of other components. Such variations can pose problems while conducting preclinical, pharmacological and clinical assessment of herbal formulations/products. Studies by Fitzloff et al. [23] showed that 26 % of the ginseng products marketed in North America did not meet the label claims of ginsenoside content of *Panax ginseng* and *Panax quinquefolius* products. An extensive study by Gilroy et al. [24] reported the reduced contents of active ingredients echinacoside or cichoric acid in Echinacea products marketed in the United States. Lack of quality control/quality assurance requirements for the dietary ingredient suppliers have been indicated as the cause of adulteration, substitution or low quality of materials being incorporated in the dietary herbal supplements [25]. In addition to this, various herb-herb interactions (incompatibilities and counteracting abilities) have been documented [26]. Also, interactions of herbal medicines with drugs such as warfarin, aspirin, midazolam, digoxin and irinotecan have been reported [27, 28]. Hence, understanding these pitfalls and taking remedial measures are crucial while integrating herbal medicine into evidence-based clinical practice. Preclinical and pharmacological assessment of herbal medicines conducted using animal model systems might sometimes not prove useful in humans as biological responses may not be species transferable. It is possible to have a positive effect of a drug/active ingredient in animals whereas it may be completely inactive in humans. Testing the toxicity levels and manifestations of a certain drug in animal models is particularly useful while assessing drug safety issues. Moreover, testing the presence of heavy metals such as arsenic, lead, copper and mercury in herbal ingredients is necessary to avoid possible adverse effects while conducting trials in humans [22]. The Consolidated Standards of Reporting Trials (CONSORT) checklist developed by the CONSORT group (www.consort-statement.org) provides a solid basis for conducting and reporting randomized controlled trials (RCT). This includes documentation of various aspects of RCT's including randomization, blinding and analysis along with detailed descriptions on patient eligibility criteria, experimental objectives and hypotheses, sample size calculation, implementation of the study and statistical methods used [29, 30]. However at times, implementing herbal medicinal trials pose problems due to their distinguishable organoleptic properties compared to placebo which could have a confounding effect on the efficacy of the treatment. In such cases, strategies adopted to control this possible bias should be well documented so as to facilitate replication of treatments by other investigators.

Although it is uncommon among the TCM practitioners to use single herbs, some specific herbs have gained attention and have been investigated for their potential to be used in the development of treatments or as therapeutic interventions. A large number of trials on herbs and their active ingredients can be retrieved from The Cochrane Central Register for Controlled Trials (www.cochranelibrary.com) and PubMed. Few examples of randomized, single/double blinded, placebo-controlled clinical trials of Chinese herbs and active ingredients for various diseases/disorders are shown in Table 2.1.

Some clinical trials on herbs provide promising results, where as some do not show any significant difference between the treatment and the placebo. In such

Table 2.1 List of few randomized, single/double blinded, placebo-controlled clinical trials of Chinese herbs and active ingredients for various diseases/disorders

Scientific name	Active ingredients (if investigated)	Health category	References
Curcuma longa L.	Curcumin	Colorectal cancer, Type-2 diabetes, Type-2 diabetic nephropathy, Gall bladder function Inflammation, Cardiovascular	[46–52]
Gingko biloba L.	Gingkolide-B	Sepsis, Multiple sclerosis, Acute ischemic stroke, Alzheimer's disease, Mild cognitive impairment, Hypertension, Diabetic nephropathy	[53–59]
Cinnamomum cassia Presl		Diabetes, Lipid profile	[60–63]
Panax ginseng C.A Mey., *Panax notoginseng* (Burk.) F.H. Chen, *Panaxquinquefolius*	Ginsenoside-Rd	Acute ischemic stroke, Type-2 diabetes, Erectile dysfunction, Psychomotor function, Neurocognitive function	[64–69]
Zingiber officinale Rosc.		Nausea, Vomiting, Hyperlipidemia	[70, 71]
Salvia miltiorrhiza		Oxidative stress, Hypertension	[5, 72]
Morus alba L	Mulberry 1-deoxynojirimycin (DNJ) Mulbery extract oil	Diabetes mellitus	[73]
		Melasma	[74]
Astralagus membranaceus (Fisch.)	Purified extract PG2	Allergic rhinitis	[75, 76]
		Hemorrhagic stroke	
		Cancer-related fatigue	[77]
Angelica sinensis (Oliv.)		Menopausal symptoms	[78, 79]

cases, investigators are led to conclude that more randomized controlled trials are recommended to understand the benefits. However, extensive research reviews on the scientific validity of clinical trials of TCM are available, which points out the various drawbacks of the studies and also provide recommendations for proper future trials [31]. Publication bias resulting from selective outcome reporting has been projected as one of the drawbacks that could diminish the strength of evidence while making informed decisions about a treatment [31]. In order to increase the transparency of randomized clinical trials and to improve the quality of trials, registration of prospective trials in international clinical trials registry such as *ClincalTrials.gov* and International Clinical Trial Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) established by World Health Organization has been highly warranted.

2.4 Market Trends in the Functional Foods and Natural Health Products Industry

The functional foods and natural health products industry is expanding with major financial implications on the world stage and shows growth in all areas including firms, sales and new product development. In 2004, the World Bank estimated the functional foods and natural health products industry to be worth 30–60 billion US dollars with estimates of it reaching $130 billion US dollars by 2015, which corresponds to 1–3 % of the total food market [32]. Three leading markets dominate this industry, the U.S, Japan and Europe, with over 90 % of the total sales for functional foods and natural health products [33]. The expansion of these markets is expected to continue over the next few years with markets also growing in China, India, and the Asia-Pacific countries [32].

An overview of the leading markets reveal that in the United States, the retail value of the functional foods and natural health products industry was $59 billion in 2007 with the natural health product segment accounting for 26.4 % of the total US health food sales [32]. The number of products on the market is increasing steadily, with new introductions increasing from 200 to 800 between 2006 and 2008 [34]. Several factors contribute to the growth of this industry including the increased awareness between health and diet, an aging population, the increasing cost of health care, increasing competition in the food industry for novel products, and the challenges consumers face while trying to meet their nutritional needs using conventional foods [32, 34]. The estimated value for functional foods and natural health products in Japan was estimated to be 16.4 billion US dollars in 2007 [32]. In Europe, the market was estimated at 8 billion US dollars, with the natural health product segment accounting for 6 billion US dollars [32]. The European Union is also the largest importer of medical plants with an estimated 100,000 tonnes of plant material being imported in 2000 [32].

Canada has a small portion of the global functional food and natural health product market which constitutes only about 1 % of the total global market. Although Canada's market share is small, it is increasing with further demands for novel products from Canadian consumers. Within Canada, the functional food and natural health product industry generates $3.7 billion in revenue with $1.7 billion coming from firms producing only natural health products [35]. The Canadian functional foods and natural health product industry has also expanded from 389 food and natural health product companies to over 680 companies between 2005 and 2007 producing over 22,062 product lines [32, 35]. Canadian firms who specialize in natural health products are targeting four main health areas: vascular health, weight control, energy and general nutrition. There is also a focus on the health of the immune system, the eyes, the bones, the urinary tract, the prostrate and the gut as well as diabetes, cancer, arthritis, menopause, anxiety and other mental health issues and sexual health and performance [32, 35].

2.4.1 Patents with Herbs

Patents granted by world governments are used in the food industry to protect the exclusive rights of the inventors or applicants of a novel product for a limited amount of time. According to the 2007 results from the Functional Foods and Natural Health Products Survey, there was a total of 999 existing patents worldwide for functional food and natural health products with another 1005 pending approval [35]. As with the overall industry, the number of patents in this sector is also expanding. For example, in the European Union functional foods and natural health patents grew from 3.2 to 7.7 % between 1994 and 2000 [32]. The United States and Canada, are also experiencing an increase in functional foods and natural health products patents. In the United States, the growth in patent applications is driven by the regulatory approval of many health claims [32]. Patents are granted by the United States Patent and Trademark Office in United States and by the Canadian Intellectual Property Office in Canada. An inventor in the United States must demonstrate that the invention is useful and new within the patent application whereas in Canada the invention must not only be first in the world or show "novelty" but also be functional and operative or have "utility" and show "ingenuity" in order for the application to be successful [32]. Patent regulation within Japan is based on the similar concept of novelty as in Canada. Between 1994 and 2001, Japan held over 22 % of the global patent applications with a major focus on dairy-based functional foods [32, 36, 37].

The majority of successful functional foods and natural health patents have been in the area of extraction and purification techniques of plants and plant parts [32]. For example, one patent provides a method of β-carotene extraction from the genus *Momordica* and yields an oil rich in β-carotene [38]. The patented process is done without the use of organic solvents and provides a stable source of β-carotene that can be used in products as a nutritional supplement for human and animal consumption as well as for pharmaceuticals and cosmetics [38]. Another process patent describes a low-temperature extraction process for several species of plants including *Zingiber officinale* (ginger), *Curcuma longa* (turmeric), *Cinnamomum cassia* (Chinese cinnamon), and *Mentha* (Mint) species for producing heat stable flavorings used in bakery applications [39]. An emulsion of edible oil, water and an emulsifier is created with the plant material and than separated to produce the liquid flavorings fraction. This fraction is then encapsulated and dried into a heat-stable powder [39]. Patents have also been obtained for the production technique used for enhancing the physico-chemical properties of beverages. Mennett et al. [40] described a method for enhancing the foam properties of a number of beverages including fermented malt beverages, beer, cappuccino, flavored coffee, tea, hot chocolate, and carbonated soft drinks by incorporating foam-enhancing formulations comprising plant materials from the mint family either to the finished beverage or into a step in the beverage manufacturing process.

2.4.2 Food Products with Added Herbs

Patents dealing with actual food products are less common but still exist. Morazzoni et al. [41], holds a patent for a medicament or a dietary supplement with gingko derived from the plant *Ginkgo biloba*, complexed with phosphatidylserine for the enhancement of cognitive function and to alleviate mental fatigue. The authors state that the product is "to improve the speed of memory and memory quality, to increase accuracy and attention in activities in normal healthy subjects, to prevent deterioration of the speed and quality of memory in people with decreased cognitive functions and to counteract cognitive fatigue, having also an influence on the mood, particularly in healthy children, young adults, middle-aged and/or old people" [41]. A dietary supplement comprised of fibre, whey and plant parts from plants of the genus *Capsicum* and *Mentha* and aimed for regulating appetite was patented [42]. It induces satiety by occupying the stomach and sending satiety signals to the brain and involve some other metabolic mechanisms. The herb *Angelica sinensis* is patented in the use of a fermented herbal drink which is effective in treating the symptoms of menopause [43]. The herb is extracted with yeast and water which allows the yeast to ferment the crushed herb. This fermentation process is carried out over seven days at 10–20 °C and is than filtered [43]. One more example of successful application of patents using herbs as part of the food product is described by Adachi et al. [44] as a flavor deterioration inhibitor for foods, drinks and/or oral care products. This product is made by extracting *Angelica keiskei*, avocado, *Cassia tora, Plantago asiatica*, hawthorn, fermented tea leaves with water, an organic polar solvent, and a deterioration smell inhibitor. The addition of the flavor deterioration inhibitor to foods will improve storage life by maintaining the product's flavor [44].

2.4.3 Natural Health Products Based on Herbal Remedies: What Is on the Market?

Health Canada with its Natural Health Product Database provides consumers with a means to search for licensed natural health products available in Canada, including vitamin and mineral supplements, herb and plant-based remedies, traditional Chinese and Indian medicines, omega 3 and essential fatty acids, probiotics, homeopathic medicines and many oral and personal hygiene products. These licensed products have been assessed by Health Canada and have been found to be of high quality, effective, and safe under the recommended usage of the products. Consumers can find information such as product name, product licence holder, Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM), product's medicinal ingredients, product's non-medicinal ingredients, product's dosage, product's recommended use, and cautions, warnings, contra-indications and known adverse reactions with the product's use (Health Canada, 2013) [45]. Several examples of natural health products in Canada using selected Chinese herbs are given in Table 2.2.

Table 2.2 Examples of natural health products in Canada using selected Chinese herbs

Selected Chinese herb	Natural product number (NPN):	Brand name(s)	License holder	Dosage form	Recommended route of administration	Recommended use or purpose	Cautions and warnings	Contra-Indications
Angelica dahurica, Poria cocos	2,230,977	Huohsiang Chengchi Pill	Wing Quon Enterprises Ltd.	Tablet	Oral	Traditional herbal medicine for relief of diarrhea and associated nausea and bloating	If diarrhea persists for more than 2 days or in the presence of high fever, consult a physician. For adults only	Do not use if pregnant
Angelica sinensis	1,995,987	Genestra Brands™ Multi Gyn; Genestra Brands™ Formula Gyn	Seroyal International	Tablet	Oral	Helps the body to metabolize carbohydrates, fats and proteins and helps in tissue formation; helps in the development and maintenance of bones and teeth and helps to maintain proper muscle function	If symptoms persist or worsen; if you are breastfeeding or if you have a liver disorder or develop symptoms of liver trouble, consult your health care practitioner prior to use	If you are pregnant; if you have had breast, uterine or ovarian cancer or taking oral contraceptive medication, do not use
Cassia obtusifolia, *Gardenia jasminoides, Polygonum multiflorum*	80,036,033	Jiangzhi Paidu Capsule	T.C. Unicorn Ltd	Capsule	Oral	This Traditional Chinese Medicine helps clear toxic heat and regulate qi	Do not use if you are pregnant or breastfeeding. Consult a health care practitioner if symptoms persist or worsen. Please consult a health care practitioner before consumption. Do not use if the cap or seal is damaged. Keep out of reach of reach of children	Do not use if you are experiencing loose stool due to deficiency of the spleen

(continued)

Table 2.2 (continued)

Selected Chinese herb	Natural product number (NPN):	Brand name(s)	License holder	Dosage form	Recommended route of administration	Recommended use or purpose	Cautions and warnings	Contra-Indications
Chrysanthemum morifolium, Dendrobium nobile, Panax ginseng, Prunus armeniaca	80,025,795	ShihuYeguang Wan	T.C. Unicorn Ltd	Pill	Oral	This traditional Chinese medicine helps replenish yin of the kidney, quench the liver-fire and improve eyesight. It is used for yin deficiency of the liver and the kidney with flaming-up of fire causing impaired vision	Consult a health care practitioner prior to use if you have liver disorders. Do not use if you have hypokalemia, high blood pressure, or a kidney or cardiovascular disorder. Consult a health care practitioner prior to use if you are taking other medications. Do not use if you are pregnant or breastfeeding. If condition persists for more than 7 days, worsens, or clears up and occurs again in a few days, discontinue use and consult a TCM practitioner. Do not use if cap or seal is damaged. Keep out of reach of children	None

(continued)

Table 2.2 (continued)

Selected Chinese herb	Natural product number (NPN):	Brand name(s)	License holder	Dosage form	Recommended route of administration	Recommended use or purpose	Cautions and warnings	Contra-Indications
Curcuma longa	80,000,032	KrippsTumeric	Kripps Pharmacy Ltd.	Capsule	Oral	Traditionally used as an anti-inflammatory	Consult a health care provider if you have a history of gallstones, biliary tract obstructions, stomach ulcers or are taking blood thinners	Do not use if you are pregnant or breastfeeding
Gardenia jasminoides	2,236,749	Anmien Tablets	Wing Quon Enterprises Ltd.	Tablet	Oral	Traditional herbal medicine helps to relief jitteriness due to feeling of fatigue and occasional insomnia	May cause drowsiness. Don't engage in activities requiring alertness. Avoid alcoholic beverages. Do not exceed recommended dose except on the advice of a doctor. If sleepiness persists continuously for more than two weeks, consult your physician. Insomnia may be a symptom of serious underlying medical illness	None

(continued)

Table 2.2 (continued)

Selected Chinese herb	Natural product number (NPN):	Brand name(s)	License holder	Dosage form	Recommended route of administration	Recommended use or purpose	Cautions and warnings	Contra-Indications
Lonicera japonica	2,239,977	Yin Chiao Herbal Tablets For Cold	Classical Remedia Ltd.	Tablet	Oral	Traditional Chinese Medicine used to provide temporary relief for symptoms of colds and flus: sore throat, fever and productive cough	Do not use when pregnant or breastfeeding. Consult a doctor if cough worsens, lasts more than 7 days accompanied by high fever or sore throat persists for more than 2 days. Do not exceed dosage	None
Panax notoginseng	2,238,959	PienTze Huang Tablets	Classical Remedia Ltd.	Tablet	Oral	Traditional Chinese Medicine: Analgesic—for pain relief	None	Do not use if pregnant or breastfeeding
Phyllanthus emblica	80,019,321	Triphala Plus-SewantiAyurvedic Series	Padmashri Naturals Inc.	Capsule	Oral	Traditionally used in Ayurvedic medicine in the treatment of indigestion, constipation, and to strengthen the eyes	Do not use if pregnant or breastfeeding. Consult a health care practitioner prior to use if you have a liver disorder. Do not use if you are taking thiazide diuretics, cardiac glycosides, corticosteroids, stimulant laxatives or other medications which may aggravate electrolyte imbalance. Discontinue use if persistent abdominal cramps, spasms, and/or pain	None

(continued)

Table 2.2 (continued)

Selected Chinese herb	Natural product number (NPN):	Brand name(s)	License holder	Dosage form	Recommended route of administration	Recommended use or purpose	Cautions and warnings	Contra-Indications
							occur. Consult a health care practitioner prior to use if you have abdominal pain, nausea, fever, vomiting, and hemorrhoids, or if you have a chronic gastrointestinal disorder	
Prunella vulgaris	80,017,024	Jiang YaPian	T.C. Unicorn Ltd	Tablet	Oral	This traditional Chinese medicine helps clear away the heat and reduce fire to help calm the liver. It is used for dizziness, vertigo and headache due to blood rising and flaming up of excessive fire of the liver	Consult a health care practitioner prior to use if you are taking other medications. Consult a health care practitioner if symptoms persist or worsen. Consult a health care practitioner prior to use if you have a liver disorder or develop symptoms of liver trouble (such as abdominal pain, dark urine or jaundice). Consult a health care practitioner prior to use if you have an iron deficiency. Not recommended for use in cases or diarrhea	Do not use if pregnant or breastfeeding

2.5 Conclusion

Growing market for dietary and medicinal herbs including TCM requires the harmonization of food and supplement regulations between jurisdictions. The new unified standards for herbal products and their clinical efficacy and safety evaluations need to be implemented in order to provide both healthcare providers and consumers with transparent and explicit information. The creation of a global database using the existing platforms (e.g., WHO, FAO, Codex Alimentarius, etc.) may provide a unique opportunity to consolidate all available information on herbal products and their nomenclature, efficacy, toxicity, applications, origin, territorial regulation and approval status.

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Part II
Root, Rhizome, Tuber, and Bulb Materials

Chapter 3
Achyranthes bidentata Bl. 牛膝
(Niuxi, Twotooth Achyranthes Root)

Minhui Li

3.1 Botanical Identity

Achyranthes bidentata Bl., a perennial herbaceous plant in the family Amaranthaceae, is widely distributed in China. The root of *A. bidentata*, usually called Niuxi or Huainiuxi in Chinese, has become one of the most important Chinese traditional medicinal herbs. It also has been frequently used as a tonic or dietary supplement. Typically, *A. bidentata* is about 70–120 cm tall with green or tinged purple stem and symmetrical branches. Leaves are elliptic or elliptic-lanceolate, rarely oblanceolate, supported by a hairy petiole of 0.5–3 cm long, with a cuneate or broadly cuneate base. The spikes are terminal or axillary, and the flowers are dense, about 5 cm long. Bracts are broadly ovate and reflexed after anthesis, the bracteoles are spiny, 0.25–0.3 cm long [1].

Niuxi grows mainly on the roadsides or hillsides, about 200–1750 m above sea level, and is widely distributed in China except for northeastern provinces, mainly in Henan, Anhui, Fujian, and Hebei provinces, etc. The Huainiuxi originated from Wuzhi, Boai, Qinyang prefectures of Henan province, is one of the famous "Four Huaiqing Chinese Medicines" at home and abroad [1]. The drug is collected in winter when aerial part withered, then removed from rootlet and soil, tied up in a small bundle, sun-dried to be wrinkled externally, cut evenly at the summit and dried thoroughly. There are also other processing methods for some specific medicinal purposes, including alcoholic Niuxi, salt Niuxi and so on [2, 3].

Chuanniuxi, mainly originated in Sichuan province, and Tuniuxi is usually harvested from the wild, has been widely used in traditional Chinese Medicine. Chuanniuxi is the dried root of *Cyathula officinalis* Kuan (Fam. Amaranthaceae), and has been recorded in Chinese Pharmacopoeia Pharmacopoeia. Tuniuxi, the

M. Li (✉)
Baotou Medical College, Baotou 014060, Inner Mongolia, China
e-mail: li_minhui@aliyun.com

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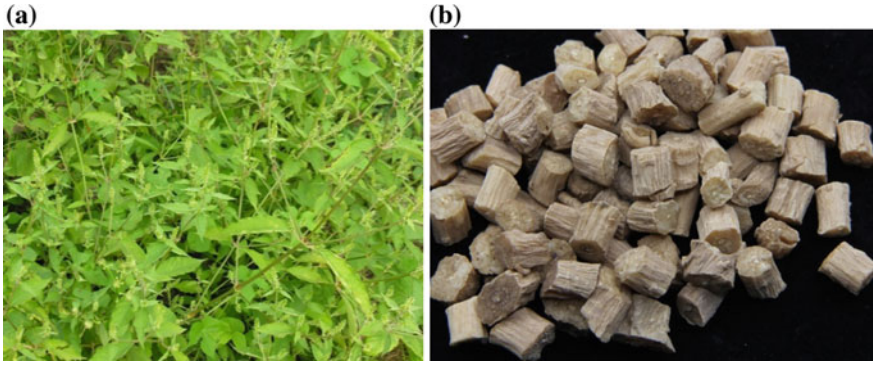


Fig. 3.1 Flowering plant (**a**) and crude drug (**b**) of Niuxi

dried root of *Achyranthes aspera* L., is one of the most important traditional Chinese medicinal materials, and has been frequently used together with other herbs (Fig. 3.1).

3.2 Chemical Constituents

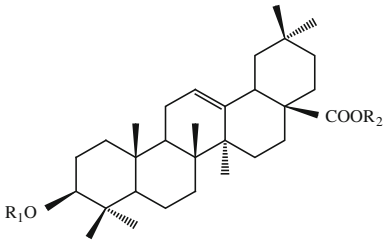
Triterpenoid saponins, polysaccharides and phytoecdysones are three major classes of bioactive compounds found in the root of *A. bidentata*.

3.2.1 Saponins

About 38 saponins have been isolated from *A. bidentata*, among which triterpenoid saponins is an important medicinal ingredient, especially the oleanane-type triterpenoid saponins. There are at least 15 oleanane-type triterpenoid saponins isolated from *A. bidentata*. 1–4 molecules of glucose, glucuronic acid or rhamnose occupy C-3 or C-28 of oleanolic acid, which composes the oleanane-type monodesmoside and bisdesmosides (shown in Fig. 3.2) [4].

3.2.2 Phytoecdysones

Phytoecdysones are the main effective components in *A. bidentata*. According to the Chinese Pharmacopoeia, β-ecdysone is the representative component used as the standard compound for evaluation of the quality of crude medicinal Niuxi [3]. A large number of phytoecdysones have been isolated from *A. bidentata*, among



Saponins	R_1	R_2
Achhybidensaponins I	Rha-(1→3)-GluA	Glc
Achhybidensaponins II	GlcA	Glc
Bidentatoside I	3′-glycolyl-2,3-dioxopropionyl-GlcA	Glc
Bidentatoside II	2′- (2"-O-glycolyl)-glyoxylyl	Glc
Chikusetsusaponin V methyl ester	Glc-(1→2)-6-Me-GluA	Glc
Ginsenoside Ro	Glc-(1→2)-GluA	Glc
PJS-1	H	Glc
Aachyranthoside I	2′-O-Glc-3′-O-(2"-OH-1"- carboxyethoxycarboxypropyl)]-GlcA	Glc
Aachyranthoside II	Glc-3′-O-(2"-OH-1"-carboxyethoxycarboxypropyl)]-GlcA	Glc
Aachyranthoside C	3-[2-Carboxy-1-(carboxymethoxy)-2-hydroxyethyl]-Glc	Glc
Aachyranthoside C dimethyl ester		
Aachyranthoside C butyl dimethyl		
Aachyranthoside E	3-[1-Carboxy-1-(carboxymethoxy)methyl]-Glc	Glc
Aachyranthoside E dimethyl ester		
Aachyranthoside Ebutyl dimethyl		

Fig. 3.2 Representative oleanane-type saponins isolated from Niuxi. *Glc* β-D-glucopyranosyl; *GluA* β-D-glucironopyranosyl; *Rha* α-L-rhamnopyranosyl; *Me* methyl

them, ecdysterone (**1**), inokosterone (**2**) and rubrosterone (**3**) being the primary ones. Recent research has found that there are other phytoecdysones in *A. bidentata*, such as serfurosterone A, achyranthesterone A, rhapontisterone B and stachysterone D (shown in Fig. 3.3) [5, 6].

3.2.3 Polysaccharides

Polysaccharide (ABP) is a purified polysaccharide isolated from *A. bidentata*. Polysaccharide sulfate (ABPS) of *A. bidentata* was a sulfated derivate from ABP, which was isolated and identified from *A. bidentata* [7, 8]. Recent studies indicate that ABP exerts a wide spectrum of immunomodulatory effects on the cells of

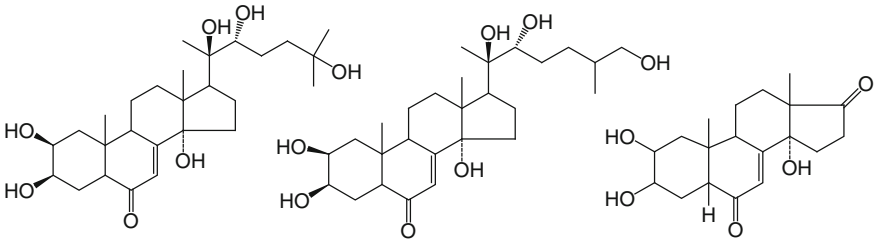


Fig. 3.3 Representative phytoecdysones isolated from Niuxi

immune system [8]. ABAB, a peptide polysaccharide, which has an immunological effect, is also isolated from *A. bidentata*. It is composed of D-glucuronic acid, D-galactose, D-galacturonic, L-arabinose and L-rhamnose. In addition, some researchers have found a water soluble polysaccharide called AbS that is composed of six glucose residues and three mannose residues [2].

3.3 Pharmacological Studies

A. bidentata is a commonly prescribed Chinese medicinal herb with the property of strengthening bones and muscles and ensuring proper downward flow of blood in terms of the therapeutic theory of traditional Chinese medicine. Modern pharmacological studies indicate that *A. bidentata* is an immunostimulant with anti-tumor, anti-fertility, analgesic, anti-bacteria, cognition-enhancing, anti-inflammation, anti-senile and anti-osteoporosis properties [2, 9]. *A. bidentata* also has a significant effect on uterine smooth muscle based on the species of animals or on whether they pregnant. The liquid extract and decoction of Niuxi have contractile effect on the isolated uterus of rabbits whether they pregnant or not. For pregnant cats, Niuxi appears to produce shrinkage effect on the uterus; however cats that are not pregnant show a flaccid [10, 11]. It has been reported that ecdysterone and inokosterone are the main components for anti-diabetic activity with low toxicity and side effects. In addition, ecdysterone and inokosterone promote protein assimilation and the synthesis of protein. RNA of cell nucleus and cytoplasm in liver are also increased observably [12]. The phytoecdysones show protective activities of heart and cerebral vessels system, respiratory system and endothelial cells [13]. ABP, as a major polysaccharide, has significant bioactivities in the aspects of immune adjustment, anti-coagulation, anti-tumor and anti-inflammatory [14]. Saponins from *A. bidentata* have been proven to possess various bioactivities such as anti-fertility, anti-tumor, analgesic and anti-inflammatory. It has also been proven to improve circulation [15].

3.4 Applications and Dietary Usage

3.4.1 Applications

Niuxi is one of the most popular herbs used in TCM. *A. bidentata* is bitter and sour in flavor, mild in nature and contributive to the liver and kidney meridians. As described previously, Niuxi is used as a tonic, emmenagogue, antiarthritic, diuretic, and antifertility agent to nourish the liver and kidneys, strengthen bones and muscles, and invigorate circulation [6]. In Chinese Pharmacopoeia 2010, Niuxi has been recorded to promote blood circulation, remove blood stasis, nourish the liver and kidney, strengthen bones and muscles, induce diuresis to treat stranguria and ensure proper downward flow of blood [3]. There are many practical formulations used historically, including Niuxi decoction, Niuxi powder, Niuxi wine, Sanmiaowan and so forth.

3.4.2 Dietary Usages

Niuxi is not only a nontoxic plant often used as a prescription ingredient, but also a valuable dietary plant, which has been included in the list of Chinese herbal medicines that can be used in health foods. Niuxi combined with other herbs can be used to prepare Niuxi wine, Niuxi paste and so on.

3.4.2.1 Niuxi Wine

Niuxi can be available to make herbal wines for hemiplegia and rheumatoid arthritis. One method for this is to soak Niuxi (roots of *A. bidentata*, 15 g), Chuanwu (parent root tubers of *Aconitum carmichaelii*, 15 g), Caowu (root tubers of *Aconitum kusnezoffii*, 15 g), Wumei (fruits of *Prunus mume*, 15 g), Daqingye (leaves of *Isatis indigotica*, 15 g) and Jinyinhua (flower buds or opening flowers of *Lonicera japonica*, 10 g) in 500 ml of Chinese spirit for ten days or more. The procedure is to drink 5–10 ml every morning and evening [16]. The other method is to boil Niuxi (roots of *A. bidentata*, 500 g) and soak sticky rice (1000 g) in the resulting juice of Niuxi. This concoction is then fermented in a warm place. Taking a daily dose of this boiled Niuxi wine orally is beneficial as a liver and kidney tonic, and invigorating the circulation [17]. In addition, Niuxi can also be used to make herbal wines in combination with many other herbs and the dose depends on the desired effect.

3.4.2.2 Niuxi Used in Medicated Foods

In some documentary records, Niuxi can be used for breast enhancement. One of the formulas is Longxiong Shiliao soup, which is composed of mutton (1000 g), pure honey (200 g), Dihuang (root tubers of *Rehmannia glutinosa*, 200 g), Danggui (roots of *Angelica sinensis*, 200 g), Xuduan (roots of *Dipsacus asper*, 200 g), Niuxi (roots of *A. bidentata*, 100 g) and Huangqi (roots of *Astragalus membranaceus*, 50 g) [17]. Niuxi (roots of *A. bidentata*, 50 g) can also be combined with Roucongrong (fleshy stems with scales of *Cistanche deserticola*, *Cistanche tubulosa*, 500 g), Danggui (roots of *Angelica sinensis*, 50 g) and double honey to make Niuxi Danggui Honey paste, which is good for preventing constipation [18].

3.5 Clinical Evidences

As a therapeutic medicine, Niuxi is widely used in clinics. It can be used alone, or in combination with other herbs.

Uncombined, Niuxi can be used to induce abortion and arthrophlogosis. In addition, the Niuxijing capsule made of Niuxi polysaccharide has a preventive effect on leukopenia caused by chemotherapy.

In clinical practice, it is used for blood stasis syndrome with irregular menstruation, dysmenorrhea, amenorrhea, postpartum abdominal pain and trauma with pain. For irregular menstruation, dysmenorrhea, amenorrhea and postpartum abdominal pain, it is usually combined with Honghua (flowers of *Carthamus tinctorius*), Taoren (seeds of *Prunus persica*, *Prunus davidiana*), Danggui (roots of *Angelica sinensis*), Ruxiang (resin of *Boswellia carterii*, *Boswellia bhaw-dajiana*), Moyao (resin of *Commiphora myrrha*, *Commiphora molmol*) and Xuduan (roots of *D. asper*), etc. In combination with Danggui (roots of *Angelica sinensis*), Mutong (lianoid steams of *Akebia quinata*, *Akebia trifoliata*, *Akebia trifoliata* (Thunb.), Koidz. var. *australis*), and Huashi (Talcum), it is used to treat hematuria, dysuria and urethralgia. Huoxue Qianjiang decoction, a classical Chinese prescription composed of Niuxi (roots of *A. bidentata*), Gouteng (hook-bearing branchs of *Uncaria rhynchophylla*, *Uncaria macrophylla*, *Uncaria hirsuta*, *Uncaria sinensis*,) and Danshen (roots and rhizomes of *Salvia miltiorrhiz*) has a significant effect on anti-hypertension. Simiao Wan, which composed of Niuxi (roots of *A. bidentata*), Cangzhu (rhizomas of *Atractylodes lancea*, *Atractylodes chinensis*), Huangbai (barks of *Phellodendron chinensis*) and Yiyiren (kernels of *Coix lacryma-jobi*), is used to relieve pain in the loins and knees as well as weakness of lower limbs due to downward flow of damp-heat [19].

3.6 Safety Evaluation and Toxicity Data

As described previously, Niuxi is one of the most popular herbs used in TCM, but it has few clinical reports on toxicity or side effects. It was reported that the HepG2 cells were selected to evaluate cytotoxicity of Niuxi, and the results indicated that this medicinal herb had no toxicity in vitro to the HepG2 cells within the dose range of 0.25–4.0 μg/ml, and that its desired biological activity could be elicited without inducing in vivo toxicity [9]. According to animal experiments on mice, the LD_{50} of ecdysterone is 6.4 g/kg, and inokosterone is 7.8 g/kg. The LD_{50} of Niuxi decoctum is 146.49 g/kg. The Niuxi decoctum of 75 g/kg was administrated to the mice intragastrically. After 3 days, there was no toxic reaction or abnormal action. In a sub-acute toxicity test, 60 g/(kg days) Niuxi decoctum was given to mice for 7 days continuously or 48 g/(kg days) for 30 days continuously, and there was no toxic reaction, abnormal blood parameters, liver-kidney function or body weight changes observed. In addition, there was no toxic reaction or side effect on the mice filled with 0.2–2 g/(kg days) of ecdysterone and inokosterone mixture for 35 days [2]. In conclusion, the toxicity of Niuxi is low.

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Chapter 4
Alisma orientalis (Sam.) Juzep. 泽泻 (Zexie, Alismatis Rhizoma)

Min Fu and Ling Wang

4.1 Botanical Identity

Alismatis Rhizoma is the dried tuber of *Alisma orientalis* (Sam.) Juzep. of the family Alismatacea. It grows plentifully in ditches and ponds in Fujian, Jiangxi, and Sichuan provinces of China. It is collected in the winter, sliced, and dried or stir baked with salt water. Alisma is also called winter plantain tuber, Alisma Plantago Aquatica or Alisma orientale.

The word Alisma is said to be a word of Celtic origin meaning "water", a reference to the habitat in which it grows. Early botanists named it after the Plantago because of the similarity of their leaves.

Alismatis Rhizoma is a hairless plant that grows in light (sandy), medium (loamy) and heavy (clay) acid, neutral and basic (alkaline) soils and also in water but not in the shade. It consists of a fibrous root, several basal long stemmed leaves (15–30 cm), and a triangular stem (up to 1 m tall). It has branched inflorescence bearing numerous small flowers with three rounds or slightly jagged, white or pale purple petals. The flowers open in the afternoon. Alisma is in flower from June to August, and the seeds ripen from July to September. The flowers are hermaphrodite (have both male and female organs) and are pollinated by flies (Fig. 4.1).

M. Fu (✉)
McGill University, 3640 University Street, Montreal, QC H3A 2B2, Canada
e-mail: fmess@163.com

L. Wang
College of Pharmacy, Henan University of Traditional Chinese Medicine, Zhengzhou 450008, China
e-mail: 465533397@qq.com

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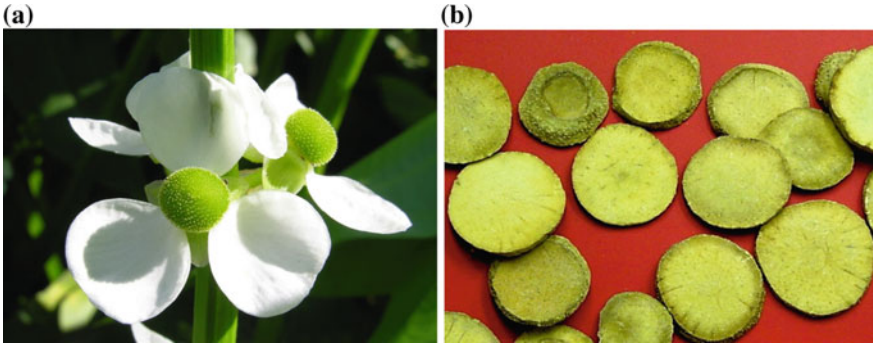

Fig. 4.1 Flowering plant (**a**) and sliced crude drug (**b**) of *A. orientalis*

4.2 Chemical Constituents

4.2.1 Triterpenoids

Triterpenoids are major and representative chemical constituents found from the rhizomes of *A. orientalis*. So far, the kind of compounds isolated from the plant include alisol A (**1**), B (**5**), C (**3**) and their monoacetates alisol A 24-acetate (**2**), alisol B 23-acetate (**6**), and alisol C 23-acetate (**4**), etc. (Fig. 4.2). Compound **2** showed the strongest activity for lowering blood lipid among these triterpenes. Compound **6** was thought to be the most important active component with the most extensive research to date [1–4].

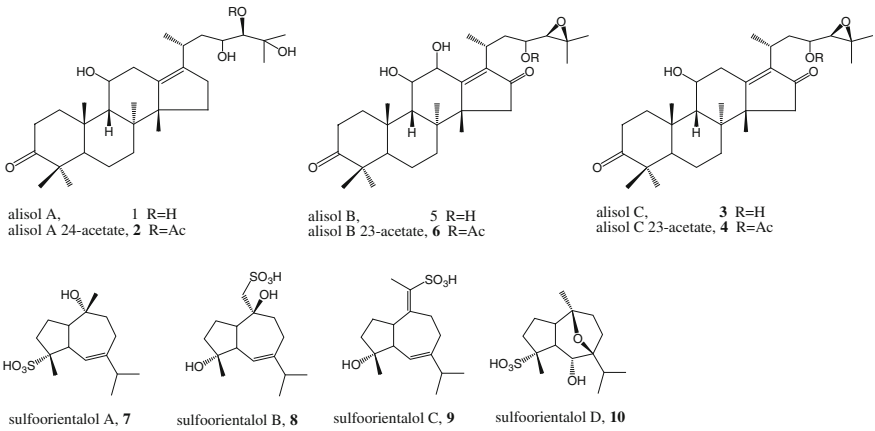

Fig. 4.2 Major triterpenoids and sesquiterpenes form *A. orientalis*

4.2.2 Sesquiterpenes

Some sesquiterpenoids reported from *A. orientalis* include sulfoorientalol A (**7**), B (**8**), C (**9**), and D (**10**), which showed the ability to inhibit the contraction of isolated bladder smooth muscle induced by carbachol [5].

4.3 Pharmacological Studies

Alismatis Rhizoma is an excellent diuretic agent, used widely for dysuria, edema, and different urological disorders, such as nephritis. It also has been used in modern practices to reduce arteriosclerosis and hyperlipemia, to improve the metabolism of fat in the liver, and to treat fatty liver, acute nephritis, swelling during pregnancy and obesity. Alisma is thought to be a good fat-reducing and anti-aging medicinal herb.

4.3.1 Diuretic Effect

Taking this herb orally by healthy people may increase the urine, sodium, and urea output. It has an obvious diuretic effect and is able to increase the excretion of urine, urea and chlorides. Its diuretic action on nephritis patients, with acute or chronic kidney inflammation, is more notable [6, 7].

4.3.2 Inhibition of Kidney Stones

The active constituents of *A. orientalis* can down-regulate the bikunin mRNA expression, decrease the calcium oxalate formation in rat kidney, and inhibit the renal stone formation in rat urolithiasis model [8]. In experiments on hamsters, the water decoction of this herb significantly lowers the renal calcium content and decreases calcium oxalate crystal formation in the renal tubule, thereby inhibiting the formation of kidney stones [9].

4.3.3 Improvement of the Cardiovascular System

This herb has hypotensive, anti-atherosclerosis, blood-sugar-reducing and lipotrophic effects. In experiments on hamsters, it significantly lowers the levels of total cholesterol and LDL-cholesterol in the serum, inhibits blood platelet aggregation

and thrombosis, and enhances fibrinolysin activity [10]. In addition, an alcohol-based extract of the herb increases isolated rabbit heart's coronary artery blood flow volume, has a slight inhibitory effect on miocardia, but does not affect the heartrate. The triterpenes, alisol M 23-acetate and alisol A 23-acetate, were isolated from *A. orientalis* and found against the Farnesoid X receptor (FXR), which is a member of nuclear receptor superfamily and viewed as one of the essential target proteins to develop antidiabetic treatments. *A. orientalis* might exert anti-hyperglycemic effect through the FXR pathway [11].

4.3.4 Enhancing Immunity and Anti-inflammation

17 beta-epoxy alisol A, alisol B 23-acetate and alisol A 24-acetate have shown immunosuppressive functions [12]. Administered to mice at the dosages of 10 and 20 g/kg, the water decoction of this herb slows down carbon clearance, and inhibits 2, 4-chloronitrobenzene-induced contact dermatitis [12, 13].

4.3.5 Lipotropic Effect

The lipid-soluble fraction has distinct anti-cholesterolemic and anti-atherosclerotic effects. It also decreased hepatic lipids in rabbits fed with a high-cholesterol and high-fat diet, indicating that the herb has lipotropic effect. The herb also exhibited a significant therapeutic effect on high fat feed-induced fatty liver due to a low-protein diet and those with liver damage due to carbon tetrachloride [14]. Administration with *A. orientalis* methanol extract 150, 300, and 600 mg/kg markedly decreased the serum and liver lipids; the high level of fasting serum glucose was reduced and insulin resistance was improved. The *A. orientalis* methanol extract treatment is helpful in preventing the oxidative stress by lessening lipid peroxidation and activating antioxidant enzymes [15, 16].

4.3.6 Promoting Weight Loss

Administering raw herb decoction (20 g/kg) to sodium glutamate-fattened hamsters lowers their Lee index, fat indices, and serum nitroglycerine content. Modern research proved that it lowers blood pressure, blood cholesterol and blood sugar. According to these properties, it not only could be used for weight loss and boosting fat loss, but it also may be good for treatment of other disease related with fat, such as diabetes, hypertension or high blood pressure, and high blood cholesterol. Therefore, Alismatis Rhizoma is a valuable remedy for weight loss [17].

4.3.7 Digestive Disorders

Dried stem bases to be, eaten, or grated and taken with water are effective in treating digestive disorders such as heartburn, cramps and stomach flu. The investigation of this herbal medicine also showed improvement in intestinal permeability and protection from alcohol-induced liver injury and intestine damage. Markers of the liver injury, aminotransferase abnormalities and hepatomegaly were improved and morphological changes, such as liver steatosis, mixed inflammation, and collagen deposition were lessened in rats treated with *A. orientalis* methanol extract 150, 300 and 600 mg/kg [15].

4.3.8 Anti-migration Activity

A fluorescence imaging based assay for screening compounds with anti-migration activity indicated one component with anti-migration activity which suggests a new proposed. The new proposed method with good precision, stability and linear range showed to analyze the inhibitory activity of anticancer compounds [18].

4.3.9 Other Pharmacological Activities

The powdered seed is an astringent used in cases of bleeding. This herb can also inhibit *Staphylococcus aureus*, *Diplococcus pneumoniae* and *Mycobacterium tuberculosis* [14]. The whole plant is also shown to promote conception.

Alismatis Rhizoma has been found to exert the effect of hypoglycemic activities and metabolism combined with other herbal medicines [19, 20].

4.4 TCM Applications and Dietary Usage

Alismatis Rhizoma has been thought of as a cure for rabies, though this has not been substantiated. This drug is sweet and tasteless in flavor and has the effects of excreting dampness. It has the effect of inducing diuresis similar to poria and can be used for various syndromes of water and dampness retention. This drug is cold in property and can expel heat in the kidney and urinary bladder, so it is very suitable for expelling heat in the Xia-jiao (lower part of body).

To treat edema, dysuria (difficult or painful discharge of urine), diarrhea, strangury (slow and painful spasmodic discharge of urine), leucorrhea, fluid retention syndromes, etc.:

(a) Edema and other syndromes due to damp-heat in the abdomen: This herb is often used together with such herbs as poria and umbellate pore fungus (*Polyporus umbellatus*), known as Umbellate Pore-fungus Decoction (Zhuling Tang), tuckahoe (*Poria cocos*), Job's tears (Semen Coicis), etc.
(b) Vertigo due to phlegm retention: This herb can be used in combination with large white head atractylodes rhizome (Rhizoma Atractylodis Macrocephalae), known as Oriental Water Plantain Decoction (Zexie Tang).

4.5 Side Effects and Toxicity

Therapeutic doses of *A. orientalis* are safe to use. One case of an allergic skin rash was reported in more than 200 cases of hyperlipidemia patients using the herb. Uncomfortable digestive disorders were also reported in a few cases of long-term use. The intravenous and intraperitoneal LD_{50} values of the methanolic extract of the rhizome in mice were 0.98 and 1.27 g/kg, respectively. No details occurred at an oral dose of 4 g/kg. No toxic effects were observed in rats fed with a diet containing the herb for two and a half month. However, it may have serious side effects or even toxic effects such as hepatotoxicity. (a) Do not use in case of damp cold or spermatorrhea or leucorrhagia as a result of kidney yang deficiency; (b) Do not use the herb in new borns, children, or pregnant or breast feeding women without first consulting a specialist.

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Chapter 5
Alpinia officinarum Hance 高良姜 (Gaoliangjiang, galangal)

Ping Ding

5.1 Botanical Identity

Gaoliangjiang, the rhizoma of *Alpinia officinarum* Hance in the family of Zingiberaceae, is one of the most popular Chinese herbal medicine. It is native to the Lingnan range in southern China, and cultivated in Guangdong province for food. The medicinal rhizome of *A. officinarum* is cylindrical, often curved and branched, and is 1–1.5 cm in diameter. The external surface is brownish-red to dark brown, with fine longitudinal wrinkles and grayish sinuous, annular nodes. The cross section is grayish brown and fibrous. The whole rhizome is acrid and pungent. There are about 250 species of genus *Alpinia* in the world, but *A. officinarum* is the only legal source recorded in The Pharmacoepia of People's Republic of China [1] and historical records of Chinese herbal works. Typically, *A. officinarum* grows to the height of 40–110 cm. Leaves are sessile or shortly petiolate, blades linear to lanceolate. Terminal racemes are white with red stripes. The fruit is spherical and turn red at maturity. Seeds are brown and packed by the aril [2].

Traditionally, Gaoliangjiang was harvested in the wild, however, investigation shows that its wild resource is on the verge of extinction. In the production area, artificial technologies of cultivation and processing are widely used. Gaoliangjiang was often harvested in later fall, between November and December, 4–6 years after artificial planting, then washed, cut into 5–6 cm sections and dried in the sun. For further processing, the raw material is sliced to 0.2–3 mm thickness after being softened by warm water. The sliced product will be dried again naturally or heated in a temperature controlled oven [3]. There is no need to worry about rot due to insects because of its spicy taste (Fig. 5.1).

P. Ding (✉)
School of Chinese Materia Medica, Guangzhou University of Chinese Medicine, Guangzhou 510406, China
e-mail: dingpinggz@126.com

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Fig. 5.1 The flowering plant (**a**) and crude drug (**b**) of Gaoliangjiang

5.2 Chemical Constituents

Diarylheptanoids, flavonoids and essential oils are three major classes of bioactive compounds found in the rhizomes of *A. officinarum* Hance [4–6].

5.2.1 Diarylheptanoids

As a major class of bioactive compounds found historically, diarylheptanoids [4–6] are mainly contained in the rhizomes of Gaoliangjiang. Curcumin is reported from the curcuma genus for the first time in 1885. A lot of natural linear diarylheptanoids have been discovered, 48 of which were obtained from Gaoliangjiang. Curcumin (**1**), dihydrocurcumin (**2**), hexahydrocurcumin (**3**) and octahydrocurcumin (**4**) are representative components and often used as standard compounds for evaluation of the quality of crude Gaoliangjiang and related pharmaceutical or natural health product preparations containing Gaoliangjiang.

5.2.2 Flavonoids

Gaoliangjiang also contains about 15 flavonoids, such as galangin (**5**), quercetin (**6**), kaempferol (**7**) [5].

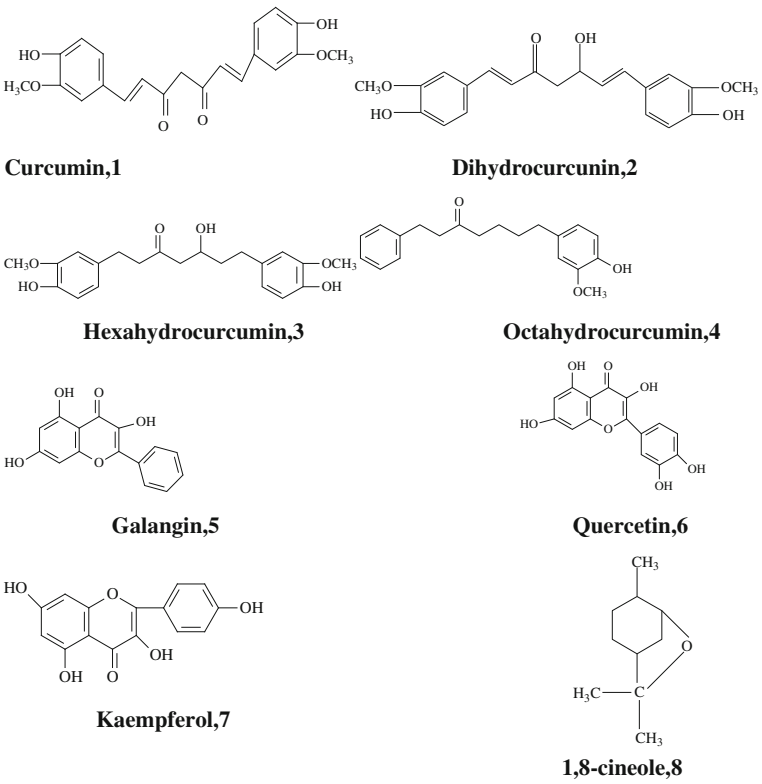

Fig. 5.2 Representative diarylheptanoids, flavonoids and essential oils isolated from Gaoliangjiang

5.2.3 Essential Oils

Essential oils were one of the main ingredients in the rhizome of Gaoliangjiang and characteristic of composition complexity. The GC-MS had shown that l,8-cineole **(8)** is the main element accounting for 47.3 % of the total volatile oil [5] (Fig. 5.2).

5.3 Pharmacological Studies

Gaoliangjiang is one of the most useful crude drugs in TCM. Modern pharmacological studies have indicated [5, 7–9] Gaoliangjiang to have bioactivities such as antibacterial, antiviral, anti-tumor, antioxidant, as well as suppressive properties of gastrointestinal bleeding. It has been claimed that Gaoliangjiang total flavonoids have beneficial effects to gastric ulcer and the gastric mucosa. The mechanism is likely to be related to antioxidant properties (removal of oxygen free radical activity). According to the report [8], galangin, quercetin and baicalein exhibited the potential

to reverse bacterial resistance to β-lactam antibiotics against penicillin-resistant staphylococcus aureus. In addition, other aspects of the research [9] reveal that dietary ginger phytochemicals, which are characterized rhizome extracts of Gaoliangjiang, target cholesterol metabolism and fatty acid oxidation in mice, with anti-obesogenic but also hypercholesterolemic consequences.

5.4 TCM Applications and Dietary Usage

5.4.1 TCM Applications

Gaoliangjiang has been used in clinical practice for thousands of years in China and the wider Eastern Asian area and plays a significant role in the Chinese healthcare system even today. The rhizome of Gaoliangjiang exerts therapeutic and health-maintaining actions in the following four aspects: relieving stomachache, treating colds, invigorating the circulatory system and reducing swelling [1]. Gaoliangjiang could be used on its own or in combination with other herbs based on TCM theory [10].

Common Gaoliangjiang preparations include the following forms: (1) Gaoliangjiang powder [10], a convenient form of administration which can be made from single Gaoliangjiang or mixed with other herbs. Lesser Gaoliangjiang rhizome is able to serve as a quick cure for acute stomach pain. The significant advantage of this form is ease of use and ready absorption. (2) Lesser Galangal and Ginger Pill [10, 11], is composed of two herbal components: *Alpinia officinarum* and *Zingiber officinale*. There are hundreds of corporations making this pill based on the same formula legally in China since there was no patent protection, although the quality varies among these products. It is mainly used for the treatment of stomachache, the stomach cold and swelling, loss of appetite through its function of warming stomach and invigorating the circulatory system. (3) Bi-gingers soft capsules is an improved formula based on lesser galangal and ginger pills. It is a relatively new preparation with low dosage as well as convenient. The products have been used clinically for the treatment of Chronic superficial gastritis, and Gastric and duodenal ulcer, etc. (4) Preparations made from active components including curcumin, dihydrocurcumin, total flavonoids and essential oils are also in the market as chemical drugs. The essential oils have been proven to function in the promotion of skin absorption and treating gastric ulcers.

5.4.2 Dietary Usages

Gaoliangjiang is not only one of the most famous herbs but also valuable dietary materials. Dietary uses include Gaoliangjiang tea, Gaoliangjiang wine, Gaoliangjiang soup, Gaoliangjiang porridge, etc. The following dietary forms can be easily made at home [4, 12].

5.4.2.1 Gaoliangjiang Teas

Herbal tea made of Gaoliangjiang alone or mixed with other herbs is the most common way to use Gaoliangjiang. Some examples are: Gaoliangjiang-xiangfu Tea composed of Gaoliangjiang (10 g) and Xiangfu (*Cyperus rotundus*, 20 g), Gaoliangjiang-jiangcan Tea, composed of the powder of Gaoliangjiang (3 g), Jiangcan (*Bombyx Batryticatus*, 3 g) and green tea (1 g), Gaoliangjiang-rougui Tea composed of Gaoliangjiang (2 g), Rougui (*Cortex Cinnamomi*, 3 g), Danggui (*Angelica sinensis*, 1 g), Renshen (*Panax ginseng*, 1 g), Houpo (*Cortex Magnoliae*, 2 g) and Scented tea (3 g). To make the herbal tea, softened water or natural water with low mineral and alkaline content is recommended in order to reduce the decomposition of phenolic acids.

5.4.2.2 Gaoliangjiang Wine [12]

Gaoliangjiang itself or combined with other herbs can be used to prepare herbal wine for gastric diseases. One example of the process is soaking Gaoliangjiang (70 g) with Huoxiang (*Agastache rugosa*, 50 g) in 500 mL of yellow wine. The juice has the function of relieving pain and warming the stomach. Drinking 25–50 mL daily is recommended. Gaoliangjiang can also be used to make herbal wines in combination with many other herbs depending on the specific need of functions. Daily intake amount will be based on the content of Gaoliangjiang, other herbs, and alcohol.

5.4.2.3 Gaoliangjiang Used in Medicated Foods

Gaoliangjiang can be used to make soups with japonica rice, rice, blue millet or sticky rice. A typical way is to boil Gaoliangjiang powder for 1–2 h. After removing the residue of crude drug by filtration, the japonica rice is added to continuously boil till fully cooked. This rice porridge can be used for relieving stomachache, treating colds and reducing swelling.

Xiangfu (*Cyperus rotundus*), chicken, Red dates (*Ziziphus jujuba*), and most vegetables can be boiled together with Gaoliangjiang. The sweet smell, nutritional value, and other health benefits of Gaoliangjiang can be utilized simultaneously. The taste of Gaoliangjiang-contained foods can be adjusted based on personal preferences.

5.5 Clinical Evidences

Gaoliangjiang belongs to the classification of interior-warming drugs. Because of its effect of warming the middle to dispel cold and reinforcing the spleen-qi, Gaoliangjiang is mainly used in combination with Xiangfuzi (*Cyperus rotundus*),

Magnolia officinalis, *Angelica sinensis*, *Corydalis yanhusuo* in traditional medicine to treat stomach ache, cold and swelling. There are 33 formulas that are composed of Gaoliangjaing and other herbs in formulas of TCM. Anzhong Tablets and Anzhong Driping Pills are two commonly used Gaoliangjiang therapeutic medicines for epigastric pain, vomiting, dyspepsia, gastric and duodenal ulcer, chronic gastritis and acute gastroenteritis. Anzhong Tablets have some clinical observation for gastro-esophageal reflux disease (GERD) and chronic gastritis. In 48 GERD cases, Anzhong Tablets demonstrated good curative effect and reduced the rate of recurrence [13]. Jiangxiang Anwei Soft Capsule made with Gaoliangjiang, Ganjiang (*Zingiber officinale*) and Muxiang (*Aucklandia lappa*), LiangFuWan and WeitongLiying Soft Capsule (developed from LiangFuWan) made with Gaoliangjiang and Xiangfuzi (*Cyperus rotundus*) are major preparations made with Gaoliangjiang. There are many clinical reports and observational studies published on the effects of Gaoliangjiang and its related preparations for gastric cavity diseases. For Liangfu Wan, a clinical report showed that the preparation could effectively relief the symptom of stomachache and peptic ulcer in 150 cases [14], and 67 cases were cured.

Decoctions, as well as Gaoliangjiang powder mixed with other prepared herbal medicines, also have extensive use in TCM. It has been clinically indicated that Jiawei Liangfu San, a formulae derived from Liangfu Wan could effectively treat gastric and duodenal ulcers in 175 cases [15]. In addition, the tincture of Gaoliangjiang can be used for coryza as carminative in clinical settings. Diarylheptanoids isolated from Gaoliangjiang were reported the function of anti Enteropathogenic *Escherichia coli* (EPEC) so that may be potential therapeutics for infectious diseases [16].

5.6 Safety Evaluation and Toxicity Data

There are few clinical reports on the toxicity or side effects directly related to the use of Gaoliangjiang. So far, the toxicology studies about it are unavailable. Nevertheless, only healthy people could take any form made of Gaoliangjiang alone because of its strong irritation [17].

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Chapter 6
Angelica dahurica (Fish. ex Hoffm.) Benth. et Hook. f. 白芷 (Baizhi, Chinese Angelica)

Minhui Li

6.1 Botanical Identity

Radix Angelicae Dahuricae is the dried root of *Angelica dahurica* (Fish. ex Hoffm.) Benth. et Hook. f. (Chinese vernacular names: Yubaizhi, Qibaizhi) or *A. dahurica* (Fish. ex Hoffm.) Benth. et Hook. f. var. *formosana* (Boiss.) Shan et Yuan (Chinese vernacular names: Hangbaizhi, Chuanbaizhi), a perennial herbaceous plant belonging to the family Umbelliferae. *A. dahurica* generally grows to 1–2.5 m. The stem diameter of *A. dahurica* is generally 2–5 cm. Most of the petals are white, but some are lavender. The herbaceous plant with its beauty is commonly used in landscaping. The morphological characteristics of two original plants are basically consistent, but they are different in the roots between *A. dahurica* and *A. dahurica* var. *formosana*. The former is cylindrical and brown, while the latter is long-coniform, grey brown, and there are lenticels and transverse processes ranking in several rows [1].

A. dahurica mainly grows on forest margins, valley grasslands and stream sides at the altitude of 500–1000 m. It is widely distributed in China (Hebei, Heilongjiang, Jilin, Liaoning, Shanxi, and Northern Taiwan), Japan, Korea, and Russia (Siberia) [2]. The drug is collected in summer or autumn when leaves turn yellow, and then it is removed from the rootlet and soil, soaked fully, cut into slabs and dried in the

M. Li (✉)
Baotou Medical College, Baotou 014060, Inner Mongolia, China
e-mail: li_minhui@aliyun.com

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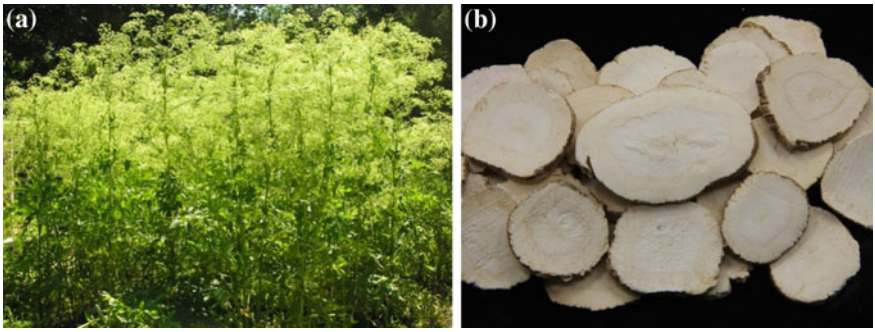

Fig. 6.1 Flowering plant (**a**) and crude drug (**b**) of Baizhi

sun or *A. dahurica* were based on the "Lei Gong's Moxibustion Theory" and "Compendium of Materia Medica", such as baking, frying, carbonizing, steaming, rhizoma polygonati's at a lower temperature [3] (Fig. 6.1).

6.2 Chemical Constituents

Coumarins and volatile oils are major chemical components in *A. dahurica*. According to research reports, the content of coumarins is much higher (approximately 1 %) than that of volatile oils. More than 50 coumarins have been isolated from *A. dahurica*. The main representative compounds are oxypeucedanin, imperatorin, isoimperatorin, byakangelicin and bergapten. Additionally, imperatorin has been used as a suitable chemical marker to evaluate and control the quality of *A. dahurica* in the Chinese Pharmacopoeia [4, 5].

122 Chemical components of the essential oil from two varieties of Radix Angelicae Dahuricae have been analyzed by GC-MS. Chemical studies have shown that *A. dahurica* mainly contains alcohols, esters, saturated alkane and various unsaturated alkane and a small amount of ketone, aldehyde and ester compounds. The two species of Radix Angelicae Dahuricae contain plenty of common components, but there still exist some differences in composition and content between them. 57 Components were noted in both species, 30 unique components in *A. dahurica* and 35 in *A. dahurica* var. *formosana*. Dodecanol is the highest level of compounds in two species of Radix Angelicae Dahuricae, which accounts for 55.197 and 43.118 % of the total volatile oil, respectively, having certain differences shown in Fig. 6.2 [6].

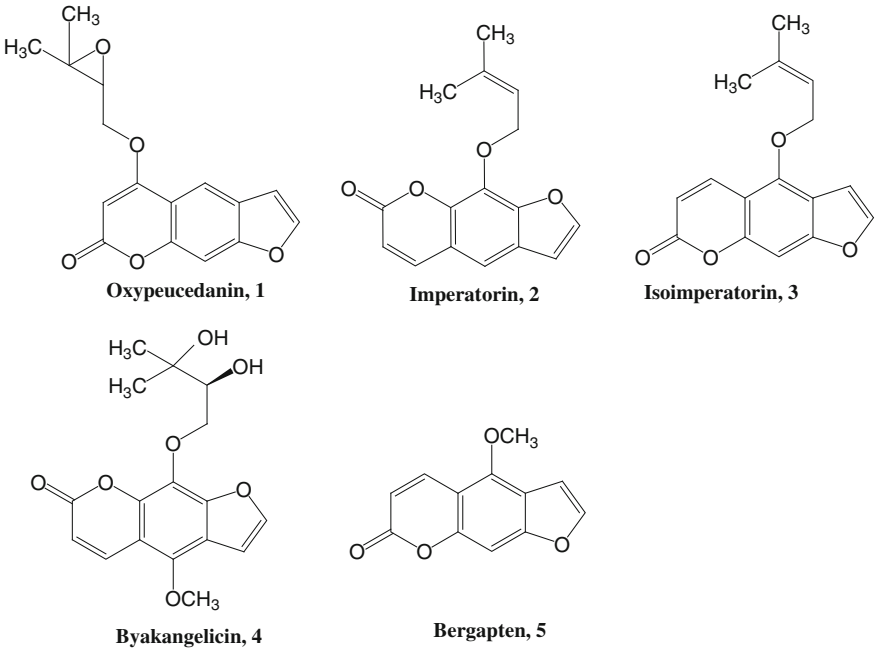

Fig. 6.2 Representative coumarins isolated from Baizhi

6.3 Pharmacological Studies

Baizhi exhibits a wide range of biological activities such as antipyretic, analgesic and anti-inflammatory effects; anti-microbial, antitumor, hepatoprotective, free radical-scavenging and more [7, 8]. Its active compounds are coumarin, essential oil, phellopterin, isoimperatorin, imperatorin, oxypeucedanin, byakangelicin and pimpinellin, having been reported to have anti-inflammatory, anti-mutagenic, anti-microbial, anti-tumor, anti-oxidant activities and analgesic effects [9]. Moreover, imperatorin can be used as a lead compound for anti-inflammatory drugs [10]. Recently, it has also reported that the polysaccharides isolated from the roots of *A. dahurica* have the ability of enhancing the proliferation of rat skin cells, acting with anti-oxidant and anti-inflammatory properties [9, 11].

6.4 Applications and Dietary Usage

6.4.1 Applications

Baizhi is a commonly traditional and folkloric medicine used in China, Japan, Korea, Russian Federation and Taiwan for the treatment of headaches, snake-bites, common colds, fevers, inflammation, sinusitis, furunculosis, etc. It has been used for thousands of years in Chinese herbal medicine where it acts as a sweat-inducing herb to counter harmful external influences. Baizhi has the folkloric reputation of being used as an analgesic, anodyne, antibacterial, antidote, carminative, diaphoretic, diuretic and stimulant. At the same time, it can also be used to treat frontal headaches, rhinitis, boils, carbuncles and skin diseases [12].

Generally, Baizhi's clinical preparations include the following forms: (1) imperatorin sustained-release tablets: imperatorin is a main active compound of *A. dahuricae*, which has anti-inflammatory, antitumor, antibacterial and anticoagulant activities, and induces vasodilatation through inhibiting voltage-dependent calcium channels and receptor mediated Ca^{2+} influx and release. It may have therapeutic potential in hypertension and atherosclerosis [13]. (2) Toufeng Yu Pill (TFY): It was firstly recorded in Chinese Pharmacopoeia in 1977, and originated from Chuanxiong Chatiao Powder which was described in the Taiping Huimin Heji Jufang, a well-known formula book edited by the office of "He Ji Ju" of the Song Dynasty (960–1279). It consists of three Chinese herbal drugs, Baizhi (roots of *A. dahurica*), Chuanxiong (rhizomes of *Ligusticum chuanxiong*) and green tea (leaves of *Camellia sinensis*) for the treatment of migraines. The study of TFY on treating migraines was mostly used in clinic settings. However, the pharmacodynamic material bases and effect mechanism of TFY were not yet understood clearly and there was a lack of rigorous scientific evaluation about it [14, 15]. (3) Cang-er-san is composed of Cangerzi (fruits of *Xanthium sibiricum*), Xinyi (flower buds of *Magnolia biondii*), Baizhi (roots of *A. dahurica*) and Bohe (aerial part of *Mentha haplocalycx*). Shin-yi-san is composed of eight herbal components such as: Xinyi (flower buds of *M. biondii*), Xixin (radixs and rhizomes of *Asarum sieboldri*), Baizhi (roots of *A. dahurica*) and etc. These two Chinese herbal formulas prescribed were used for treating allergic rhinitis in Taiwan [16].

6.4.2 Dietary Usages

Baizhi has been applied in the diet as an ingredient in dipping sauces and Dieda medicinal wine. The dipping sauce is made of 1 % salt, 2 % sugar and 0.8 % Baizhi, etc. Dieda medicinal wine is composed of Baizhi (roots of *A. dahurica*, 0.05 g), Chuanhuangbo (rinds of *Phellodendron Chinese Cortex*, 0.05 g) and Dahuang (roots and rhizomes of *Rheum palmatum*, 0.1 g) [17, 18].

6.5 Clinical Evidences

Baizhi, one of the most commonly used Chinese traditional drugs, is officially listed in the Chinese Pharmacopoeia. Baizhi injection is composed of Baizhi (roots of *A. dahurica*), Xixin (radixs and rhizomes of *Asarum sieboldii*) and Fangfeng (roots of *Saposhnikovia Divaricata)*. In 78 cases of patients with headache, toothache, trigeminal neuralgia, by intramuscular injected, they can quickly relieve pain and cure respectively. Oral administered Baizhi with black light irradiation was used for the treatment of psoriasis and resulted in the clinical cure by almost half, and the total effective rate was 90 %. A Chinese medical facial mask containing Baizhi (roots of *A. dahurica)* and Danggui (roots of *A. sinensis*), etc.) was used for the treatment of 154 cases of patients with acne, 97 cases of patients with melasma, 69 cases of patients with rhagadia, and the rates of cure were 86.36, 90.92 and 95.6 % respectively. 63 cases of patients with acute rhinitis and 32 cases of patients with allergic rhinitis were treated with Xingfangbai nasal drops (Xinyi (flower buds of *M. biondii*), Fangfeng (roots of *S. divaricata*), Radix Danggui (roots of *A. sinensis*) and Cangerzi (fruits of *X. sibiricum*)). The effective rates were 93.7 and 83.5 % respectively. *A. dahurica* in combination with holly leaves and Toosendan treated 70 cases of patients with ulcers; 62 cases were cured, six cases were improved, and the total effective rate was 91 % [19].

6.6 Safety Evaluation and Toxicity Data

LD_{50} of the Baizhi decoction to mice is 42–45 g/kg. LD_{50} of Hangbaizhi decoction or ether extract in mice is 43 g/kg (crude drug) and 54 g/kg (crude drug). LD_{50} of *Angelica dahurica* photosensitive capsule to mice is 1.5–1.7 g/kg. Ethanol solvent extract of Hangbaizhi is 1200 mg/kg and 800 mg/kg for stomach perfusion, once a day, continuing 5 days, and there was no death occurrence within 72 h. 200 mg/kg and 400 mg/kg of *A. dahurica* were given to mice by intragastric administration, once a day for consecutive two and four weeks. Medication administration team shows that blood, liver and kidney function tests and histological examination returned to no abnormalities. In the subacute toxicity test, *Angelica dahurica* photosensitive capsule can cause mild renal function change, slow down weight gain, decrease activities and solid organ has a slight deformation, however, all symptoms return to be normal after discontinuation.

Orally administered *Angelica dahurica* photosensitive capsule 40 mg/kg with black light irradiation show no obvious toxic effect on dogs. When at the concentration of 80–160 mg/kg, it can cause loss of appetite, vomiting, weight loss, and produce phototoxic reactions on the skin such as unhairing (erythema, edema, erosion, etc.), but there are no malignant phenomena. In addition, it also produces phototoxic reaction in the corneal, causing corneal opacity. Patients with psoriasis oral administered photosensitive capsules (Hangbaizhi extract), after 1.5–2 h irradiated

UVA, six times a week, total 20–30 times, which makes the rate of peripheral blood lymphocytes sister chromatid exchange (SCE) significantly higher than previous treatment ($P < 0.01$), so this therapy has the potential carcinogenic risk. LD_{50} of imperatorin to mice by intraperitoneal injection is 373 mg/kg. LD_{50} of imperatorin and xanthotoxin by intramuscular injection in rats are 373 and 160 mg/kg [20].

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Chapter 7
Angelica sinensis (Oliv.) Diels 当归 (Danggui, Dongkuai)

Jun Xu, Hubiao Chen and Quanbin Han

7.1 Botanical Identity

Angelica sinensis (Oliv.) Diels is a common perennial herb in the family of Umbelliferae. Its dried roots, named Angelicae Sinensis Radix (Danggui, Dongkuai), have been frequently used as one of the most distinguished traditional Chinese medicines for dual medicinal and tonic purposes (Fig. 7.1). It is somewhat cylindrical, with 3–5 or more branched at the lower part, 15–25 cm long, externally yellowish-brown to brown in color, and longitudinally wrinkled and transversely lenticel-like protruded. The whole Danggui could be divided into three botanical parts: (1) root stocks (Guitou) (1.5–4.0 cm in diameter, annulated, apex obtuse and rounded or with several obvious protrudent rhizome scars), (2) main root (Guishen) (lumpy on the surface) and (3) branching roots (Guiwei) (0.3–1.0 cm in diameter, the upper portion thick and the lower protion thin, mostly twisted and exhibiting a few rootlet scars).

Danggui has been cultivated across Northwest China, in places such as Gansu, Yunnan, Sichuan, and Qinhai Province, etc. It is normally collected in late autumn, removed from therootlet and soil, sightly dried and tied up in small bundles, placed on a shelf and then smoke-dried. It can not be used medically if the roots become woody, withered and not oily, or greenish-brown on the fracture [1]. There are several methods for preparing processed Danggui for different preferable tonic and medicinal purpose, such as slices, wine-wishing and coal-frying [2].

J. Xu · H. Chen · Q. Han (✉)
School of Chinese Medicine, Hong Kong Baptist University, Hong Kong, China
e-mail: hqb0402@yahoo.com

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Fig. 7.1 Dried roots (**a**) and sliced crude drug (**b**) of Danggui

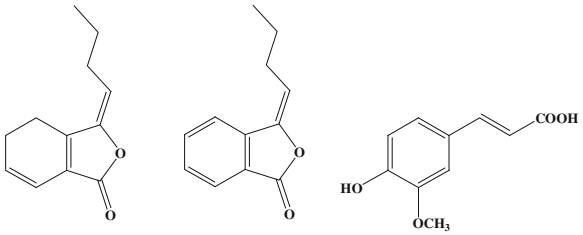
7.2 Chemical Constituents

The chemical constituents in Danggui are complicated. To date, over 70 chemicals have been isolated and identified from Danggui, including carbohydrates, volatiles and organic acids, etc.

7.2.1 Small Molecules

Small molecules in Danggui have been well investigated and could be divided into two kinds, volatiles and water-soluble compounds, mainly including organic acids, vitamins, amino acids and trace elements, etc.

Danggui is very rich in volatile components, in which phthalides are dominant, for example, *Z*-ligustilide and *Z*-butylidenephthalide. Terpenes are also frequently found in the volatile components of Danggui. Of the water-soluble components, organic acids are the main compound of concern in Danggui, with ferulic acid being the most representative one (Fig. 7.2). These characteristic bioactive components are intensively employed as the chemical markers for quality evaluation of Danggui and Danggui-containing pharmaceutical and natural prescriptions and products for medicinal or tonic applications [3].



Z-Ligustilide **Z-Butylidenephthalide** **Ferulic acid**

Fig. 7.2 Representative small molecular components in Danggui

7.2.2 Polysaccharides

There are significant amounts of polysaccharides in Danggui that have been experimentally proven to exert multiple biological properties, such as immuno-modulation, anti-tumor and anti-oxidant activity. As indicated by a recent study, polysaccharides rather than volatile oils are required in the traditional use of Danggui [4].

To date, about 40 kinds of polysaccharides have been isolated and purified from Danggui. Isolation, purification, and in-depth structural elucidation of the polysaccharides in Danggui have been intensively reported. There is much variety in the molecular weights of purified polysaccaharides from Danggui, rangingfrom less than 10^4 kDa to more than 10^6 kDa.

Glucose, mannose, galactose, arabinose and galacturonic acid, are most frequently found, and are the five main monosaccharides and uronic acid comprising the polysaccharides isolated from Danggui. In addition, other monosaccharides such as rhamnose, xylose and glucuronic acid, also occasionally appear in the backbone or branched and terminal residues of purified Danggui polysaccharides. Moreover, diverse glucosidic bonds mainly 1 → 4, 1 → 6 or 1 → 3 linkages are found in Danggui polysaccharides [5].

7.3 Pharmacological Studies

In the light of traditional Chinese medicine theories, Danggui is historically used for nourishing blood. Based on modern research, multiple pharmacological effectsof Danggui have beenexperimentally proven, such as hematopoietic effect, cardiovascular effects (protection of the cardiovascular system against ischemia, relaxation of blood vessels and vascular protection effect in endothelial cells, anti-oxidation, anti-platelet aggregation, and regulation of hemorrheology), effects on gynecological imbalances (dysmenorrhea alleviation, estrogenic activity, and anxiolytic effects), neuro-protective activity, wound healing, and anti-cancer effects

[6]. In addition, the bioactive effects of Danggui fractions and individual components were also intensively studied. For example, polysaccharide fractions in Danggui are hematopoietic, anticancerous, antioxidative, and immunoregulatory [7] while essential oil fractions possess the effects of anti-platelet aggregation, muscle relaxation and antianxiety [8]. Vessel relaxation, neuro-protective and anti-tumor effects of Z-Ligustilide as well as anti-oxidation, anti-platelet aggregation, anti-bacterial activities of ferulic acid have also been undoubtedly verified [9].

7.4 TCM Applications and Dietary Usage

7.4.1 TCM Applications [10]

As one of the most important Chinese medicines, Danggui has been used in the treatment of cardiovascular and cerebrovascular conditions in China for years and is usually combined with other herbs for clinical use. For instance, Danggui plus Radix Astragalus in a 1:5 ratio form a famous prescription: Danggui Buxue Tang which is traditionally used for blood deficiency disorders. Thanks to its positive effect, this formula has been getting more and more attention in recent years and many experimental studies have been conducted to provide scientific testimony to its favourable effects in promoting hematopoiesis, regulating immunity, and protecting cardiovascular aspects. Another example of a well known tradition prescription is Siwu Tang. It consists of *Angelica sinensis*, *Ligusticum chuanxiong*, *Paeonia lactiflora* and *Rehmannia glutinosa* (processed), and is a well regarded ancient Chinese prescription that is prized throughout East Asia and used to enrich the blood and regulate menstruation. Moreover, other Danggui-containing formulas with more complicated compositions, such as Guipi Tang, Xiaoyao San, Danggui Sini Tang and Danggui Liuhuang Tang, are also widely used in individualsfor blood-related diseases.

Apart from use in traditional medicinal formulas, Danggui is also employed in many medicinal products with modern dosage forms, for example, ointments (Danggui fluid extract), tablets (Danggui Tablets and Danggui Longhui Tablets), pills (Danggui Yangxue Pills and Concentrated Danggui Pills), oral solution (Danggui Buxue Oral Liquid), granules (Danggui Shaoyao Granules), injections (Danggui Jisheng Injections and Fufang Danggui Injections) and mixtures (EJiao Danggui Mixtures).

7.4.2 Dietary Usage

Due to the outstanding tonic effects, Danggui is also well-accepted in dietary usage as a popular food supplement to treat many conditions. It is used mainly for the

treatment of dysmenorrhea, amenorrhoea and other female reproductive problems. Danggui is also used to enrich blood as an aid to recovery from blood loss after child birth or surgery [11]. Danggui itself or combined with other herbs can be used to prepare herbal wine, herbal tea, and medicinal foods such as congees and other dishes, which could be easily made at home.

7.4.2.1 Danggui Wine

Herbal wine made of Danggui itself or mixed with other herbs is commonly used for irregular menstrual cycles as well as coronary diseases. For example, Guiqi Wine, prepared by Danggui (150 g), Huangqi (roots of *Astragalus mongholicus*,150 g), Dazao (fruits of *Ziziphus jujuba var. inermis*, 100 g) and Chinese spirit (500 mL), is a well-known kind of tonic wine for regulating menstruation. Drinking 20–30 mL daily for 3 months is recommended [12]. Danggui can also be used to make herbal wines in combination with Cordycepsand Sanqi (roots of Panax notoginseng) for treating coronary diseases [13].

7.4.2.2 Danggui Teas

Danggui alone or combined with other herbs can be used to prepare herbal tea for enriching blood. Some examples are: Danggui Tea composed of Danggui (10 g); Shanzha Danggui Tea composed of Danggui (15 g), Shanzha (fruits of *Crataegus pinnatifida*, 30 g), and moderate amounts brown sugar; Danggui Chuanxiong Yimucao Tea composed of Danggui (60 g), Yimucao (45 g), and Chuanxiong (10 g); Danggui Dihuang Tea composed of Danggui (15 g), Prepared Dihuang (roots of *Rehmannia glutinosa*, 15 g), and Dazao (fruits of *Ziziphus jujuba* var. *inermis*, 5 pieces). Danggui can also be used to make herbal teas in combination with many other herbs depending on the specific need of functions including enriching *Qi* and promoting blood circulation.

7.4.2.3 Danggui Used in Medicinal Foods

Danggui can be used to make medicinal foods like congees and dishes as food supplement for treating women's reproductive problems such as relieving cramps, irregular menstrual cycles, infrequent periods, premenstrual syndrome (PMS) and menopausal symptoms. Danggui is commonly used with rice and other herbs for making congees. For example, Danggui Fangfeng Congee, prepared by Danggui (15 g), Fangfeng (roots of *Saposhnikovia divaricate*, 10 g) and rice (100 g); Chidou Danggui Congee, prepared by Danggui (20 g), Chixiaodou (seeds of *Phaseolus calcaratus*, 100 g) and rice (100 g).

7.5 Clinical Evidences

For clinical applications, Danggui is always combined with other herbal medicines as complex prescriptions, such as Danggui Buxue Tang and Siwu Tang, etc. The favorable clinical effects of these traditional formulas have been well investigated and proven for many diseases, including gynaecopathia and angiocardiopathy. Danggui Buxue Tang has been clinically proven to be antanemic, liver-protective and *Qi*-beneficial therapy while the intensive clinical investigations demonstrated that Siwu Tang was an ideal formula for nourishing blood and regulating menstruation [14]. Some modern dosages of Danggui or Danggui-containing combinations are also clinically investigated. For Compound Danggui Huoxue Tablets, a clinical study showed that the compound could be used for treating thromboangiitis obliterans in 40 cases, which was better than Compound Danshen Tablets used in control groups [15]. For Compound Danggui Pills, clinical research was carried out on 200 cases with the symptoms of dysmenorrheal and irregular menstruation. The efficiency of the treatment group was as high as 95.1 %, showing the significant difference compared with the control group [16]. For Danggui Buxue Tang (DBT) which is a famous Chinese herbal medicine preparation, a randomized, double-blind, multiple-dose escalation trial (phase II clinical trial) was completed. This clinical study investigated the dose-response relationship of DBT on 60 postmenopausal women experiencing severe hot flashes and night sweats. The resulted showed that DBT preparations at 6.0 g/day significantly improved physical and psychological scores and significantly reduced vasomotor symptoms from baseline [17].

The clinical effects of Danggui Buxue Oral Liquid for mild and moderate anemia [18], Danggui Shaoyao Granules for menoxenia [19], Danggui Buxue Decoction No.1 for auxiliary therapy in treating patients of non-small-cell lung cancer at peri-operational stage [20] have all been experimentally proven as well.

7.6 Safety Evaluation and Toxicity Data [17]

In “Shennong Bencao Jing”, an ancient book on medicinal herbs, Danggui was recorded as a “top grade” non-toxic herbal medicine. Few clinical reports on the toxicity or side effects of Danggui are available. According to toxicity studies on animals, the MLD (Minimum Lethal Dose) of Danggui fluid extract by intragastric administration for SD rats is 30–90 g/kg, the LD_{50} of Danggui water extracts by single dose i.g. and i.p. (mice) are more than 8 and 6.58 g/kg, respectively. The LD_{50} of Danggui diethyl ether extracts by single dose i.g. and i.p. (mice) are more than 10 and 5 g/kg, separately, and the LD_{50} of Danggui methanol extracts by single dose i.g. and i.p. (mice) are both more than 6 g/kg. Furthermore, 0.06 and 0.02 mL/kg diethyl ether extracts of Danggui by single dose i.v. could lead to the death of dogs and cats, respectively.

As described above, Danggui is a relatively safe herbal medicine often used for the treatment of gynaecopathia and angiocardiopathy. However, there are several issues you must be aware of when you decide to use this herb without doctor's advice. Breast cancer sufferers should not take Danggui since its estrogen components could significantly promoting the proliferation of breast cancer cells. Danggui should also not be used in combination with anticoagulants because their synergistic effect could increase the risk of hemorrhage. It's strongly suggested to use Danggui under your doctor's professional advice.

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Chapter 8
Asparagus cochinchinensis (Lour.) Merr. 天冬 (Tiandong, Chinese Asparagus)

Feng Zhang, Yin Lu, Wenhui Qian and Zifan Pei

8.1 Botanical Identity

Asparagus cochinchinensis (Lour.) Merr. is a perennial plant (*Liliaceae*), whose dry root tubers are used as a traditional Chinese medicine, called Tiandong (Fig. 8.1). It is usually harvested in the autumn or winter months. After rinsing and removing their stems, peel and fibrous roots, they are boiled or steamed and then dried.

Tiandong has been used in traditional Chinese medicine for a long time. Nearly 2000 years ago, it was initially described in Shennong's Classic of Materia Medica and was listed as a top grade herb. *Asparagus cochinchinensis* is widely distributed throughout China, mainly in Hebei, Shanxi, Shaanxi, Gansu, Anhui, Henan, Jiangsu, Zhejiang, Jiangxi, Hunan, Hubei, Sichuan, Guizhou, Yunnan, Guangxi, Guangdong, Fujian, Taiwan as well as other regions. Although it grows widely in China, the region of Southern Yangtze River is the major place of origin of this plant. Among all of these regions, Guizhou province produces the herb with the highest quality.

8.2 Chemical Constituents

Many kinds of steroidal saponins have been identified in this herbal medicine, including asparagus furan sterol oligosaccharides, methylprotodioscin, pseudoprotodioscin, and other six steroidal saponins, whose aglycones include yamogenin **(1)**,

F. Zhang · Y. Lu (✉) · W. Qian · Z. Pei
Department of Pharmacology, Nanjing University of Chinese Medicine, 138 Xianlin Avenue, Nanjing 210023, Jiangsu, China
e-mail: luyingreen@126.com; nucmzf@163.com

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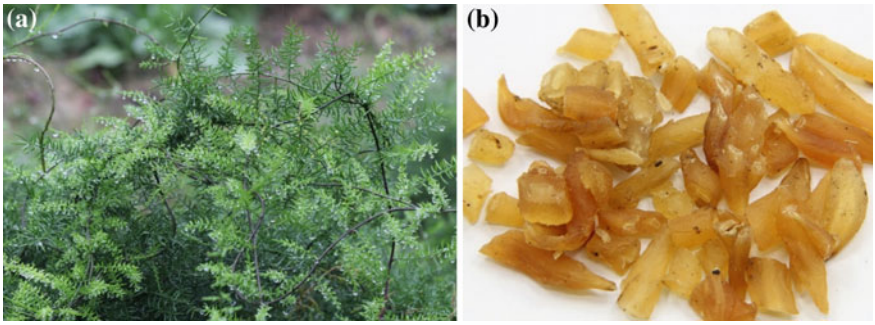

Fig. 8.1 Growing areal part (**a**) and crude drug (**b**) of *Asparagus cochinchinensis*

diosgenin **(2)**, sarsasapogenin and smilagenin. This herb also contains saccharides including oligosaccharides, glucose, fructose, sucrose, and asparagus polysaccharides. There are 17 amino acids isolated in this herb, including asparagine **(3)**, citrulline **(4)**, serine, threonine, proline, glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, aspartic acid, glutamic acid, arginine, histidine, and tyrosine. In addition, β-sitosterol **(5)** and 5-methoxymethylfurfural **(6)** are also found in this herb [1]. Representative structures of these constituents are shown in Fig. 8.2.

8.3 Pharmacological Studies

Current pharmacological studies of Tiandong mainly focus on anti-oxidative, anti-tumor and anti-bacterial properties [2]. Studies showed that the major component asparagus polysaccharide ACP1 could clear superoxide anion free radicals produced by NADH-PMS-NBT system in vitro, reduce the content of hepatic microsomal lipid peroxidation malonaldehyde in mice, and inhibit hydrogen peroxide-induced hemolysis of red blood cells in rats, suggesting that ACP1 had potent free radical scavenging and anti-lipid peroxidation activities [3]. Furthermore, the water decoction of Tiandong was found to inhibit the growth of many Gram-positive bacteria, including *Anthrax, Hemolytic streptococcus, Corynebacterium diphtheriae, Streptococcus pneumoniae, lemon Staphylococci, Staphylococcus aureus* and *Bacillus subtilis* [4]. The same study showed that the methanol extract of Tiandong at 150 μg/ml exhibited significant anti-bacterial activities against *Escherichia coli* and Shigella dysenteriae [5].

In terms of anti-tumor activity, the ethanol extract of Tiandong could potentially inhibit the leukocyte dehydrogenase in acute lymphocytic leukemia, chronic myelogenous leukemia and acute monocytic leukemia, and suppress the white cell respiration in acute lymphocytic leukemia [6]. Moreover, the 80 % ethanol extract of Tiandong could inhibit S_{180} sarcoma in mice with the tumor inhibition rate

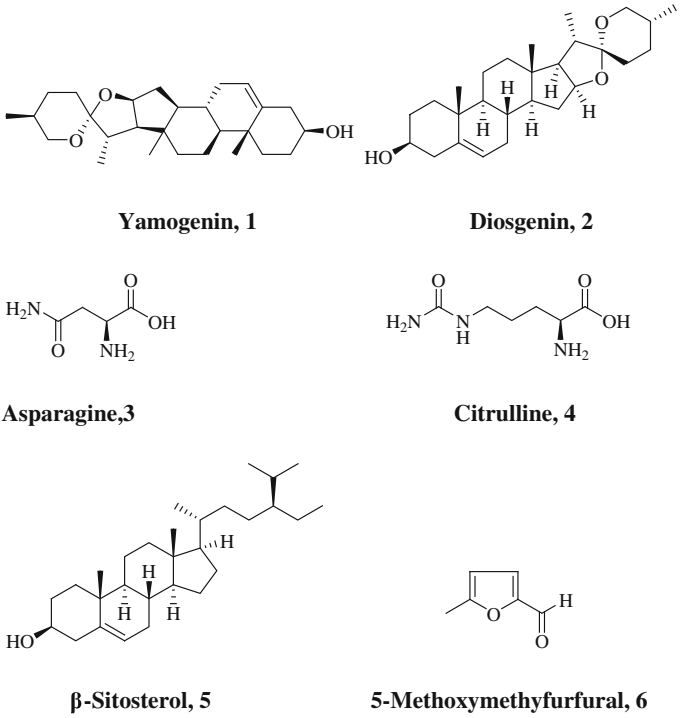

Fig. 8.2 Chemical structures of major constituents in Tiandong

falling between the ranges of 35–45 % [7]. Oral administration with water decoction of Tiandong (5 and 15 g crude herb/kg/day) could inhibit the growth and reduce the weight of S_{180} sarcoma and H_{22} liver tumours in mice.

8.4 TCM Applications and Dietary Usage

8.4.1 TCM Applications

The main functions of Tiandong as described in Chinese Pharmacopoeia are for nourishing Yin and clearing fluid retention in the lungs. It relieves symptoms such as coughing, sticky phlegm, and dry throat. In clinical applications, Tiandong is usually prepared in a variety of different forms depending on the medical conditions of patients. Some of these forms are as follows: Tiandong Ointment for moistening the lung; Tiandong powder for emaciation; Tiandong decoction for coughing and sticky phlegm; and Tiandong pill for consumptive lung disease, cough, and emaciation after typhoid [8, 9].

8.4.2 Dietary Usages

Tiandong is a traditional Chinese medicine that has the function of nourishing Yin. Not only is it considered for medicinal purposes, but is also known to be a form of food nourishment. The raw material of the nourishing medicinal food is used to create products such as medicinal liquor, or implemented into the ingredients of porridge to increase the health benefits of the product.

8.4.2.1 Tiandong Tea

Tiandong can be used to brew tea individually or with the combination of other herbs. The most common way is to place 8 g of Tiandong slices and 1 g of green tea in boiling water for 5 min. Tiandong tea promotes the secretion of saliva, and is thought to quench thirst, and eliminate phlegm.

8.4.2.2 Tiandong Wine

Tiandong can be used alone or with other herbal medicines to aid in the improvement of health benefits in certain wines. The most common way is to put Tiandong (center part of root removed) into the bottle of wine for approximately 15 days. Tiandong wine provides a range of health benefits for women, and has a sweet and refreshing taste.

8.4.2.3 Tiandong Maidong Snow Pear Soup

The soup ingredients comprise 10 g of Tiandong, 10 g of Maidong (root tuber of *Ophiopogon japonicus*), one snow pear (core removed), sugar, and water. After boiling, it is left to simmer for 1 h. Tiandong and Maidong are the cold properties that contain nourishing components for women, while the snow pear is rich in dietary fiber and pectin.

8.4.2.4 Sugar-Free Tiandong Sweetmeat

Tiandong Sweetmeat is traditionally a famous food of Sichuan province in China [7], which is sweet and tasty. Usually fresh Tiandong is used, and xylitol is used instead of white granulated sugar. This sugar-free sweetmeat is suitable for special populations such as patients with diabetes, hypertension, hyperlipidemia, and obesity, and the elderly people.

8.4.2.5 Tiandong Black Bean Porridge

The porridge is made by cooking 30 g of Tiandong with black beans, black sesame seed, glutinous rice, and a little bit sugar. It is suitable for those who always feel dizzy or for people with blurring vision and tinnitus. In addition, it improves soreness of waist, neurasthenia, and constipation.

8.5 Clinical Evidences

Oral administration of Tiandong Tablet (each tablet contains 0.3 g crude herb), 9 tablets/time, 3 time/day, or intravenous injection with Tiandong (60 g/time) diluted with saline or glucose solution 10–30 ml, 1 time/day and 20 days as a course of treatment, was effective for the treatment of breast lobular hyperplasia. The interval between two courses could be 7–10 days. In clinical trials, 42 cases received this treatment, and 16 cases were cured and 19 cases showed efficaciousness and improvement. Generally, the tumors were softened and reduced, and vanished after 2–3 courses of treatment [10, 11].

8.6 Safety Evaluation and Toxicity Issues

Clinical reports on toxicity and side effects of Tiandong are rare.

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Chapter 9
Astragalus membranaceus 黄芪 (Huangqi, Milkvetch Root)

Hua Wei

9.1 Botanical Identity

Huangqi has been used in Traditional Chinese Medicine for over 2000 years. The genus Milkvetch, belonging to the Pea Family, is a very large group of more than 2000 species distributed worldwide. Huangqi is traditionally prepared from the dried roots of the Chinese species *Astragalus membranaceus* (Fisch.) Bge. and the related *A. membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao, and it has been recorded in the Chinese Pharmacopoeia 2010 [1].

A. membranaceus and *A. membranaceus* var. *mongholicus* are similar plants botanically. They are perennial plants, approximately 50–80 cm tall with erect stems. They have hairy stems with leaves made up of 13–37 pairs of leaflets. Inflorescence with 10–20 flowers is raceme, with 2–5 mm long linear and lanceolate bracts. The fruit has a typical pea-pod shape and it is membranous. They are in flower from June to August, and the seeds ripen from July to September. In China, it is distributed in regions of the north, northeast, and northwest. As wild ones are increasingly scarce, Huangqi is mostly obtained from cultivated plants. *A. membranaceus* is cultivated in the northeastern part of Heilongjiang province and the southwestern part of Sichuan province of China. *A. membranaceus* var. *mongholicus* is cultivated mainly in the northern part of Shanxi, Inner Mongolia, Hebei, and Gansu provinces. In recent years, most of the herb sold commercially is *A. membranaceus* var. *mongholicus* [1–3].

H. Wei (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: weihua20@126.com

H. Wei
Key Laboratory of Plant Resources Conservation and Utilization, College of Biology and Environmemtal Science, Jishou University, Jishou 416000, China

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Fig. 9.1 Flowering *Astragalus membranaceus* (Fisch.) Bge. (**a**) and processed slices (**b**) of Huangqi

Huangqi is harvested from four-year-old plant roots in spring and autumn. Fresh roots are white, yellow, or cream-colored with many small fibrous shoots. After removing the aerial part, fibrous roots, soil and other impurities, the root will be dried either as a whole or after being cut into slices. Other processing methods include stir-fried with honey, alcoholic, salt, rice, bran, etc. [1, 4] (Fig. 9.1).

9.2 Chemical Constituents

The main constituents of Huangqi include flavonoids, saponins, and polysaccharides [3–6].

9.2.1 Flavonoids

About 30 flavonoids were isolated and identified from Huangqi, which belong to four structural groups as flavones, isoflavones, isoflavanones, and pterocarpans. The main bioactive flavonoids include calycosin, calycosin-7-O-β-D-glucoside, formononetin, ononin, (3R)-8,2′-dihydroxy-7,4′-dimethoxyisoflavan, 9,10-dimethoxypterocarpan-3-O-β-D-glucoside, 3-hydroxy-9,10-dimethoxypterocarpan, quercetin, and kaempferol. These are shown in Fig. 9.2.

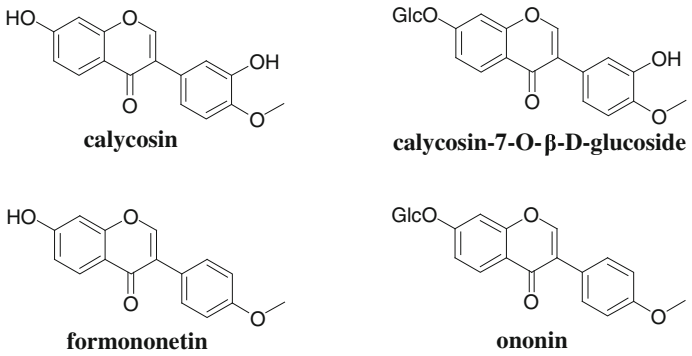


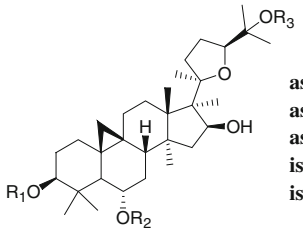
Fig. 9.2 Structures of main flavonoids in *A. membranaceus*

Calycosin has potential in the prevention and treatment of vascular disease, and has antihypertensive and neuroprotective effects. Formononetin can protect osteoblasts from hypoxia and enhance the osteogenic differentiation of osteoblasts, and also has positive effects on osteoblasts. Formononetin also has antihypertensive, antiperoxidase, phytoestrogenic and hemorrheology improving effects. Calycosin-7-O-β-D-glucopyranoside exerted significant antiviral activities against CVB3 both in vitro and in vivo, and it is one of active ingredients in *A. membranaceus* for the treatment of viral myocarditis. Calycosin-7-O-β-D-glucopyranoside can also modulate endothelial cell dysfunction by ameliorating AGEs-induced cell apoptosis and inflammation [7, 8].

9.2.2 Triterpenoid Saponins

In recent years, about 40 saponins were isolated and identified from the roots of *A. membranaceus* and *A. membranaceus* var. *mongholicus*. Many saponins are cycloartane tetracyclic triterpenoids, including the structures of three rings without furan ring and the structures of three rings with a furan ring, while a few saponins are oleanane pentacyclic triterpenoids. The main bioactive saponins include astragaloside I, astragaloside II, astragaloside IV, isoastragaloside I, isoastragaloside II, acetylastragaloside I, astramembrannin II, and soyasaponin I. Some of these are shown in Fig. 9.3.

Astagaloside IV is a main active constituent of Huangqi. It is widely used for the treatment of cardiovascular disease, such as coronary heart disease, heart failure, hypertension. Astragaloside IV was reported to provide immune regulation, organ protection, hypoglycemic effects, apoptosis regulation, anti-inflammatory, and antiviral effects [9].



astragaloside I: R_1=2,3-di-Ac-Xyl, R_2=Glc, R_3=H
astragaloside II: R_1=2-Ac-Xyl, R_2=Glc, R_3=H
astragaloside IV: R_1=Xyl, R_2=Glc, R_3=H
isoastragaloside I: R_1=2,4-di-Ac-Xyl, R_2=Glc, R_3=H
isoastragaloside II: R_1=3-Ac-Xyl, R_2=Glc, R_3=H

Fig. 9.3 Structures of main saponins in *A. membranaceus*

9.2.3 Polysaccharides

Several polysaccharides have been isolated from Huangqi, which play important roles in the pharmacological effects of this medicinal herb. Astragalus polysaccharides (APS), an extract of Huangqi, is one of the main effective components. APS-I and APS-II are well known to be the major structural components of APS. APS-I (molecular weight = 1,699,100 Da) consists of arabinose and glucose in a molar ratio of 1:3.45, while APS-II (molecular weight = 1,197,600 Da) consists of rhamnose, arabinose and glucose in a molar ratio of 1:6.25:17.86. In China, APS has been extensively used to treat viral infections, acute myocarditis, glomerulonephritis, diabetes, tumors, and many other illnesses, with no toxic record in clinic. APS have been widely studied, especially with respect to their immunopotentiating properties, their ability to counteract the side effects of chemotherapeutic drugs, and their anticancer properties. APS has been reported to increase insulin sensitization and to ameliorate diabetes in animal models. APS has anti-inflammatory, antioxidant, antihypertensive, and anti-aging effects. APS is also a potential natural cholesterol lowering agent, working through mechanisms distinct from statins [3, 10–12].

9.2.4 Quantitative Determination

The quality of Huangqi was predicated on the analysis and determination of several compounds like isoflavones or saponins. For example, the Chinese Pharmacopoeia 2010 specifies that the content of astragaloside IV should not be less than 0.04 %, while calycosin-7-O-β-D-glucoside not less than 0.02 %, respectively as determined by HPLC, in order to control the quality of Huangqi. The typical HPLC chromatogram of crude Huangqi is shown in Fig. 9.4 [13].

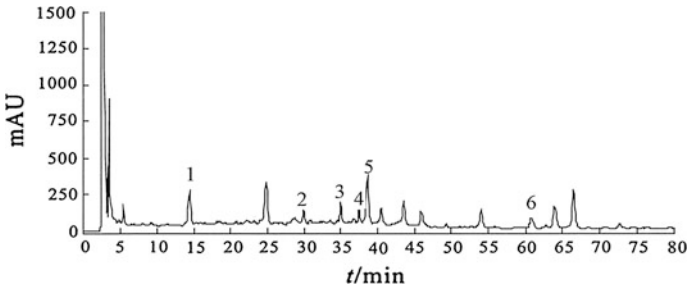


Fig. 9.4 HPLC chromatogram of *A. membranaceus*

9.3 Pharmacological Studies

It was reported that the pharmacological activities of Huangqi include cardioprotective, immunomodulation, anti-oxidative, anti-aging, anti-tumor, anti-viral, anti-inflammatory, anti-diabetic, neuron protective, hepatoprotective, diuretic, and hematopoiesis activities [3–6].

Studies show that astragalosides, aqueous extracts of Huangqi and lyophilized Huangqi powder have cardioprotective effects. Aqueous and ethanol extracts of Huangqi and APS have immunopotentiating properties. Total flavonoids, total saponins of Huangqi and aqueous extracts of Huangqi have anti-oxidant effects. Aqueous extracts of Huangqi and astragaloside IV have antitumor effects. APS, aqueous extracts of Huangqi, astragaloside II and isoastragaloside I have antidiabetic effects. Aqueous extracts of Huangqi and calycosin-7-O-β-D-glucopyranoside have anti-inflammatory effects.

9.4 TCM Applications and Dietary Usage

9.4.1 TCM Applications

In traditional Chinese medicine (TCM), Huangqi is used to "invigorate vital energy (*Qi*) and strengthen body resistance." It has been used for symptoms of *Qi* deficiency such as diarrhea, fatigue, and lack of appetite. It also raises the *Qi* of the stomach, thus preventing prolapses of organs such as the uterus, stomach, or anus. In this capacity it can also address uterine bleeding. Huangqi tonifies the lung *Qi* and is used in cases of frequent colds, spontaneous sweating, and shortness of breath. Other traditional indications include wasting disorders, night sweats, chronic ulcerations and sores, numbness and paralysis of the limbs, and edema [4, 14].

Huangqi is typically prescribed as a dried root, powdered, or in a decoction. Classically, it is often combined with other herbs to strengthen the body against disease, depending on the desired therapeutic effect and the specific TCM

diagnosis. Common Huangqi preparations clinically used include the following: Huangqi Injection (Astragalus injection): a preparation of an aqueous extract of Huangqi. The major components are astragalosides, and the other pharmacological ingredients include polysaccharides, flavones and amino acids. It is mainly used for the treatment of *Qi* deficiency, cardiac insufficiency, viral myocarditis caused by obstruction of blood, and hepatitis caused by *Qi* deficiency and phlegm-wet, and used for treatment of chronic hepatitis and chronic active hepatitis caused by low cellular immune function. It also can be used for the treatment of leukopenia, thrombocytopenia purpura, chronic nephritis, nephrotic syndrome and diabetic nephropathy. Huangqi Jing: a mixture of aqueous extract of Huangqi and honey. The major components are polysaccharides and other water soluble compounds. It is used for blood enriching, *Qi* tonifying, body strengthening, and hidroschesis. It is also used for shortness of breath and palpitation, deficiency of *Qi* and blood, hypodynamia, spontaneous perspiration, and loss of appetite and energy. Huangqi granule: the total extract of Huangqi. It is used for *Qi* tonifying, body strengthening, shortness of breath and palpitation, exhaustion, spontaneous perspiration, chronic nephritis, prolapse of rectum, protracted diarrhea, and promoting granulation.

9.4.2 Dietary Usages

Huangqi is a typical traditional Chinese medicinal plant, used as food, and has been present on the Western market (in Europe and USA) as a food supplement for many years. The following preparation forms can be easily made at home [4].

9.4.2.1 Huangqi Tea

Composition: Huangqi 15–25 g, red tea 0.5–1 g.

Preparation: Sliced Huangqi is decocted in water until boiling, and then continually boiled for 5 min. The red tea is then put into the water while it is hot. Consume three times daily.

Function: *Qi* tonifying, body strengthening, inducing diuresis to alleviate edema, evacuation of pus, spontaneous perspiration, and chronic trachitis.

9.4.2.2 Huangqi Porridge

Composition: Huangqi 30 g, rice 100 g.

Preparation: Huangqi is soaked in 10 times the volume of water for 30 min. The water then is boiled and keep the boiling status for another 30 min with mild heat. After removing the first decoction, the residue was added with 10 times volume of water and boiled. Repeat the decocting procedure for 3 times. Three decoctions are

mixed and residue of Huangqi is discarded. Rice is put into the decotion solution and boiled to porridge.

Function: it is good for *Qi* deficiency, weakness, elderly, recovering from illness and operation, and chemotherapy patients. It is suitable to be taken in the morning, but not for flu patients.

9.4.2.3 Huangqi-Danggui Tea

Composition: Huangqi 30 g, Danggui (root of *Angelica sinensis* (Oliv.) Diels) 6 g.

Preparation: Put Huangqi and Danggui in 10 times the volume of water, then boil for 30 min. Drink it when it becomes cold.

Function: benefitting *Qi* and blood. It is suitable for persons in illness and operation recovery periods, as well as the elderly. However, it is not good for flu patients, females on their menstrual period, and people with excess fire for *Yin* deficiency.

9.4.2.4 Huangqi Wine

Composition: Huangqi 60 g, yellow wine 500 mL.

Preparation: Ground Huangqi is put into a container, add yellow wine, seal and soak for 7 days. Drink 20–30 mL of wine each time, twice daily.

Function: deficiency of the *Qi* and stomach, eating less with poor appetite, indigestion, palpitations, shortness of breath, limb weakness, and hyperidrosis for deficiency of the body.

9.4.2.5 Huangqi-Gouqi Tea

Composition: Huangqi 5 g, Gouqizi (fruits of *Lycium barbarum* L.) 10 g.

Preparation: Put Huangqi and Gouqizi into a cup. Add 10 times the volume of boiling water and cover for about 75 min. Drink it like an ordinary tea. Add water repeatedly until the color of the tea become very light and tasteless.

Function: Nourishing the liver and kidney, diuretic and antihypertensive, suitable for the elderly with mild hypertension.

9.4.2.6 Huangqi-Honey Drink

Composition: Huangqi 30 g, Chenpi (fruit peel of *Citrus reticulata* Blanco) 10 g, honey 30 g.

Preparation: Put Huangqi and Chenpi in a water pot or other glass container, add about 300 mL of water and boil for 20 min. Then add honey into it and it is ready for consumption.

Function: It is beneficial to treat constipation.

9.4.2.7 Huangqi-Shandi Porridge

Composition: Huangqi 30 g, Shanyao (roots of *Dioscorea opposita* Thunb.) 100 g, Dihuang (roots of *Rehmannia glutinosa* Libosch.) 15 g.

Preparation: First decoct Huangqi and Dihuang, then add ground Shanyao slowly into the boiling decoction and keep stiring until it becomes porridge.

Function: high blood pressure, diabetes, deficiency of *Qi* and Yin, thirst, dry mouth, and frequent urination.

9.4.2.8 Shenqi-Dazao Porridge

Composition: Huangqi 15 g, Danshen (roots of *Salvia miltiorrhiza* Bunge) 10 g, Dazao (Dry fruit of *Ziziphus jujuba* Mill.) 30 g, rice 100 g.

Preparation: First decoct Huangqi and Dangshen, then put Dazao and rice into the decoction and cook until it becomes porridge.

Function: It is beneficial to deficiency of *Qi*, fatigue, sweating, eating less, and improving the immune system instead.

9.4.2.9 Huangqi-Chicken Soup

Composition: Huangqi 50 g, a medium sized black-bone chicken.

Preparation: Cut black-bone chicken into pieces, mix with Huangqi, stew until the meat become soft.

Function: nourishing *Qi* and lung, *Yin* and blood.

9.5 Clinical Evidences

Current applications of Huangqi are primarily for restoring and strengthening the immune response, enhancing cardiovascular function, and increasing vitality. Indications supported by clinical trials include impaired immunity, adjunctive cancer treatment, viral infections, bronchial asthma, diabetes, peptic ulcer, cancer, respiratory tract infection, and the common cold [4]. The most common preparation is Huangqi injection, which is now clinically used to treat psoriasis, coronary disease, diabetes, cancer, heart failure, nephropathy, and hepatitis B [4, 15–17].

9.6 Safety Evaluation and Toxicity Issue

Huangqi is used in doses of 9–15 g daily. Oral ingestion of Huangqi decoction (7.5 g/kg) cannot be determined in rats. Doses as high as 100 g/kg of the herb have been given to I.G rats with no adverse effects. The LD_{50} of Astragalus in mice was

determined to be approximately 40 g/kg when administered by intraperitoneal injection [14].

Cases displaying adverse reactions of Huangqi were reported, including fever, allergy, nausea, abdominal distension, pruritus, skin reactions. Among various types of adverse reactions the skin reactions were very common. All the cases were recovered after immediate cessation of medication and there were no deaths or serious long term effects [18]. The causes of adverse reactions mainly related to the production of the drugs, the choice of the clinical indication, and the route of administration. The quality control of drug production should be improved. Also, the drug application should be based on the theory of TCM.

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Chapter 10
Codonopsis pilosula 党参 (Dangshen, Pilose Asiabell)

En-yuan Zhu

10.1 Botanical Identity

The genus Asiabell is composed of 40 species in the world, 39 species in China, including 21 species for medicine use. Dangshen is mainly distributed in the Shanxi, Sichuan, Shaanxi, Gansu provinces.

C. pilosula: Root is length cylindrical, 1–1.7 cm in diameter, root apex at the top of the root, with the majority of warty stem scar, externally ivory yellow to grayish brown, with vertical and horizontal wrinkles. Stems are twining, long, multi-branched the lower part has rough bristles, the upper smooth or nearly smooth. Flowers are solitary, with a slender stalk, green calyx, 5 lobes, oblong-lanceolate, 1–2 cm long, apex obtuse, smooth or slightly hairy. The corolla is 2–2.5 cm diameter, yellowish green with purple violaceum spots, 5 crack tips, lobes triangular to broad triangular and erect. There are five stamens filaments under the center to expand. In the inferior ovary there are three rooms, short in style, with three stigmas that are extremely wide and funnel-shaped, capsule conical, with persistent calyx. It has small seeds, brown and shiny ovate. It flowers August to September, fruiting September to October. *C. pilosula* is distributed mainly in the Shanxi, Gansu, Shaanxi, Sichuan provinces and northeastern China.

C. pilosula var. modesta is different from *C. pilosula,* in which *C. pilosula var. modesta* is nearly smooth and hairless; calyx lobes are small, about 10 mm. *C. pilosula var. modesta* is distributed mainly in the west of Sichuan and parts of the Gansu provinces adjacent to Sichuan.

C. tangshen: The difference of *C. tangshen* is that the leaf base, i.e. the lower part of stem is wedge-shape or slightly obtuse, and only occasionally shows a heart-shape; the calyx only grows close to the lowest part of the ovary, the ovary superior.

E. Zhu (✉)
Shanghai University of Traditional Chinese Medicine, Shanghai, China
e-mail: wxzey@163.com

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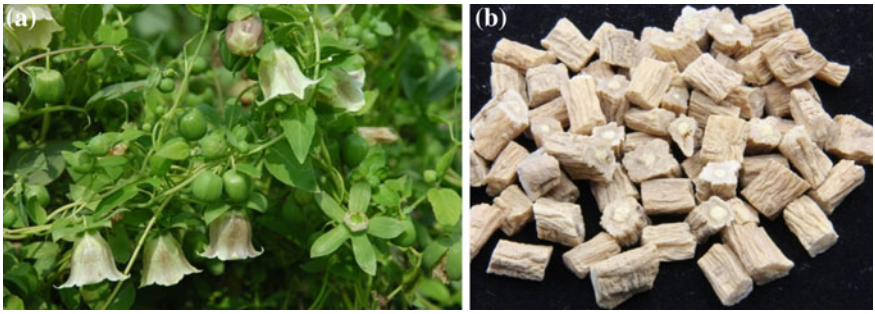

Fig. 10.1 The flowering plant (**a**) and processed slices (**b**) of Dangshen

Flowering and fruiting from July to October. *C. tangshen* is distributed mainly in the Chongqing, Sichuan, Hubei, Hunan, and Guizhou provinces.

The drug is collected in autumn when the color of fruit becomes brown, washed clean and then dried in the sun [1, 2] (Fig. 10.1).

10.2 Chemical Constituents

In recent years, there are many studies on the chemistry compositions of Dangshen, and so far, we have found that carbohydrates, glycosides and polyacetylene glucosides are the main chemical compositions of Dangshen.

10.2.1 Carbohydrates and Glycosides

The traditional medication experience held that the sweeter the taste, the better the quality of Dangshen. And we find that there are many carbohydrates and glycosides from Dangshen, such as fructopyranose, synanthrin, tangshenoside I (**1**), tangshenoside II (**2**), tangshenoside III (**3**), tangshenoside IV (**4**), syriginoside (**5**). Some of them are showed in Fig. 10.2 [3]. It is worth mentioning that tangshenoside I had been considered the exclusive ingredient of Codonopsis before.

10.2.2 Polyacetylene Glucosides

Polyacetylene glucosides widely exist in Platycodon. The most common are lobetyolin (**1**) and lobetyolinin (**2**) [4]. Because of the higher contents in different regions, good specificity and characteristics, the lobetyolin has been used as a sign of the quality of Dangshen. The structures are showed in Fig. 10.3.

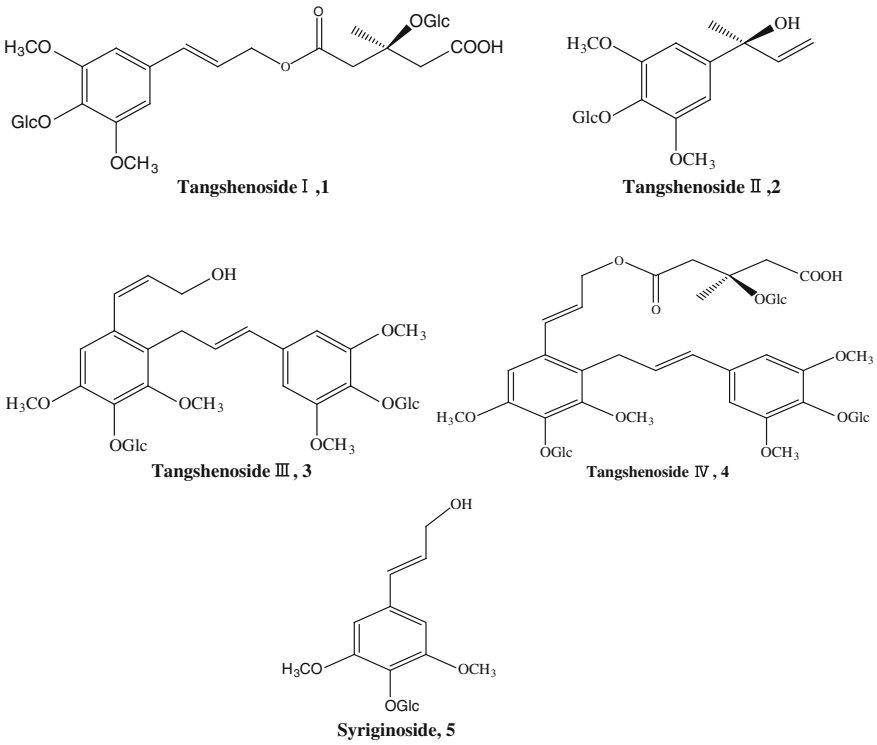

Fig. 10.2 Main carbohydrates and glycosides from Dangshen

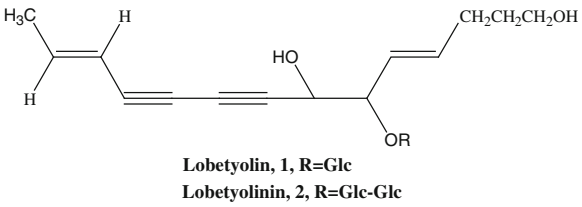

Fig. 10.3 The structure of lobetyolin and lobetyolinin

10.2.3 Others

It also has many other series, such as steroids, alkaloids, terpenes, volatile components, amino acids, inorganic elements and so on.

10.3 Pharmacological Studies

Dangshen can regulate the digestive system, and enhance the function of the immune system. It is worth mentioning that it also plays a significant role in the cardiovascular system.

10.3.1 Effects on Digestive System

For the digestive system, it can adjust the functions of gastrointestinal motility. With chronic gastric electrodes implant methods, the scientists observed a Dangshen alcohol solution which is decocted by water at first has regulatory functions to the stomach, namely dysrhythmia. It can also partially solve the stress-induced increase of gastric motility and accelerated gastric emptying caused by stress response.

10.3.2 Effects on Cardiovascular System

Dangshen can strengthen the contractile force of myocardium and increase the cardiac output without affecting the heart rate.

10.3.3 Other

Other pharmacological effects have been discovered. The Dangshen has been used to treat inflammation, insomnia, and hypomnesia [5].

Some studies were carried out on investigating the protective effect of the Dangshen extract on kidney transplantation and some successful results were achieved [6].

10.4 TCM Applications and Dietary Usage

10.4.1 TCM Applications

Dangshen is one of the most common herbal materials traditionally used as herbal medicine and health-maintaining products. It is one of the famous herbs used clinically for the lienogastric diseases, such as fatigued cumbersome limbs, short breath and fatigue, and so on. Some important prescriptions are introduced as follows.

10.4.1.1 Wuwei Yigong Powder [7]

Composition: Dangshen (root of *Codonopsis pilosula*), Baizhu (rhizome of *Atractylodes macrocephala*), Fuling (sclerotium of *Poria cocos*), prepared Gancao (root and rhizome of *Glycyrrhiza uralensis*), Chenpi (fruit pericarp of *Citrus reticulata*).

Function: Strengthens the lienogastric function. Modified Wuwei Yigong Powder is used for the treatment for pernicious vomiting and ptyalism in children.

10.4.1.2 Shenling Baizhu Powder [8]

Composition: Dangshen (root of *Codonopsis pilosula*), Baizhu (rhizome of *Atractylodis macrocephala*), Shanyao (rhizome of *Dioscorea opposita*), Baibiandou (seed of *Dolichos lablab*), Sharen (seed of *Amomum villosum*), Lianzi (seed of *Nelumbo nucifera*), Yiyiren (seed of *Coix lacryma-jobi*), Fuling (sclerotium of *Poria cocos*), Jiegeng (root of *Platycodon grandiflorum*), Gancao (root of *Glycyrrhiza uralensis*).

Function: Strengthens the lienogastric function. Modified Shenling Baizhu Powder is used for the treatment for edema, alopecia and paediatric allergic rhinitis.

10.4.1.3 Sijunzi Decoction [9]

Composition: Dangshen (root of *Codonopsis pilosula*), Fuling (sclerotium of *Poria cocos*), Baizhu (rhizome of *Atractylodis macrocephala*), prepared Gancao (root of *Glycyrrhiza uralensis*).

Function: Invigorates the Spleen, improving and regulating functional gastrointestinal disorders. Modified Sijunzi Decoction is used for chronic gastritis and peptic ulcer disease.

10.4.1.4 Buzhong Yiqi Decoction [9]

Composition: Dangshen (root of *Codonopsis pilosula*), Huangqi (root of *Astragalus membranaceus*), Shengma (rhizome of *Cimicifuga foetida*), Chaihu (root of *Bupleurum chinensis*), Chenpi (fruit pericarp of *Citrus reticulata*), Danggui (root of *Angelica sinensis*), Baizhu (rhizome of *Atractylodis macrocephala*), prepared Gancao (root of *Glycyrrhiza uralensis*).

Function: Strengthens the exterior and reduces sweating. Modified Buzhong Yiqi Decoction is used for the treatment for headaches, uterine prolapse and gastroptosis.

Sometimes the mixture of Dangshen (root of *Codonopsis pilosula,* 100 g), and Huangbai (bark of *Phellodendron chinense*, 50 g) is used to treat children's cankers.

10.4.2 Dietary Usages

Dangshen can stimulate the nervous system and enhance the body's immunity, so it can be used in many ways as a nutritional ingredient of food, and it can be easily made in home normally.

10.4.2.1 Dangshen Frog Decoction

Composition: Dangshen (150 g), frog (500 g), Shengjiang (fresh rhizome of *Zingiber officinale*, 3 pieces), a pinch of salt.

Function: Strengthens the spleen and supplements the lungs, it is suited for the person who is physically weak, with a weak appetite except for pregnant women and somebody who is limosis.

10.4.2.2 Dangshen Wuweizi Pork Liver Porridge

Composition: Dangshen (20 g), Gouqizi (fruit of *Lycium barbarum,* 30 g), pork liver (50 g), rice (60 g).

Function: For senile cataracts.

10.4.2.3 Dangshen Kuxingren Pork Lung Soup

Composition: Dangshen (20 g), pork lung (200 g), Kuxingren (seed of *Prunus armeniaca* var. *ansu*, 10 g).

Function: To treat chronic bronchitis in a person with a weak Spleen and Lungs.

10.4.2.4 Dangshen Tea

Composition: Dangshen (10 g), Scented tea (3 g).

Function: Reduce blood pressure.

10.5 Clinical Evidences

In clinical trials Dangshen is always used in combination with other Chinese medicines. In clinical trial in treatment of myasthenia gravis, 30 patients were treated with a Buzhong Yiqi decoction containing Huangqi (root of *Astragalus membranaceus*), Dangshen (root of *Codonopsis pilosula*), Baizhu (rhizome of *Atractylodes macrocephala*), Chenpi (fruit pericarp of *Citrus reticulata*), Shengma

(rhizome of *Cimicifuga heracleifolia*), Chaihu (root of *Bupleurum chinense*), Danggui (root of *Angelica sinensis*) and prepared Gancao (root and rhizome of *Glycyrrhiza uralensis*), and symptoms were significantly improved [10]. Another clinical observation showed that Yiqi Jianpi decoction, a compound prescription containing Dangshen, can be used for treatment of functional dyspepsia [11], Compound Dangshen capsule, which is composed of Dangshen, Shashen (root of *Adenophora stricta*) and Danshen (root of *Salvia miltiorrhiza*), was used to prevent altitude sickness [12].

10.6 Safety Evaluation and Toxicity Issue

There was little clinical report on the toxicity and side effect directly related with Dangshen and its preparations. Animal tests also did not show clear toxicity for various organs through i. p. and oral administration. Dangshen is definitely a relatively safe herbal medicine. It's essential to take the medicine according to medical advice given by a doctor.

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Chapter 11
Curcuma longa L. 姜黄 (Jianghuang, Common Turmeric)

Jing-jing Zhu

11.1 Botanical Identity

Curcuma longa L. is a perennial herb. The plant grows to a height of three to five feet, and is cultivated extensively in Asia areas with a tropical climate [1–3]. It has oblong, pointed leaves and bears funnel-shaped yellow flowers.

Turmeric, the dried rhizomes of *C. longa*, is extensively used in traditional medicine and used commonly as a gold-colored spice in the Indian subcontinent, not only for health care but also for the preservation of food [3].

The traditional processing method of turmeric for medicine is to collect the rhizome of *C. longa* in winter when the aerial part withers, clean, boil or steam thoroughly, dry, and prepare the rhizome for herbal pieces. Its traditional processing method for dietary is to clean, boil, dry, and powder the rhizome of *C. longa* [3] (Fig. 11.1).

11.2 Chemical Constituents

Curcuminoids, sesquiterpenoids, curcumin-related phenolics, and their derivatives are widely distributed in plants of *C. longa.* Many of these compounds exhibit antitumor, anti-oxidative, anti-inflammatory, and hypoglycaemic activities.

J. Zhu (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, 100700 Beijing, China
e-mail: zhujj15@163.com

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Fig. 11.1 Flowering plant (**a**) and processed slices (**b**) of Jianghuang

11.2.1 Sesquiterpenes

Twenty-eight sesquiterpenes, curculonone A, curculonone B, curculonone C, curculonone D, 6a-hydroxycurcumanolide A, 1,10-dehydro-10-deoxy-11-oxozedoarondiol, ar-turmerone (1), curlone, β-atlantone, zedoarondiol, curcumanolide A, and curcumanolide B, β-turmerone bisacumol, zingiberene, curcumenone, curcumenol, procurcumenol, dehydrocurdione and germacrone-13-al, (4S, 5S)-(+)-germacrone-4,5-epoxide, procurcumadiol, turmeronol A (2), turmeronol B (3), bisacurone (4), bisabola-3,10-dien-2-one, 4-hydroxybisabola-2,10-diene-11-one, 4-methoxy-5-hydroxy-bisabola-2,10-diene-11-one, 2,5-dihydroxybisabola-3,10-diene were isolated from *C. longa* [4, 5].

11.2.2 Curcuminoids

Three curcuminoids, curcumin (5), demethoxycurcumin (6), and bisdemethoxycurcumin were reported [6] (Fig. 11.2).

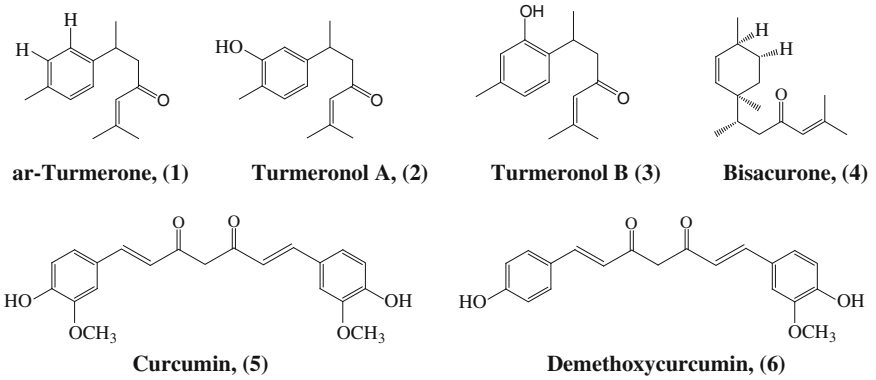

Fig. 11.2 Chemical structures of constituents in *C. longa*

11.3 Pharmacological Studies

Turmeric has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses. It was also proved that turmeric possessed therapeutic effects including the reduction of blood cholesterol level, prevention of low density lipoprotein (LDL) oxidation, inhibition of platelet aggregation, suppression of thrombosis and myocardial infarction, suppression of symptoms associated with type II diabetes and multiple sclerosis, inhibition of human immunodeficiency virus (HIV) replication, enhancement of wound healing, increase of bile secretion, protection from liver injury, cataract formation and pulmonary toxicity and fibrosis, exhibition of anti-leishmaniasis and anti-atherosclerotic properties, as well as prevention and treatment of cancer [7–10]. Current pharmacological research has focused on turmeric's antioxidant, anti-inflammatory, anti-cancer, anticarcinogenic, anti-HIV, antimicrobial, hepatoprotective properties, and its use in cardioprotection and gastrointestinal disorders.

11.4 TCM Applications and Dietary Usage

Turmeric is a gold-colored spice commonly used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Turmeric is one of the earliest health natural pigments promulgated by Chinese government [3].

11.4.1 TCM Applications

Jianghuang has been used in the Chinese medical system for 1000 years to treat flatulence, menstrual difficulties, colic, gastrointestinal disorders, arthritis and rheumatoid arthritis [2]. Jianghuang could be used in a single form or by combining forms with other herbs based on TCM theory. Turmeric preparations clinically used include the following forms:

1. Jianghuang powder (cited from Shengji Zonglu, an ancient medical works, 1117 AD): It is composed of four herbal components: Jianghuang, Danggui (root of *Angelica sinensis*), Muxiang (root of *Aucklandia lappa*). It is mainly used for the treatment of cardiodynia.
2. Jianghuang pill (cited from Taiping Shenghui Fang, an ancient medical works, 1112 AD): It is composed of eighteen herbal components: Jianghuang, Mudanpi (root bark of *Paeonia suffruticosa*), Chishao (root of *Paeonia lactiflora*), Guizhi (twig of *Cinnamomum cassia*), Yuanhua (bud of *Daphne genkwa*), Danggui (root of *Angelica sinensis*), Houpo (bark of *Magnolia officinalis*), Yanhusuo (tuber of *Corydalis yanhusuo*), Muxiang (root of *Aucklandia lappa*), Lingxiaohua (flower of *Campsis grandiflora*), Sanleng (tuber of *Sparganiuum stoloniferum*) et al. It is mainly used for the treatment of menstrual difficulties.
3. Xiaopi pill (cited from Qixiao Liangfang, an ancient medical works, 1470): It is composed of fifteen herbal components, the main components were as follows: Jianghuang, Baizhu (rhizome of *Atractylodes macrocephala*), Zhishi (immature fruit of *Citrus aurantium*), Banxia (rhizome of *Pinellia ternata*), Renshen (root of *Panax ginseng*), Huanglian (rhizome of *Coptis chinensis*), Huangqin (root of *Scutellaria baicalensis*), Houpo (bark of *Magnolia officinalis*), Zhuling (sclerotium of *Polyporus umbellatus*), Ganjiang (rhizome of *Zingiber offcinale*), Dahuang (root and rhizome of *Rheum palmatum*). It is mainly used for the treatment of gastrointestinal disorders.

11.4.2 Dietary Uses

Turmeric also is a famous dietary pigment and spice that is used extensively in foods for both its flavor and color in Middle Eastern and Asian countries, especially on the Indian subcontinent [9]. Turmeric has the potential to use as dietary supplements for treating osteoarthritis [10].

Extensive research within the last half century has proven that most of these activities once associated with turmeric, are due to the active principle curcumin or diferuloylmethane. Curcumin can be considered an ideal “Spice for Life” [3].

11.4.2.1 Curry

Turmeric is one of the most widely used spices in Indian subcontinent. Vast quantities go into curries and give them their brilliant yellow color.

11.4.2.2 Spice in Diet

It is also an important spice in dal, the most frequently eaten dish of lentils in rural Nepal. The daily serving per person contains around 0.5–1.5 g turmeric. (A typical dal recipe consists of: 2 cups of dal, 5 cups water, 2 teaspoons turmeric, 5 drops asa-foetida water, 1teaspoon black pepper, 1 teaspoon black cumin seeds, 30 g fresh ginger, 1/2 cup ghee (clarified butter), 1 big onion, 2 teaspoons chopped coriander leaves, 2 green chillies, and salt to taste. The dal is washed and soaked for 15 min. Chopped onion and ginger are fried in ghee until light brown, cumin seeds are then added and the mixture fried for an additional minute. Dal, turmeric, and salt are added to boiling water followed by cooking on a low fire. When the dal is nearly cooked, fried onion, ginger, cumin seeds, chopped coriander leaves, green chillies and black pepper are added and all is cooked for 5 min. It is served with rice.) [11].

11.4.2.3 Natural Food Additive

Turmeric is used as a natural food additive in China. It is the earliest one of nine health natural pigments promulgated by Chinese government. Turmeric can be used safely to change the color of the food. It can be widely used in beverages, cakes, candy, ice cream and other food.

11.5 Quality Evaluation and Assurance

Four sesquiterpenes, α-turmerone, β-turmerone, ar-curcumene and ar-turmerone, were the most important markers for quality control of the oil of rhizome (Jianghuang). And three curcuminoids, curcumin, demethoxycurcumin, and bis-demethoxy-curcumin, were the significant chemical components of the non-volatile of turmeric [6]. It was provided that the content of oil of turmeric was not less than 7.0 % and the content of curcumin was not less than 1.0 % in Chinese pharmacopeia [2].

11.6 Safety Evaluation and Toxicity Issues

Typical dietary intake of turmeric is estimated to be as high as 2.5 g/d (approximately 100 mg curcumin/d) in some countries. While up to 8 g/d of curcumin, that constitute 3 % of the total rhizome, is without evidence of side effects in Phase I clinical trials [12]. Pilot phase I clinical trials have shown curcumin to be safe even when consumed at a daily dose of 12 g for 3 months.

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Chapter 12
Dioscorea opposite Thunb. 山药 (Shanyao, Chinese Yam)

Sue-Joan Chang, Chun-Yung Huang and Yin-Ching Chan

12.1 Botanical Identity

Yam (*Dioscorea* species), a member of the monocotyledonous family *Dioscoreaceae*, is a nutritious food in West Africa, Southeast Asia, and the Caribbean. Yam has a deciduous perennial vine climbing to twenty feet with heart-shaped leaves and tiny green flowers. The tuberous rhizome of yam is pale brown, cylindrical, and twisted. There are over 600 species of *Dioscorea* in the world, about 40–50 of which are edible and widely used as medicinal food. Among them, Chinese yam (*D. opposite* Thunb.) (Fig. 12.1), mainly cultivated in Korea, Japan, and China [1, 2], is included in the Pharmacopoeia of the People's Republic of China [3] and is reported containin gallantoin, diosgenin, dioscine, gibberellins, dopamine, ergosterol, and mucilage [2, 4, 5]. It is widely used in traditional medicine for the treatment of anorexia, chronic diarrhea, asthma, dry coughs, oligunia, diabetes, seminal emission and excessive leucorrhea [3]. In Taiwan, 14 species, including *D. alata*, *D. alata* L. var. *purpurea*, *D. batatas*, *D. benthamii*, *D. bulbifera*, *D. collettii*, *D. cumingii*, *D. doryophora*, *D. esculenta*, *D. formosana*, *D. hispida*, *D. japonica*, *D. japonica* Thunb. var. *pseudojaponica*, and *D. japonica* Thunb. var. *oldhamii* are cultivated and consumed as a food with tonic functions. *D. alata* cv. Tainung No. 2 released by the Taiwan Agricultural Research Institute (TARI) for commercial production in 1996 is one of

S.-J. Chang (✉)
Department of Life Sciences, National Cheng Kung University, Tainan, Taiwan
e-mail: sjchang@mail.ncku.edu.tw

C.-Y. Huang
Department of Seafood Science, National Kaohsiung Marine University, Kaohsiung, Taiwan

Y.-C. Chan
Department of Food and Nutrition, Providence University, Taichung, Taiwan

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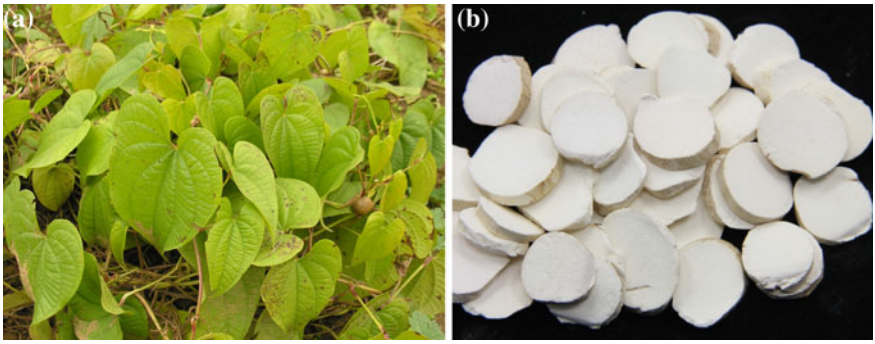


Fig. 12.1 Areal part of Chinese yam (*Dioscorea opposite*) with bulbils in leaf axil (**a**) and sliced dry roots as crude drug (**b**)

the most popular and widely cultivated yams in Taiwan due to its superior characteristics such as high nutritional values, resistance against anthracnose, high and stable productivity, and wide adaptability [6].

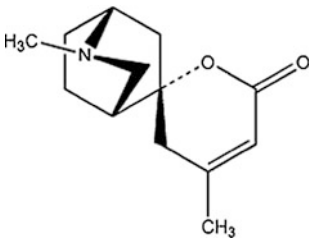
12.2 Chemical Constituents

The medicinal use of yam is mainly its tuber which contains two major classes of bioactive compounds, dioscorin and saponin (diosgenin and dioscin).

12.2.1 Dioscorin

Dioscorin (Fig. 12.2), the major storage protein of yam tuber, was successfully purified by using ammonium sulfate fractionation, DE-52 ion exchange chromatography, and Sephadex G-75 column from *D. batatas* Decne [7]. Two protein bands (82 and 28 kDa) were found under nonreducing conditions after SDS-PAGE; but only one band (32 kDa) was detected under reducing conditions. The purified dioscorin showed both CA (carbonic anhydrase) dehydration activity using sodium

Fig. 12.2 Chemical structure of dioscorin



bicarbonate as a substrate and CA activity staining after SDS-PAGE [7]. Dioscorin from *D. alata* L., purified and identified by ion-exchange chromatography, gel chromatography, SDS-PAGE, and MALDI-TOF-MS was made up of both dioscorin A (M.W. ~33 kDa) and dioscorin B (M.W. ~31 kDa) [8].

12.2.2 Diosgenin and Dioscin

Diosgenin and dioscin (aglyconediosgenin) are two major steroidal saponins in yams (Fig. 12.3). Teng et al. [9] found that diosgenin existed in both tubers and burbils of *D. opposite* in an amount of 0.0164 and 0.0213 %, respectively. Diosgenin is structurally similar to cholesterol. After oral administration, it is metabolized in the liver and eliminated via the bile [10]. Estrogenic and

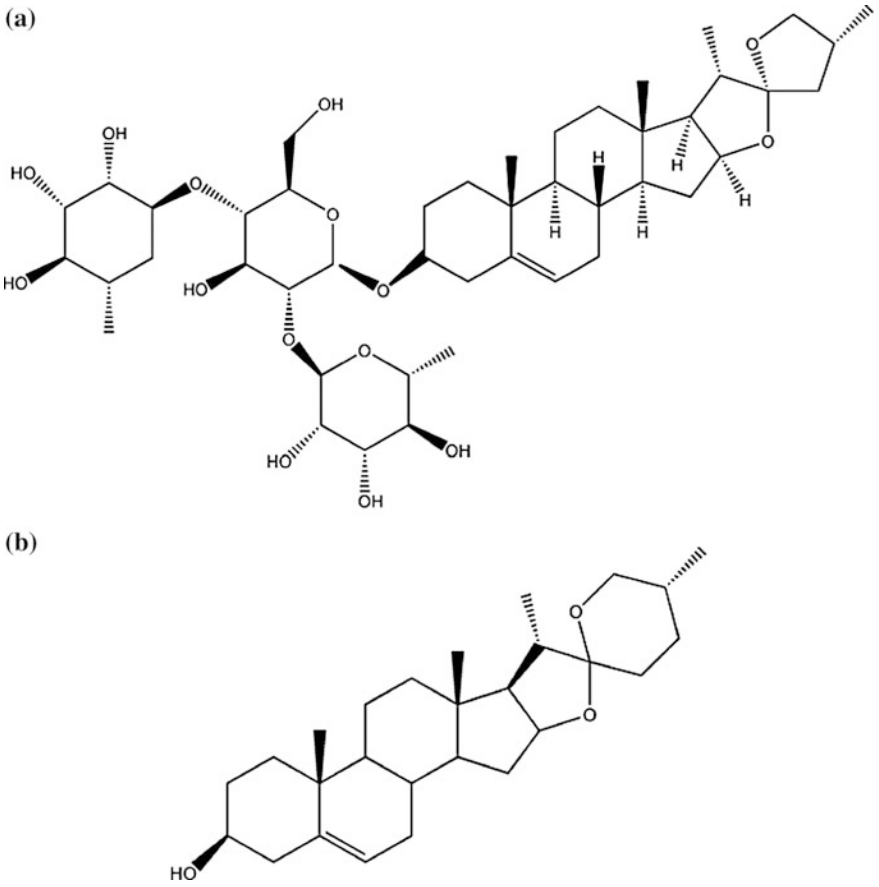


Fig. 12.3 Chemical structures of dioscin (**a**) and diosgenin (**b**)

anti-inflammatory effects of diosgenin have been hypothesized due to its structural similarity to estrogen precursors. Diosgenin has long been used as a raw material for the industrial production of steroid drugs [11] to suppress cholesterol absorption, increase cholesterol secretion through biliary excretion [12] and induce differentiation of the human erythroleukemia cell line by changing lipoxygenase activities [13]. It is also found to induce apoptosis and cell cycle arrest in a human osteosarcoma cell line [14] and exhibit prebiotic effect [15].

12.3 Pharmacological Studies

The medicinal use of yam is its tuber containing saponins, including dioscin or diosgenin, as well as alkaloids such as dioscorin, which are used as precursors for the manufacture of cortisone, estrogen, and progesterone-like compounds. Diosgenin exhibits estrogen-like functions in most people after ingesting yams, although human body lacks the enzymes to convert diosgenin into estrogen or any other steroid. Dioscorin and diosgenin with anti-inflammatory and muscle relaxant properties is beneficial for the arthritis and rheumatism. Moreover, yam tubers containing compounds that lower high blood cholesterol and reduce the risk of gallstone formation.

12.3.1 Hyperhomocysteinemia (HHcy)

In our laboratory, we found that freeze-dried yam (*D. alata*) feeding significantly alleviated hyperhomocysteinemia (HHcy) induced by methionine (Met) in rats. Thrombin-induced platelet aggregation (PA), plasma malondialdehyde levels (indicator of lipid peroxidation) and hepatic reactive oxygen species (indicator of oxidative stress) of HHcy rats were significantly lowered. Hepatic antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GRx) and glutathione reductase (GR) adaptively enhanced by Met feeding were unchanged by yam feeding. The beneficial effects of yam on HHcy are attributed to its antioxidant functions in alleviating PA, lipid peroxidation, and oxidative stress which is not due to the induction of antioxidant enzymes that have already been adaptively increased by HHcy [16].

12.3.2 Hyperlipidemia

Autolysate and enzymatic hydrolysates from *D. opposite* Thunb. tubers revealed extremely high antioxidant activities and high angiotensin I-converting enzyme (ACE) inhibitory activities, suggesting that yam tubers are an excellent source of

antioxidant compounds with great antihypertensive activity [17]. The starch separated from the tuber of *D. opposite* cv. Anguo significantly decreased the serum total cholesterol (TC), triglyceride (TG) and LDL-cholesterol (LDL-C) levels by approximately 33.8, 46.2, and 27.5 %, respectively in hyperlipidemia rats, showing that starch from Chinese yam lowers blood lipid levels [18]. In our lab, three species of *D. alata* (TA01, TA03, and TA05) of Taiwan-cultivated yam (*Dioscorea*) were studied to examine the antioxidant and hypolipidemic functions in animal model. TA01 and TA03 were found to exhibit beneficial effects on lipid profile (TC, TG and LDL-C), fatty liver (TC) and antioxidant status (catalase and GR) for hyperlipidemia induced by a high fat and high cholesterol diet. Among these species, TA03 revealed the best efficacy in both hypolipidemic and antioxidant effects. With its function in regulating lipid profile and oxidative status, TA03 has the potential to be developed as a functional food for the prevention of cardiovascular disease [19]. Chen et al. found that a Taiwanese yam, *D. japonica* Thunb var. *pseudojaponica* Yamamoto, decreased gastric villous width. Diets consisting 25 and 50 % yams increased brush-border leucine aminopeptidase activity and decreased sucrase activity. The 50 % yam diet consistently improved the cholesterol profile in plasma and the liver, whereas the 25 % yam diet decreased the level of LDL-C cholesterol in plasma. Changes in blood lipid levels were associated with reduced fat absorption. This study suggests that a 25 % uncooked yam diet may benefit the function of upper gut and prevent hypercholesterolemia in humans, but the 50 % yam diet negatively affects protein absorption [20].

12.3.3 Hypoglycemic Effect

Diabetes mellitus is characterized by elevated plasma glucose levels resulting from absolute or relative insulin deficiency. The rhizomes of *D. opposite* Thunb. were traditionally used in diets to control Xiaokezheng (diabetes) in China. Certain reports confirmed that the water decoction of *D. opposite* has an anti-hyperglycemic effect to experimental diabetic mice [21]. Chemical components of *D. opposite,* dioscin and diosgenin, may be responsible for its medicinal efficacy [22, 23]. The anti-diabetic effects of *D. opposite* on dexamethasone-induced insulin resistance in vitro and in vivo found that *D. opposite* extract significantly decreased the blood insulin and glucose levels in dexamethasone-induced diabetic rats. *D. opposite* extract significantly enhanced insulin-stimulated glucose uptake in 3T3-L1 adipocytes in vitro. *D. opposite* extract also increased the mRNA expression of GLUT4 glucose transporter in 3T3-L1 adipocytes, suggesting that *D. opposite* restored insulin sensitivity via the regulation of GLUT4 expression [24]. McAnuff et al. [25] found that diabetic male Wistar rats fed with sapogenin extract from bitter yam (*D. polygonoides*) altered glucose metabolism with reduction in plasma glucose concentration. The Na^+-K^+-ATPase activity in the intestine was significantly reduced, which accounts for their hypoglycemic properties [26]. Supplementation of sapogenin extract from bitter yam (*D. polygonoides*) resulted in a significant

decrease in lactase and maltase activities in the intestine of diabetic rats, indicating the bitter yam sapogenin extract exhibits hypoglycemic properties [27].

12.3.4 Reno- and Hepato-Protective Effects

Endemic liver disease has been one of the ten leading causes of death in Taiwan for many years [28]. Liver cirrhosis, caused by alcoholism, is a public health impact in Taiwan. Lee et al. evaluated the protective effects of the aqueous extract of the yam (*D. alata* L.) on acute kidney dysfunction by BUN (blood urea nitrogen) and creatinine, as well as on liver injuries by sGOT, sGPT and s-rGT in rats induced by ethanol. The pharmacological, biochemical, and pathological results indicated the decreased damage in renal tubules as well as decreased inflammation in the central vein and necrosis in the liver of rats treated with the extract of Chinese yam [29]. Crude water extract of yam (*D. alata* L.) revealed kidney secureness and liver fortification in rats with hepato-nephro-toxicity induced by acetaminophen (APAP). The pathologic sections exhibited improvements in renal tubular degranulation changes, necrosis, and disintegration. Protection against the inflammation of the central vein and necrosis of liver tissue was also reported. These results suggest that the yam protects the liver and kidneys against damage to preserve their functions [30]. Daily administration of yam significantly reduced the area of r-glutamino-transpeptidase (GGT)-positive foci and the proliferating cell nuclear index. The antioxidant activities of liver were also elevated in CCl_4-induced hepatic fibrosis of rats at a dose-dependent manner, suggesting that yam attenuates CCl_4-induced liver injury [31].

12.3.5 Improvement of Gastrointestinal Function

The Chinese yam, *D. opposite* Thunb., has been used to improve gastrointestinal function and cure diarrhea in traditional Chinese medicine (TCM) for many years [32]. Starch, a major polysaccharide, is the most abundant carbohydrate found in Chinese yam (20–60 %) [33]. Studies reported that Chinese Yam polysaccharides (CYPs) enhanced beneficial gut microbiota, but suppressed bacterial pathogens. Diversity of gut microflora was increased in CYP-supplemented rats compared to that in non-supplemented. CYP enriched beneficial gut microbiota, but suppressed bacterial pathogens in rat cecum, indicating that CYP is a good source of carbon and energy, and may improve bacterial community diversity and modulate short-chain fatty acid production in hindgut of rats [34]. Ingestion of 40 % ethanol extract of Chinese yam flour (*D. rhizoma*) suppressed the secretion of gastric acid and increased gastrointestinal motility and fecal quantity in Sprague-Dawley (SD) rats. The Chinese yam extract did not affect the growth of normal intestinal bacteria. However, a great deal of lactose-fermenting bacteria was observed in the fecal

samples of rats fed with 2 % Chinese yam extract for 6 weeks. This finding would appear to suggest that Chinese yam extract not only induces an improvement in digestive capability, but also affects the conversion of some intestinal flora to probiotics. The serochemical analyses indicated that serum glucose, neutral lipid, and total cholesterol levels were reduced to certain degree by long-term feeding Chinese yam extract. This finding bolsters the notion that Chinese yam extract may be a useful alternative for patients suffering from hyperglycemia or hyperlipidemia [35].

12.3.6 Radio Protective Effect

Wang et al. using four lyophilized extracts obtained from yam rhizomes aqueous extract (YAE); 30 % ethanolic extract (YEE); aqueous extract boiled for 30 min (BYAE); and 30 % ethanolic extract boiled for 30 min (BYEE) to evaluate the protective effect on calf thymus DNA and plasmid DNA strand breakage. They found that YAE, YEE, and BYEE effectively inhibited the copper-driven Fenton reaction-induced damage of DNA, and the X-ray—induced strand breakage of plasmid DNA to a small extent. BYAE potently inhibited X-ray—induced strand breakage in plasmid pGL3 DNA but failed to inhibit, even greatly enhance copper-H_2O_2 induced damage of calf thymus DNA. These results demonstrate strong copper chelating and weak hydroxyl radical scavenging activities which may vary depending on the preparation procedures used for yam rhizome extract [36].

12.3.7 Delayed Aging

Dioscorea species have been traditionally used in treatment of memory-related diseases, such as Alzheimer's disease and other neurodegenerative diseases. Studies revealed that $CHCl_3$ soluble extract from *D. opposite* improved spatial learning and memory performance of mice via Morris water maze and passive avoidance tests. The in vitro pretreatment of primary cultured cortical neurons of rats with the extract demonstrated significant neuronal protection against glutamate- and H_2O_2-induced neurotoxicity of primary cultured cortical neurons of rats. The in vivo and in vitro results suggest that *D. opposite* reveals neuronal protection on the memory impairment associated some neurodegenerative diseases [37]. In our lab, yam tuber (*D. alata* L. var. *purpurea*) administered to senescence accelerated mice (SAMP8) showed that yam significantly improved learning and memory ability, lowered thiobarbituric acid-reactive substances (TBARS), and reduced brain morphological changes. The lyophilized yam was more effective than the yam dried with hot-air, due to the preservation of more antioxidant phytochemicals [38]. Different concentrations of lyophilized yam supplemented in the diet of SAMP8

reduced the cognitive deterioration (learning and memory), amyloid â (Aβ) accumulation, monoamine oxidase B (MAO) activity and increased total thiol level and superoxide dismutase (SOD) activity in brain at a dose dependent manner [39]. The protective components in yam responsible for delayed aging need to be further studied.

12.3.8 Immunological Activity

D. opposite is considered to be beneficial for improvement of immune functions. Diosgenin, the major steroidal sapogenin contained in the rhizomes of *D. opposite*, may be an active constituent contributing to the biological functions induced by *D. opposite*, including anti-inflammatory, antitumor, and immunomodulatory activities. Administration of diosgenin to ovalbumin (OVA)-sensitized mice, the serum level of IgE was diminished while IgG2a was enhanced. Similar to the profile of antibody production, diosgenin suppressed the expression of interleukin (IL)-4, but enhanced IFN-γ expression by splenocytes [40, 41]. In addition, administration of diosgenin markedly attenuated the intestinal expression of IL-4 and GATA3 in ovalbumin (OVA)-sensitized BALB/c mice. Administration of diosgenin reversed the diminished density of intestinal $Foxp3^+$cells induced by OVA oral challenges and enhanced the expression of IL-10 by $Foxp3^+$cells markedly. These results suggest that the suppressive effect of diosgenin on allergen-induced intestinal Th2 responses is closely associated with an up-regulation of the regulatory T-cell immunity in the inflammatory site [42]. A new polysaccharide (YP-1) purified from *D. opposite* Thunb. Stimulated ConA-induced T lymphocyte proliferation and its branches play a significant role in the enhancement of immunological activity. These pharmacological findings may help to elucidate the use of *D. opposite* Thunb. roots in TCM [43].

12.4 TCM Applications and Dietary Usage

12.4.1 TCM Applications

The tuberous rhizome of yam is pale brown, cylindrical, and twisted. Wild yam has been used medicinally for at least 2000 years in China, Japan, and Southeast Asia. Fresh tuber slices are widely used as functional foods in Taiwan, and the dried slices are used as TCM for strengthening stomach function, improving anorexia, eliminating diarrhea [32], and treating hypothyroidism, nephritis, and diabetes.

12.4.2 Dietary Usages

Yam is a nutritious food found in West Africa, Southeast Asia, and the Caribbean. The fresh tuber is used as a nutritious food in Taiwan, China, Japan, and Southeast Asia. It can be served in raw, fried, boiled, barbecued, roasted, baked and processed into a dessert recipe, cereal powder and noodle.

12.5 Clinical Evidences

Many women seek alternatives to hormonal therapies for the management of menopausal symptoms, including osteoporosis, hot flashes, and Alzheimer's disease. Currently, extract of wild yam (*D. villosa*) applied topically in the form of a cream is the most popular treatment. These preparations are known to contain steroidal saponins, including diosgenin, which has been claimed to influence endogenous steroidogenesis. Komesaroff et al. conducted a double-blind, placebo-controlled, cross-over study in 23 healthy women suffering from troublesome symptoms of menopause. Treatment of yam cream for 3 months, no significant side effects or changes in body weight were observed. Systolic and diastolic blood pressures, levels of total serum cholesterol, triglyceride, HDL-cholesterol, FSH, glucose, estradiol and serum or salivary progesterone were unaffected post treatment. Symptom scores showed no statistical difference on diurnal flushing number and severity, total non-flushing symptom scores, and nocturnal sweating, suggesting that short-term treatment with topical wild yam extract is free of side effects, but appears to have little effect on menopausal symptoms [44]. After ingestion of yam (*D. alata*), serum estrone, sex hormone binding globulin (SHBG), and estradiol were significantly increased without changes in serum dehydroepiandrosterone sulfate, androstenedione, testosterone, FSH, and LH. Free androgen index estimated from the ratio of serum total testosterone to SHBG was decreased. Levels of plasma cholesterol and urinary genotoxic metabolite of estrogen, 16α-hydroxyestrone, were significantly decreased. Lag time of LDL oxidation was prolonged significantly and urinary isoprostane was significantly decreased. For the control subjects fed with sweet potato, all three hormone parameters measured were not changed post intervention. Replacing two thirds of staple food with yam for 30 days improved the status of sex hormones, lipids, and antioxidants, although the exact mechanism is not clear. These effects might reduce the risk of breast cancer and cardiovascular diseases in postmenopausal women [45].

Anxiety and depression are major symptoms in postmenopausal women. Interleukin-2 (IL-2) has recently been implicated as a modulator of neuronal function. Anxiety levels in rats are correlated with IL-2 levels in brain. Ho et al. found that anxiety behavior in EPM (elevated plusmaze) was increased in half of ovariectomized (OVX) rats. After chronic treatment with *Dioscorea* (*D. L. alata.* Var. *purpurea* Tainung No. 1), a decrease in anxiety and IL-2 levels were observed in

HA (high anxiety) OVX rats. Despair behavior in the FST (forced swim test) was inhibited by the highest dosage of *Dioscorea*. The OVX-induced anxiety and changes in neuroimmunological function in the cortex reversed by *Dioscorea* suggest that yam is beneficial for alleviating anxiety and depression in postmenopausal women [46].

Generally, decreased skeletal bone mass owing to estrogen deficiency after menopause leads to osteoporosis [47]. Vascular VEGF-A plays an important role in bone-related angiogenesis, a critical process occurs during bone formation and fracture healing. Yen et al. found that diosgenin, extracted from the root of a wild yam (*D. villosa*), elevated VEGF-A mRNA and protein expression in murine MC3T3-E1 preosteoblast-like cells in a concentration dependent manner. The estrogen receptor binding assay revealed that diosgenin interacted with estrogen receptor. In addition, diosgenin up-regulates VEGF-A and promotes angiogenesis in preosteoblast-like cells by a hypoxia-inducible factor-1α–dependent mechanism involving the activation of src kinase, p38 MAPK, and Akt signaling pathways via estrogen receptor. Diosgenin not only generates angiogenic activity in mouse MC3T3-E1 osteoblasts by elevating VEGF-A levels, but also induces VEGF-A up-regulation through activation of HIF-1 by the estrogen receptor-dependent PI3K/Akt and p38 MAPK signaling pathways. This study provides a further insight into the possible therapeutic use of diosgenin for the treatment of certain bone-related diseases or alleviating osteoporosis in menopausal women [48].

12.6 Safety Evaluation and Toxicity Issue

Liao et al. evaluated the toxicity of yam tuber powder at a single high dose and a 28-day continuous feeding in SD rats. They found that a single dose of 5000 mg/kg BW of yam tuber powder revealed no death or toxic effect in rats. The LD_{50} of acute oral feeding appears to be greater than 5000 mg/kg BW in rats. In a 28-day study, yam tuber powder was fed daily by gavage to each treated group consisting of 10 male and 10 female rats with doses of 0, 500, 1000, and 2000 mg/kg BW for 28 days. No significant changes related to the yam tuber powder were evaluated by clinical observation, mortality, body and organ weights, food consumption, ophthalmology, hematology, biochemistry and pathology. According to the results, the no observed adverse effect level (NOAEL) of yam tuber powder in the 28-day feeding toxicity (by gavage) is greater than 2000 mg/kg BW in rats. Therefore, long-term supplementation with yam tuber powder is safe in mammalian [49]. Grindley et al. investigated the protective effects of yam (*D. cayenensis*) on diabetic nephropathy in streptozotocin-induced diabetic rats. They found that malic enzyme activity was significantly reduced in diabetic rats on normal diet and feeding of yam raised the activity of malic enzyme towards normal. Alanine transaminase in the kidney of diabetic rats fed with yam extract was shown to be significantly higher than that of healthy controls. These results demonstrate an overall aggravation of diabetic nephropathy by yam, suggesting that a dietary staple of yam may be a factor

associated with the prevalence of diabetes mellitus and the development of renal disease [50]. Moreover, yam sapogenin extract was reported to adversely affect the integrity of kidney membrane [27]. Rubbing the skin with yam can cause allergic contact dermatitis [49]. Yam may also induce asthma [51]. Large doses of yam taken orally may produce emesis. Yam is not recommended for pregnant women because it is considered to induce uterine contractions [52]. In addition, yam is not traditionally used or recommended for consumption during childhood [53].

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Chapter 13
Gastrodia elata Blume. 天麻 (Tianma, Gastrodia Tuber)

Hui-Min Gao

13.1 Botanical Identity

Tianma, the steamed and dried rhizome of *Gastrodia elata* Blume. (Orchid Family), is one of the most popular traditional Chinese medicines and a famous foodstuff in China. It was first recorded in Shen-nung-pen-tsao-ching as a high-grade drug and widely used for the treatment of headache, dizziness, vertigo, convulsion, hypertension and other neurodegenerative diseases [1]. The orchid *G. elata*, lacking green leaves and chlorophyll, is a saprophytic perennial herb and it grows in the glades or at the edge of forests in humid mountain areas with the altitude of 400–3200 m. This species lives in symbiotic association with the honey mushroom (*Armillariella mellea*) and its whole growth cycle except for florescence, is in the underground [2]. The wild *G. elata* distributed in China's southwest, northeast and central regions, and especially, the rhizomes collected in the western *Guizhou*, southern *Sichuan* and northeastern *Yunnan* are considered to be the genuine medicinal material with good prestige. Due to the increasing market demand, natural reserves of *G. elata* have drastically decreased and the species has been listed as rare and endangered one in China and even around the world. Since the 1970s, *G. elata* has been extensively cultivated in *Shaanxi*, *Anhui*, *Sichuan*, *Guizhou* and *Yunnan*, and to date, *Lueyang* in *Shaanxi* province, has become the biggest production base all over the country.

The rhizome is harvested from early winter to late spring, washed clean immediately, steamed thoroughly, spread out and dried at a lower temperature. Traditionally, the rhizome collected prior to late December was considered to have the better quality than those before early April. The dried rhizome could be brought from the medicinal market as the crude material and they are characterized by ellipsoid or

H.-M. Gao (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, 100700 Beijing, People's Republic of China
e-mail: huimin_gao@126.com

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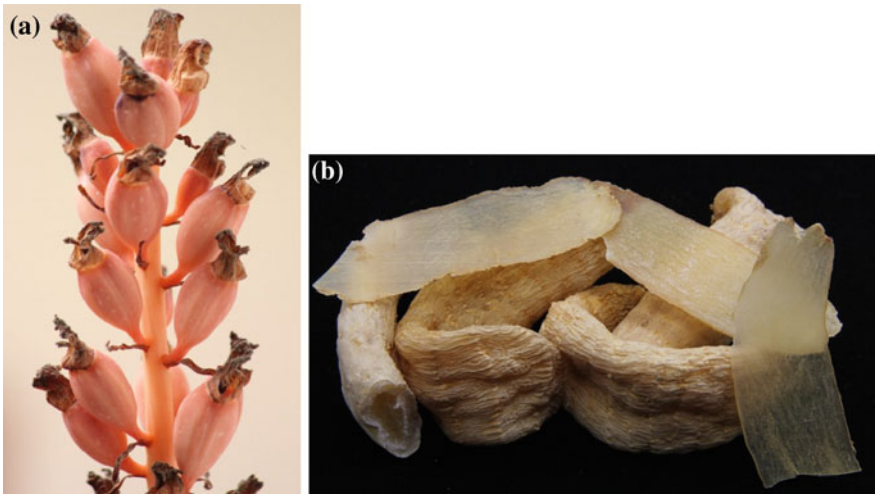

Fig. 13.1 Fruiting plant (**a**) and dried roots with slices (**b**) of Tianma

slat-shaped, slightly compressed, shrunken and somewhat curved, 3–15 cm long, 1.5–6 cm wide, 0.5-2 cm thick (Fig. 13.1). The crude material is further processed by softening thoroughly or steaming soft and then cutting into thin slices and drying. The dried slices are also processed for the different medicinal purposes according to the traditional techniques such as by frying, stewing, soaking with wine and etc.

13.2 Chemical Constituents

The rhizome of *G. elata* contains a variety of constituents including phenolic glycoside, organic acid, volatile oil, sterol, polysaccharide and etc. Among them, phenolic glycosides are considered as main bioactive compunds in the fresh or steamed and dried rhizome as well as the commercial products from the medicinal market. As the representative of this class of constituents, gastrodin (**1**) and its aglycone gastrodigenin (4-hydroxybenzyl alcohol, **2**) are paid much attention to their direct extraction from natural resources, through chemical synthesis and biotranformation as well as their bioactivities such as anticonvulsant, sedative, and analgesic actions. Because of its easy water solubility and significant activity, gastrodin has been used intravenously and intramuscularly in clinical practice in China. Closely related components, including 4-hydroxybenzaldehyde, vanillyl alcohol, vanillin, and 4-hydroxybenzyl methyl ether, and the compounds containing two or more 4-hydroxylbenzyl alcohol moieties (**3**) as well as citric acid tricarboxylic acid ester parishin (**4**), parishin F (**5**), dicarboxylic acid esters parishin B (**6**), C (**7**), D (**8**) and monocarboxylic acid ester parisin E (**9**) and G (**10**) are also present in this species [3–5] (Fig. 13.2). In addition, the presence of minor

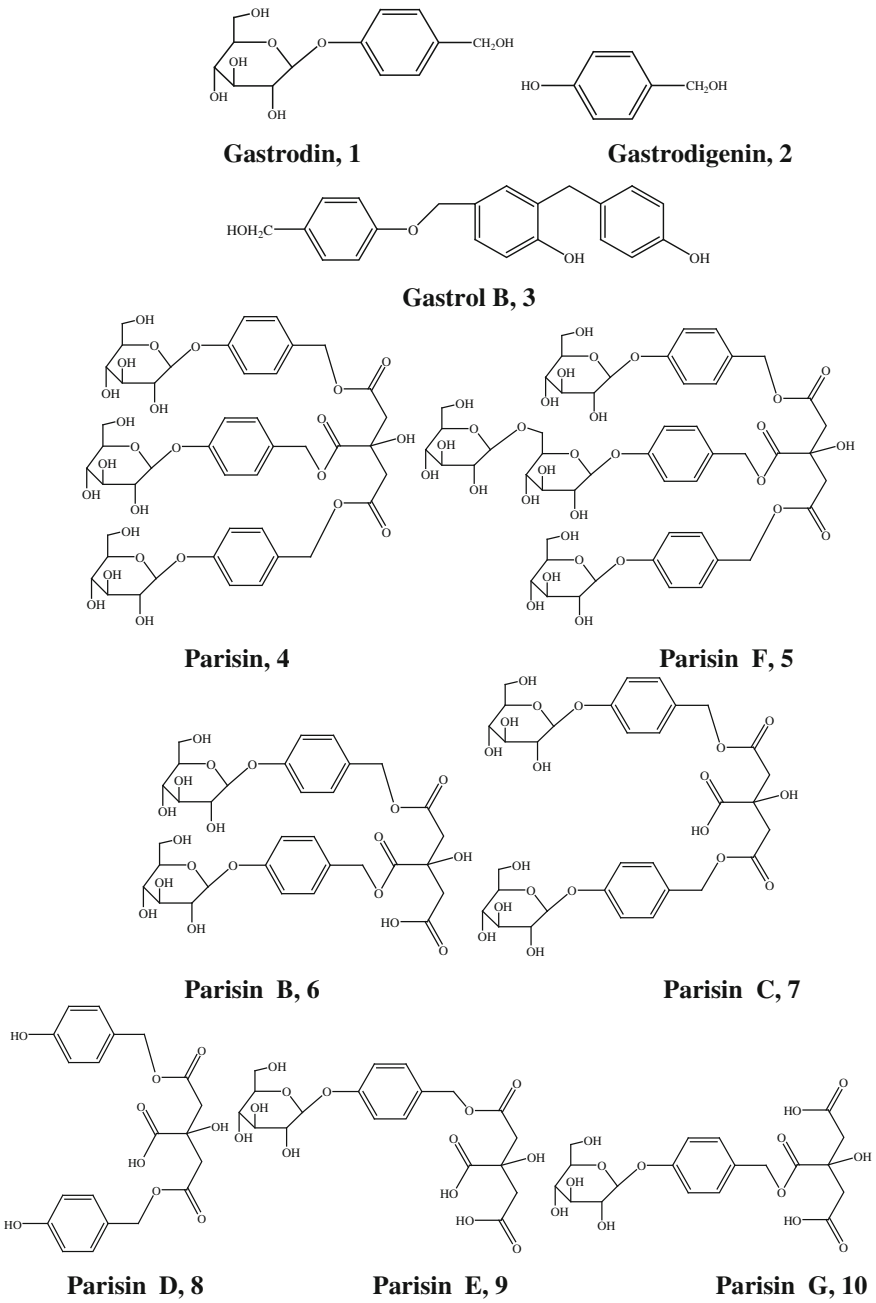

Fig. 13.2 Representative phenolic compounds isolated from Tianma

component 5-hydroxymethylfurfuralin in steamed and dried rhizome resulted from the derivatization of carbohydrate by processing the fresh rhizome.

13.3 Pharmacological Studies

As an important medicinal herb to control convulsion, epilepsy, tetanus, headache and dizziness, paralyzed limbs and other neurodegenerative disorders [1], Tianma showed various pharmacological effects including anticonvulsant, sedative, analgesic, neuroprotective, antioxidative and immunomodulatory activities as well as anti-aging, anti-hypertension, expanding the coronary blood vessel, improving peripheral circulation and learning memory and etc. [6]. The antiepilepsy mechanism of Tianma or its active constituents such as gastrodin, gastrodigenin, 4-hydroxybenzaldehyde, vanillyl alcohol and vanillin, appear to act via the γ-aminobutyric acid (GABA) pathway, either through inhibition of degradative enzymes of GABA or by an effect on the GABAA/benzodiazepine receptor [7]. The therapeutic action related to cardiovascular system resulted from the antioxidative activity of Tianma or its active ingregients.

13.4 TCM Applications and Dietary Usage

13.4.1 TCM Applications

As one of 34 famous and expensive Chinese Traditional Medicines announced by China, Tianma could be used in a single form or in combination with other herbs for the treatment of convulsion, epilepsy, tetanus, headache and dizziness, paralyzed limbs, and other neurodegenerative disorders. There are hundreds of manufacturers making single Tianma or its formula preparations in China. The former includes Quan Tianma tablets, capsules and a series of gastrodin tablets, capsules, oral liquid and injections. The latter have Tianma tablets, capsules, pills, injections and concentrated capsules as well as Tianshu capsule, Dachuanxiong pill and oral liquid, etc.

Quan Tianma capsule is composed of single crude material, tall gastrodia tuber, and is widely used to treatheadache, dizziness and paralyzed limbs.The drugs derived from single chemical entity gastrodin are clinically available not only in oral administration, but also in intravenous and intramuscular forms such as Gastrodin injection and capsule.Tianshu capsule and a series of Dachuanxiong preparations are composed of two herbal ingredients: Chuanxiong (rhizome of *Ligusticum chuanxiong* Hort.) and Tianma (rhizome of *G. elata*) with a ratio of 4:1 (W/W). It is mainly used for treating the blood stasis type of headache by promoting blood circulation and pain relief. Tianma Gouteng capsule is prepared from twelve herbal components: Tianma (rhizome of *G. elata* Blume), Gouteng

(stem and twig of *Uncaria rhynchophylla* (Miq.) Miq. Ex Havil), Shijueming (shell of *Haliotis diversicolor* Reeve), Zhizi (friut of *Gardenia jasminoides* Ellis), Huangqin (root of *Scutellaria baicalensis* Georgi), Niuxi (root of *Achyranthes bidentatae* Blume), Duzhong (bark of *Eucommia ulmoides* Oliv.) processed with salt, Yimucao (the whole plant of *Leonurus japonicus* Houtt.), Sangjisheng (leaf and twig of *Taxillus chinensis* (DC.) Danser), Shouwuteng (stem of *Polygonum multiflorum* Thunb.) and Fuling (sclerotium of *Poria cocos* (Schw.) Wolf.). It is used for the headache and dizziness caused by hypertention.

13.4.2 Dietary Usages [8]

Besides the important therapeutic action, Tianma has the great nutrition and health value. It is often used as famous culinary and dietary material. Tianma candy and packed Tianma slice are favorite of many people and it is a good alternative to present them to the family or friends. In addition, some culinary and dietary forms are listed as followed.

13.4.2.1 Tianma Wine

Tianma Duzhong wine is made by soaking Tianma (rhizome of *G. elata* Blume, 50 g), Duzhong (bark of *E.ulmoides* Oliv., 50 g), and Mugua (fruit of *Chaenomeles speciosa* (Sweet) Nakai, 50 g) in 500 g of Chinese spirit for more than a week to drink daily for strengthening the body. Compound Tianma Yiyin wine and Renshen Tianma wine are also legally authorized to be available on the Chinese medicinal market, which are prepared with Tianma combining with other herbs and alcohol. Daily intake amount can be based on indication of each drug.

13.4.2.2 Tianma Tea

Tianma mixed with other herbs can be used for the preparation of the healthy tea. For example, Tianma Chuanxiong tea, which was composed of Tianma (rhizome of *G. elata* Blume, 3 g), Chuanxiong (rhizome of *L. chuanxiong* Hort., 10 g), Baizhi (root of *Angelica dahurica* (Fisch.) Benth. et Hook., 3 g) and spring tea (3 g).

13.4.2.3 Tianma Used as Culinary and Dietary Material

When it is used as culinary and dietary material, fresh rhizome of *G. elata* is more preferred than dried one. It is often enjoyed as main ingredients for making soup or porridge with various foodstuffs such as meat, fish, chicken and rice, etc. Tianma Gouqi soup can be prepared as followed: Fresh rhizome of *G. elata* (25 g) and

Gouqi (fruit of *Lyciumbarbarum* L., 12 g) are boiled for 20 min and then mixed with pork (220 g). Tianma Dazao porridge was preprared with fresh Tianma (rhizome of *G. elata* Blume, 50 g), rock candy (50 g), Dazao (fruit of *Ziziphus jujuba* Mill., 14 pieces) and rice (200 g).

13.5 Clinical Evidences

Multiple studies in humans have been reported that it is directly related to the use of Tianma or its formula preparations for the treatment of various diseases. However, much of the literatures are difficult to interpret due to incomplete study design descriptions, discrepancies and inconsistencies among preparations of Tianma. The large-scale, multi-centered and randomized blind method of RCTs is still to be adopted.

Three trials in humans evaluated the preparations containing Tianma in multiple disease states. One study described its effect on senile vascular dementia. 60 patients with senile vascular dementia were divided into three groups, and Tianma Cuzhi granules were given to each group for 2 months (four times, three times and twice a day). The scores on the Mini-Mental State Examination of all tested patients treated with drugs were improved as compared with baseline [9]. In a randomized controlled clinical trial in the treatment of diabetic peripheral neuropathy, 36 patients were treated with reinforced Tianma Duzhong capsules, containing Tianma (rhizome of *G. elata* Blume) and Duzhong (bark of *E. ulmoides* Oliv.), and another 26 patients in the control group were treated with 40 mg of aspirin daily. Both symptoms and electromyographic changes were significantly improved in the capsule-treated group [7]. A meta-analysis of randomized control trials on the effect of Tianshu capsule in treatment of migraine, including a total of 10 studies including 937 migraine patients, indicated it had a higher effective rate in treating migraine, and there is no significant heterogeneity between Tianshu capsule group and control group. Tianshu capsule alone compared to conventional therapy also showed the advantages, and there was low heterogeneity [10].

13.6 Safety Evaluation and Toxicity Issue

Toxicity of Tianma in humans is very low. When it is overcommitted or inappropriately used, there will be suffering from some side effects including skin rash, vertigo, chest tightness, shortness of breath, nausea and vomiting, etc. Acute toxicity in animals is also low. The LD_{50} in adult mice injected intraperitoneally with crude Tianma extract was 51.4–61.4 g/kg [7]. Although Tianma is a relatively safe herbal medicine often used as the culinary and diet purposes, it is still strongly recommended to use it under the proper condition.

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Chapter 14
Glycyrrhiza uralensis 甘草
(Gancao, Licorice)

Sue-Joan Chang, Yin-Ching Chan and Wen-Jen Yu

14.1 Botanical Identity

Licorice (Gan-Cao) is a perennial herb of Fabaceae family cultivated mainly in Shanxi, Gansu and Xinjiang regions of China. "Gan" of licorice in Chinese means umami taste of licorice, therefore, licorice is an important constituent in many traditional Chinese medicine (TCM) to reduce the bitter taste of other herbal medicine. The height of licorice plant for medicinal use is 30–100 cm. The medicinal part of licorice is the cylinder root and underground stem with a diameter of approximately 3–4 cm. The botanical traits of licorice are axillary raceme flower with purple and white colors, odd number pinnately compound leaf (Fig. 14.1a, b), and legume fruit. *Glycyrrhiza uralensis* (*G. uralensis*) is the most common species for TCM use, although several species of licorice are used in similar ways as TCM including *Glycyrrhiza glabra* L., *Glycyrrhiza inflata*, and *Glycyrrhiza kanscensis* [1].

Licorice is considered as a "Jun" (emperor) herb in TCM prescription composed of several constituents to treat asthma, coughs and peptic ulcers [1]. Cleaned and dried licorice root is sliced obliquely into 3–5 mm thickness with the oval shaped piece as the raw material for market (Fig. 14.1c).

S.-J. Chang (✉)
Department of Life Sciences, National Cheng Kung University, Tainan, Taiwan
e-mail: sjchang@mail.ncku.edu.tw

Y.-C. Chan
Department of Food and Nutrition, Providence University, Taichung, Taiwan

W.-J. Yu
Department of Biotechnology, Hung Kuang University, Taichung, Taiwan

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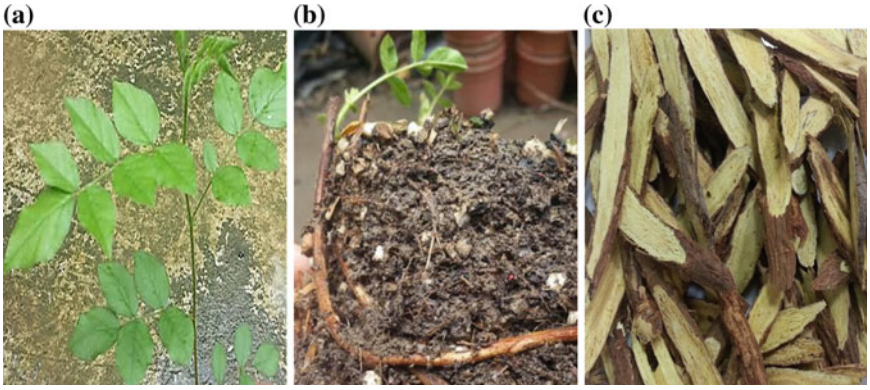
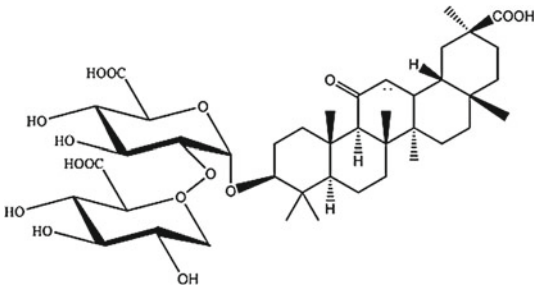


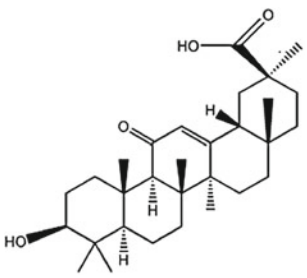
Fig. 14.1 The plant with tender shoots (**a**), roots in the soil (**b**), and crude drug (**c**) of licorice

14.2 Chemical Constituents

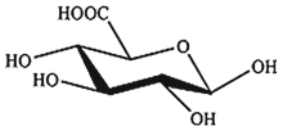
The chemical constituents of licorice were identified and classified into several categories including triterpenoid saponins, flavanoid, coumarin, and alkaloid [1, 2].



Glycyrrhizin or Glycyrrhizic acid, 1



18β-Glycyrrhetic acid, 2



D-Glucuronic acid, 3

Fig. 14.2 Triterpenoid saponins and its components isolated from licorice

14.2.1 Triterpenoid Saponins

Glycyrrhizin (glycyrrhizic acid, GA) (1), indicative compound of licorice and the common name of the major triterpenoid saponin including potassium and calcium salt of glycyrrhizic acid, is composed of one molecule of 18β-glycyrrhetinic acid (2) and two molecules of glucoronic acid (3), shown in Fig. 14.2.

14.2.2 Flavanoids

Flavanoids and their derivatives in licorice root extract were identified and the representative compounds were shown in Fig. 14.3 as liquiritin (4), isoliquiritin (5), neoliquiritin, neoisoliquiritin, licoricidin (6), licoricone (7), liquiritigenin (8),

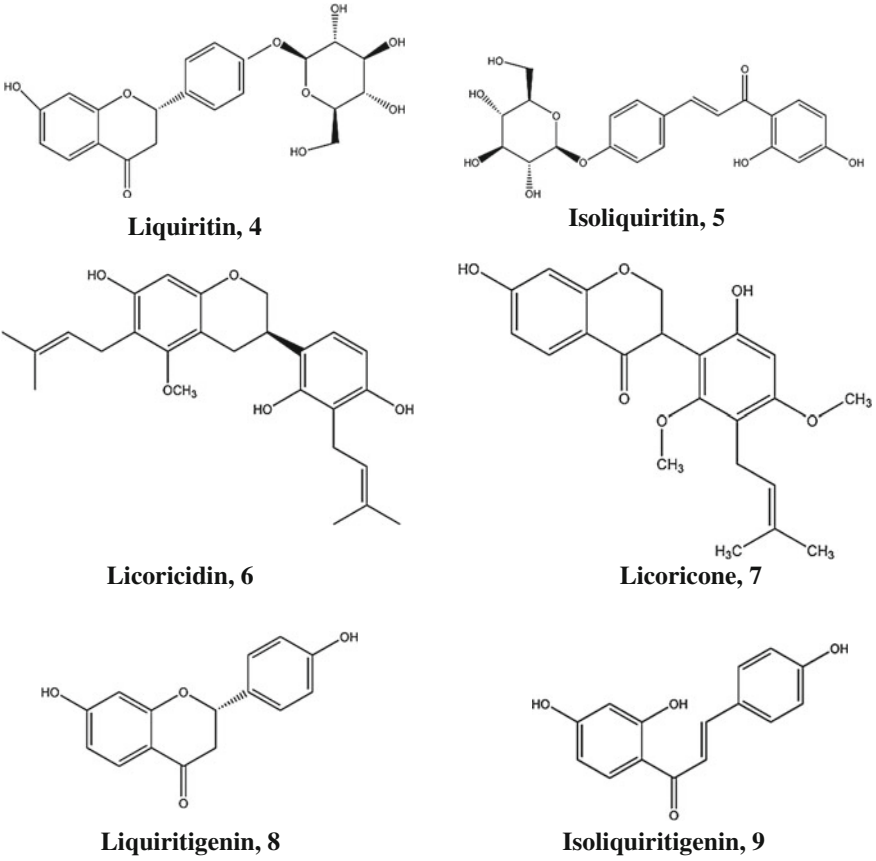
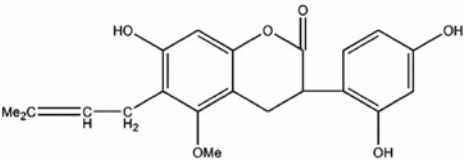


Fig. 14.3 Representative flavanoids isolated from licorice

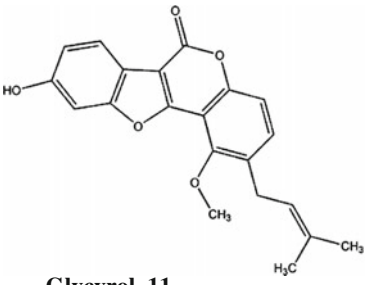
isoliquiritigenin (9), formononetin, 5-O-methyl-licoricidin, liquiritigenin-4′-apiofuranosyl (1 → 2) glucopyranoside, apioliquiritin, apioliquiritigenin-7-4′-diglucoside, vicenin II, isolicoflavonol, isoliquiritigenin-4′-apiofuranosyl (1 → 2) glucopyranoside, licurazid, and apioiso liquiritin.

14.2.3 Coumarins

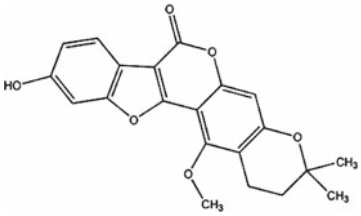
Coumarin derivatives identified in licorice root extracts were shown in Fig. 14.4 including glycycoumarim (10), glycyrol (11), isoglycyrol (12), glycyrin (13), neoglycyrol, licopyranocoumarin (14), and licocoumarione.



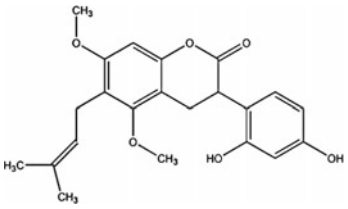
Glycycoumarim, 10



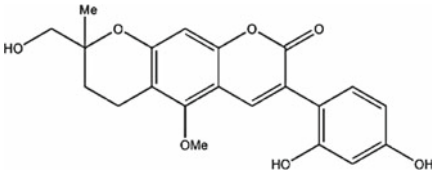
Glycyrol, 11



Isoglycyrol, 12



Glycyrin, 13



Licopyranocoumarin, 14

Fig. 14.4 Representative coumarins isolated from licorice

14.2.4 Alkaloid

Alkaloids in the licorice extract were identified including 5,6,7,8-tetrahydro-4-methylquinoline, 5,6,7,8-tetrahydro-2,4-dimethylquinoline, 3-methyl-6,7,8-trihydropyrrolo[1,2-]pyrimidin-3-one.

14.3 Pharmacological Studies

Pharmacological studies of licorice root extract, including anti-virus, anti-inflammation, anti-oxidation, hepatoprotection, anti-tumor, and anti-asthma [3–7], were extensively documented due to its common use in TCM prescription.

14.3.1 Anti-inflammatory Effects

β-glycyhrritinic acid (GA) has been shown to inhibit glucocorticoid metabolism leading to the accumulation of glucocorticoid with anti-inflammatory effects [2]. GA inhibited reactive oxygen species (ROS) generated in neutrophils which was suggested to be the modulator of anti-inflammation tissue [3]. *G. glabra* and glyderinine, a derivative of GA showed an anti-inflammation and reduced myocardial inflammatory edema [4]. Inhibition against interleukin-1β(IL-1β)-induced prostaglandin E_2 (PGE_2) production in normal human dermal fibroblasts by derivatives of glycyrrhetinic acid has been reported [5]. GA was suggested as the active antiviral component of *G. uralensis* against enterovirus 71 and coxsackievirus A16 infection for hand, food and mouth disease [6]. Nano- or micronized GA were prepared by using the supercritical anti-solvent (SAS) procedure, inhibited by PGE2 and TNF-α production, which was induced by LPS more effectively than that of unprocessed GA [7].

G. uralensis extract (GUE) at a dose of 400 mg/ml cures rotaviral enteritis by coordinating antiviral and anti-inflammation related cytokines (IL8, IL10, IFN-β, INF-γ and TNF-α) [8]. Glycyrrhetic acid is also effective on anti-inflammatory functions [9].

14.3.2 Hepatoprotection

Glycyrrhetic acid or 18β-glycyrrhetinic acid was documented to cure the rotavirus infection [10]. GA was reported to exhibit direct protection of hepatocyte from apoptosis through an IL-6 dependent way and indirect inhibition of T-Cell mediated inflammation through an IL-10 dependent way.

Hepatoprotective function of licorice extract was proved in CCL_4-induced hepatitic rat model and GA being the main component responsible for this effect [11].

14.3.3 Immunomodulatory Effects

Immunomodulatory effects of licorice are attributed to its active compounds, glycyrrhizin and glycyrrhetinic acid [12, 13]. GA selectively activated extrathymic T cells and enhanced Fas-mediated apoptosis without alteration of caspase-3 like activity [14, 15].

Flavonoids isolated from *G. uralensis* revealed anti-asthma effect by reducing eosinophilia pulmonary inflammation, serum IgE, IL-4 and IL-13, and increasing IFN-γ in lung cell culture of allergic asthma model [16].

Liquiritigenin inhibited LPS-induced NF-κB DNA binding activity and suppressed the production of tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β) and interleukin-6 (IL-6) from Raw264.7 cells after LPS treatment [17].

14.3.4 Antitumor Effects

The ethanol extract of *G. uralensis* root induced apoptosis and GI cell cycle arrest in MCF-7 human cancer cells [18]. Glycyrrhetinic acid triggered the mitochondrial permeability transition which may lead to the apoptosis of tumor cells [19, 20].

14.3.5 Neurogenesis Protective Effects

G. uralensis exhibited anti-depressive effects by increasing the sum of line crosses and number of rears, decreasing the fecal boli number in the open field, and lowering the immobility time in forced swim and tail suspension tests in a chronic unpredictable stress of depression model rats [21]. *G. Radix* (GR) was noted to prevent the Aβ (25–35) induced neuronal apoptotic death by decreasing the expression of Bax and active caspase-3, and increasing the expression of Bcl-2. Furthermore, GR also significantly inhibited Aβ (25–35) induced elevation of the intracellular Ca^{+2} concentration and ROS generation [22]. An active component isolated from *G. uralensis* isoliquiritigenin (ISL), was demonstrated to reverse the glutamate-induced ROS production and mitochondrial depolarization, and regulate the glutamate-induced changes of Bcl-2 and Bax in HT22 hippocampal neuronal cells. These results suggest that *G. uralensis* plays a therapeutic role for preventing the progresses of neurodegenerative diseases such as Alzheimer's disease [23].

14.3.6 Estrogenic Effects

Licorice was reported to be effective on the prevention of osteoporosis after menopause. Extracts of *Glycyrrhiza* species induced estrogen responsive alkaline phosphatase activity in endometrial cancer cells. Meanwhile, increase of estrogen responses of these extracts were approved using estrogen responsive element (ERE)-luciferase reporter system in MCF-7 cells, and increased *Tff*1 mRNA expression was found in T47D cells [24]. Isoliquiritigenin was demonstrated to be the major estrogenic compound in the licorice extract due to its ERβ selectivity, partial estrogen activity, and non-enzymatic conversion of isoliquiritigenic to liquiritigenin [24].

14.3.7 Anti-metabolic Syndrome

GA, a potential agonist to PPARγ, was investigated for its anti-metabolic syndrome effects. It indicated that oral administration of 100 mg/kg GA for 24 h improved insulin sensitivity and lipid profiles and induced up-regulation of PPARγ and LPL expression in adipose, muscle, liver and kidney tissues [25].

GA, a bioactive component in licorice, significantly reduced the AGEs-induced apoptosis by increasing the SOD activity, decreasing the MDA production, inhibiting ROS over generation, and down-regulating the TGF-β1 and NF-kB protein expressions in human umbilical vein endothelial cells, indicating that GA might be an alternative for the prevention and treatment of diabetic vascular complications [26].

14.4 TCM Applications and Dietary Usage

TCM prescriptions are usually composed of several herbal medicines called "fufang", based on the herbal nature and classified as "Jun-Chen-Zuo-Shi" medicines in a prescription. Licorice is commonly used as a "Jun" (emperor) or "Shi" (courier) medicine to treat the main cause of the disease or to guide the other herbs to the target organs, respectively.

Licorice was documented to treat a lot of diseases in Five-Zang (heart, spleen, liver, lungs and kidneys) and Six-Fu organs (gallbladder, stomach, large intestine, small intestine, bladder and sanjiao). The traditional therapeutic effects of licorice are to clean the evil influence of cold and heat, to strengthen the bones and muscles, and detoxification. Long term treatment of licorice is also beneficial for antiaging [1]. Licorice can be used in TCM either in raw form or prepared form (roasted by honey). Raw licorice is used to clear interior heat; on the other hand, prepared licorice is used for releasing the exterior cold. Combined used of licorice in other prescriptions functions to cure sore throat, tonify spleen and stomach, and nourish the lung.

14.4.1 TCM Applications

One of the most famous Chinese medical book "Treatise on Cold Pathogenic Diseases" described that many cold induced diseases such as cough, sore throat, and omitting could be restored by treating with licorice related prescriptions. Licorice was named as "King of the herbs" to point out the importance of its application in TCM.

Licorice decotion ("Gancao Tang") and Prepared licorice decotion ("Zhigancao Tang") are two prescriptions that only licorice was used to relief sore throat and anti-cough through nourishing the lung, respectively. "Gancao Xiexin Tang" combined licorice, Huangqin (root of *Scutellaria baicalensis*), Ganjiang (rhizome of *Zingiber officinale*), Banxia (tuber of *Pinellia ternata*), Dazao (fruit of *Ziziphus jujuba*), and Huanglian (rhizome of *Coptis chinensis*) is used to relieve the illness of stomach and nourish stomach. "Gancao Ganjiang Tang" combined licorice and prepared ginger is focusing on the spleen and stomach nourishing. "Gancao Fuzi Tang" combined licorice, prepared Fuzi (daughter root of *Aconitum carmichaeli*), Baizu (*Atractylode smacrocephala*), and Guizhi, (twig of *Cinnamomum cassia*) are prescribed to relieve the pain of Rheumatoid arthritis. "Ganjiang Linzu Tang" combined licorice, Baizhu, dried ginger, and Fuling (sclerotium of *Poria cocos*) are mainly used to remedy the abnormality of renal function caused by cold.

14.4.2 Dietary Usages

Dietary usage of licoriceis mainly as a sweetener in addition to its physiological functions in many soft drinks, food products, candy, chocolate, chewing gums, and herbal medicines. The habitual consumption of licorice derived sweetener is more popular in hot environments. The major compound in licorice used as a sweetener is GA which is 50–100 times sweeter than that of sugar. Although GA and water soluble licorice extract were thought to be nontoxic food additives due to its less bioavailability, accumulated evidences indicated that over ingestion of GA or licorice extract may cause some side effects such as cortisol-induced mineralocorticoid syndrome. Limitations for use of licorice or licorice derivatives in food supplement was stipulated by US FDA (Table 14.1) [27].

Table 14.1 Limitations for the use of licorice and its derivatives in foods, US Food and Drug Administration

Food category	Maximum allowable levels in foods as % glycyrrhizin content	Functional use
Baked goods	0.05	1, 2
Alcoholic beverages	0.1	1, 2, 3
Nonalcoholic beverages	0.15	1, 2, 3
Chewing gum	1.1	1, 2
Hard candy	16.0	1, 2
Soft candy	3.1	1, 2
Herbs and seasonings	0.15	1, 2
Plant protein products	0.15	1, 2
Vitamin or mineral dietary supplement	0.5	1, 2
All other foods, except sugar substituents	0.1	1, 2

1 Flavor enhancer; *2* flavoring agent; *3* surface-active agent

14.5 Clinical Evidences

Scientific clinical evidences of licorice are limited, although use of licorice in TCM is extensively documented in Chinese medical books, especially on anti-hepatitis, anti-hyperglycemia, and GI diseases.

14.5.1 Anti-hepatitis

GA is available in a multiplicity of non-standardized oral formulations [28, 29]. Stronger neominophagen C (SNMC), containing 0.2 % GA, 0.1 % cysteine, and 2 % glycine in physiological solution and administering intravenously 80–200 mg/day, is used in Japan for the treatment of acute and chronic hepatitis [30].

14.5.2 GI Function

The curative effect of deglycyrrhizinized licorice (DGL) in gastric ulcer patients was confirmed during 1970s by clinical trials. Clinically, DGL has been used as a main source for the treatment of GI ulcerative disorders including peptic ulcer, canker sores and inflammatory bowel diseases. A randomized, double-blind, placebo-controlled study indicated that extract of *G. glabra* improved the severity and symptom score of dyspepsia [31]. Liver enzymes, ALT and AST were significantly decreased following administration of 2 g licorice root extract per day for two months in non-alcoholic fatty liver disease patients [32].

14.6 Safety Evaluation and Toxicity Issues

For many years, licorice was believed to be a healthy and safe natural substance without side effects [27]. The major component of licorice is GA with poor bioavailability and low animal toxicity. Oral acute toxicity test showed that LD_{50} of GA was 4320 mg/kg bodyweight in mice. Glycyrrhetic acid, the active inhibitor of 11-ß-hydroxysteroid dehydrogenase enzyme type 2, was generated by intestinal bacterial ß-glucuronidase after GA was ingested. The acute toxicity data showed that LD_{50} of glycyrrhetic acid in mice was 308 mg/kg bodyweight through i.p. injection. Glycyrrhetic acid is further metabolized to glucuronide and sulfate conjugates in liver, then excretes into the bile. Patients ingest GA either long term or periodically, might accumulate glycyrrhetic acid and its derivatives leading to toxicity such as cortisol-induced mineralocorticoid effect, elevated sodium and reduced potassium levels [27] in blood.

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Chapter 15
Lilium lancifolium 百合
(Baihe, Tiger Lily)

Yanze Liu

15.1 Botanical Identity

Lily, a perennial ornamental crop belonging to the family Liliaceae, has great decorative, medicinal, and edible value. The genus *Lilium*, which includes approximately 100 species, is native to Asia, Europe, and North America in the Northern Hemisphere. There are about 55 species in China. China is the diversity center of wild *Lilium* in the world [1]. The flowers of lilies are often fragrant, and come in a range of colors including whites, yellows, oranges, pinks, reds and purples. More and more ornamental hybrids have been developed around the world. Numerous species have been widely grown in the garden as ornamental plants in the West.

In China, there are three bulbs of *Lilium* species (*Lilium lancifolium* Thunb, *L. pumilum* DC., and *L. brownii* F.E. Brown var. *viridulum* Baker) that have been used as legal resources of medicinal purpose recorded in The Pharmacopeia of People's Republic of China and other historical Chinese herbal records [2]. Its Chinese name Baihe means "hundred meetings", referring to the many tightly overlapping scales that form the bulb.

The plant of *L. lancifolium* has an erect stem that is non-branched, and can be grass green, red or purple with brown spots. With underground bulbs, bulbs form a broadly ovate or lanceolate shape, and are white or orange. Fleshy scales hold the synthetic spherical outer membranous layer, making the bulb 6–8 cm in diameter. The flowers of *Lilium* species are borne on an erect stem that is 20–100 cm tall, clothed with the more or less linear leaves that are 6–10 cm long and 1–2 cm broad.

Y. Liu (✉)
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, 100193 Beijing, China
e-mail: yzliu@implad.ac.cn

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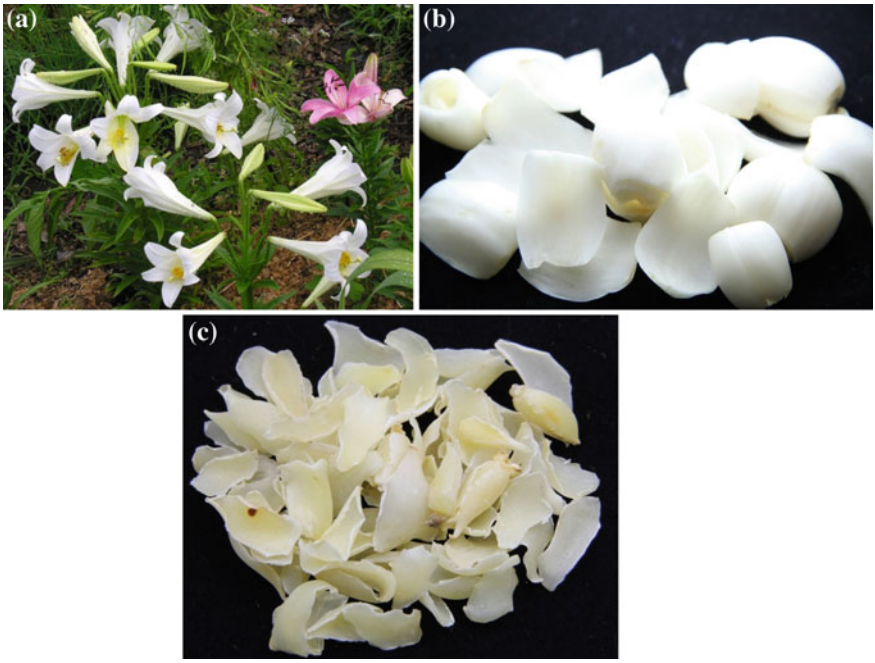
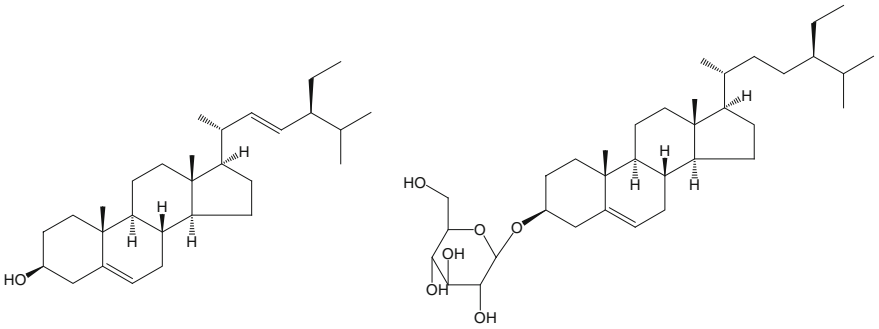


Fig. 15.1 The flowering plant (**a**), fresh bulb scales (**b**), and dried bulb scales (**c**) of *Lilium. brownii* F.E. Brown var. *viridulum* Baker

The part used in Chinese medicine is the bulb. For medicinal use, the lily bulbs should be harvested in the fall. Harvesting includes excavation, washing, stripping scale leaves, dipping in boiling water briefly and drying. Quality of Baihe consists of white bulb scales that are hard and fleshy. Dried bulb scales for medicine are hard and fragile, fracture relatively even, horny, odorless, and taste slightly bitter (Fig. 15.1).

15.2 Chemical Constituents

Either as a common nutritional food or as a frequent used herbal medicine for *Yin*-deficiency, Baihe is frequently used in life. However, the chemical components, especially the marker and/or active one are not certain so far. There are many reports dealing with alkaloids like colchicine [3], phenolic compounds like gallic acid, epicatechin, kaempferol, and rutin [4, 5], and polysaccharides, but steroidal saponins seem to be more significant components for some pharmacological or clinical effects. Stigmasterol (**1**) and *β*-daucosterol (**2**) are two representative compounds among such kind of components, and stigmasterol showed activity to relieve cough and decrease inflammation reaction [6, 7] (Fig. 15.2).



Stigmasterol, **1** β-daucosterol, **2**

Fig. 15.2 Representative steroidal saponins isolated from Baihe

15.3 Pharmacological Studies

Phenolic compounds naturally occur in all plant material, and are prominently ubiquitous in fruits, vegetables, seeds, and herbs, but also in plant products, such as beverages, wine, and cocoa [8]. These compounds are potent antioxidants and play an important role in human nutrition as preventative agents against several diseases, and protecting the body tissues against oxidative stress [9]. As an important group of secondary metabolites presented in *Lilium*, phenolic compounds play an important role in the quality and nutrition value of lily species [10]. Recent reports disclosed three major classes of bioactive antibacterial compounds of the methanol extract of lily bulbs that exhibited strong antioxidant activity: total phenolic contents, total flavonoid contents and total flavanol contents [6]. The difference of phenolic composition might explain the different antioxidant abilities of lily bulb extracts observed. It can be also speculated that phenolic compounds present in the extracts may exert their antioxidant capacity individually as well as synergistically. Flavanols, a subgroup of the flavonoid family, have demonstrated positive effects with human health, including the recovery of endothelial function, improvements in insulin sensitivity, decreased blood pressure, and reductions in platelet aggregation [11].

Rutin is a type of flavonol with various biological activities that may protect against spatial memory impairment accompanying hippocampal pyramidal neuron loss [10]. Kaempferol was mainly abundant in *L. lancifolium.* The flavonols kaempferol and quercetin have been reported to effectively recycle vitamin E (an antioxidant) and are also known to reduce inflammation, tumorogenesis, and cell damage caused by oxidation [12, 13].

Researchers had investigated the anti-inflammatory effects of methanol extract of *L. lancifolium* Thunb root in LPS-stimulated Raw264.7 cells. The results showed that methanol extract significantly inhibited NO, PGE, IL-6, and TNF-production in LPS-stimulated cells. They also found that the iNOS and COX-2 expression was

suppressed simultaneously. The mechanism-based study in this paper indicates that anti-inflammatory effects of methanol extract from *L. lancifolium* Thunb root are due to down-regulation of iNOS and COX-2 via suppression of NF-B activation and nuclear translocation as well as blocking of ERK and JNK signaling in LPS-stimulated Raw264.7 cells [14].

Water extract of *L. lancifolium* Thunb root was found to significantly inhibit the number of macrophages and neutrophils in BALF due to pulmonary inflammatory response in a CS-exposed mouse. It also reduced the protein secretion levels of TNF-α, IL-6, IL-1β, and MCP-1 in BALF and the RNA expression levels of TNF-α, IL-6, IL-1β, MCP-1, and MMP-12 in lung tissue compared with mice only exposed to CS. Moreover, MMP-12 in serum was down-regulated in *L. lancifolium* Thunb root water extract treated mice contrasted with CS-exposed mice. The water extract treated mice demonstrated a significant reduction in air space size compared to mice only exposed to CS [15].

15.4 TCM Applications and Dietary Usage

15.4.1 TCM Applications

Due to their health promoting properties to treat chronic bronchitis, pneumonia fatigue, anxiety, and some sleep problem related symptoms [12, 16], Baihe has been extensively used as a traditional Chinese herbal medicine for many centuries in China.

Based on TCM theory, Baihe's major Chinese medicine uses are: moisten the lung and nourish lung yin, relieve coughs, calming state of mind and calming anxiety. Syndromes to be treated: cough due to yin deficiency, sputum with blood, insomnia and restless sleeping. Some formula has been used widely: (1) Liqi Dingchuan Pill: cough due to yin deficiency; (2) Jieyu Anshen Granule: clearing heart and anti-anxiety.

15.4.2 Dietary Usages

Baihe has been broadly used as nutritional food to provide nourishment as a tonic [17, 18], as well as herbal medicine for many centuries in China, Korea, Japan, and other countries. Baihe bulbs are sweet and can be eaten in dried or fresh form. In China, the bulb scales are commonly cooked in water, or fresh fried as a regular vegetable. They may also be baked, grated or ground into flour. They are traditionally eaten in the summer season, as they have been believed to have cooling and moistening effects to all the body organs.

15.4.3 Soup and Tea

Lily Almond Porridge consists of 30 g of Lily, 9 g of peeled almonds in a wok with 100 g of rice. Lily porridge is used for the treatment of dry cough caused by lung-yin deficiency. It can also be a treatment for heart deficiency caused by insomnia, irritability, and anxiety etc.

15.5 Safety Evaluation and Toxicity

Lilium bulbs have been used as a medicine and a nutrient for centuries in China. For medical purposes, the recommended dose is around 9–30 g. To date, there is no clinical report on the toxicity or side effect available, which could be directly related to the use of *L. lancifolium* and other species.

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Chapter 16
Morinda officinalis How 巴戟天 (Bajitian)

Ping Ding

16.1 Botanical Identity

Bajitian, the root of *Morinda officinalis* How in the family of Rubiaceae, is one of the most popular Chinese herbal medicine native to the Lingnan range in southern China. It is cultivated in Guangdong and Fujian provinces, and is used as a health food. The medicinal root of *M. officinalis* is cylinder-shaped (with round circumference of the section) and slightly curved. The surface is yellowish-gray or dark gray. The bark of the root is thick, violet or light violet in colour, and easy to separate from the xylem. It is used for medicinal purposes. There are 20–25 species of genus *Morinda* in the world. But some related species, such as *M. shuanghuaensis* C.Y. Chen et M.S. Huang, *M. parvifolia* Bartl. et DC. are often adulterants. Only *M. officinalis* How is the legal source recorded in the Pharmacoepia of People's Republic of China [1] and all historical records of Chinese herbal works. Typically, *M. officinalis* grows to the height of between 40 and 60 cm. Leaves are opposite, oblong, 5–12 cm long, and 2–5 cm wide. Flowers are white and sessile with 2–10 jointed together to form a subglobose head that is 5–9 mm across. Fruits are syncarpous, yellow-red in color, 6–11 cm across, fleshy, and contain many pyrenes. Seeds are oblong and wingless [2].

Bajitian mainly comes from artificial cultivation. The root is harvested in late-fall, between November to December of the fourth or fifth years plant. Then washing, drying in the sun, individually beating with a wooden club when the root is 70–80 % dry, and returning them to the sun until completely dried. The final product often appears as broken 1–2 cm sections after removing the xylem as raw material, they have the appearance of a chicken's intestine, hence called "Ji-chang-feng" (Chicken

P. Ding (✉)
School of Chinese Materia Medica, Guangzhou University of Chinese Medicine, Guangzhou 510406, China
e-mail: dingpinggz@126.com

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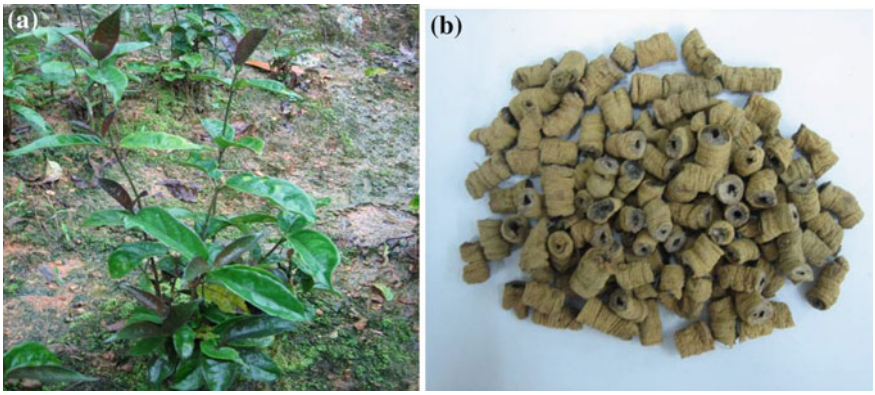

Fig. 16.1 The plant (**a**) and crude drug (**b**) of Bajitian

Intestine Feng). For different medicinal purposes, the raw materials are prepared as steamed Bajitian, salted Bajitian and liquoriced Bajitian, etc. [3] (Fig. 16.1).

16.2 Chemical Constituents

Anthraquinones, iridoids and oligosaccharides are the main bioactive compounds in the root of *M. officinalis* How. Other constituents, such as steroid, amino acid, volatile components and microelements can also be found [4, 5].

16.2.1 Anthraquinones

As the main effective component in the root of Bajitian, anthraquinones were first studied in 1986 [6]. They have extensive pharmacological effects as antibacterial, antivirus, antihypertensive lipid et al. So far, more than 20 anthraquinones have been isolated from Bajitian, which all share the same basic skeleton structure of anthraquinone with different other substituting groups like-methyl, -methoxyl, -hydroxy, and -hydroxymethyl. Rubiadin (**1**), Rubiadin 1-methylether (**2**) and Physcion (**3**) (shown in Fig. 16.2) are representative components and used as standard compounds for evaluation of the quality of crude drug Bajitian and related pharmaceutical or natural health product preparations containing Bajitian [4].

16.2.2 Iridoids

Iridoids, as one of the major classes of bioactive compounds in Bajitian, were found in 1987, right after anthraquinones. Monotropein (**4**) possesses a strong anti-

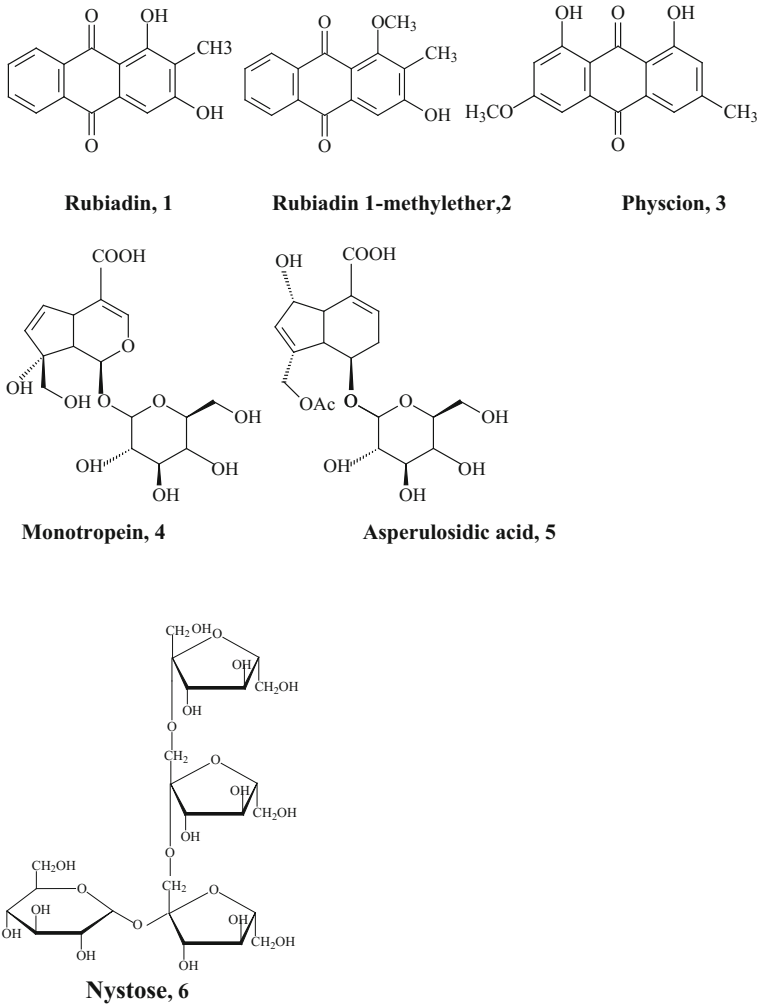

Fig. 16.2 Representative anthraquinones, iridoids, and oligosaccharides isolated from Bajitian

inflammatory and analgesic effect, which is consistent with the effect of removing wind-dampness of Bajitian. Monotropein (**4**) and asperulosidic acid (**5**) are representative iridoids isolated from Bajitian [7] (shown in Fig. 16.2).

16.2.3 Oligosaccharides

Oligosaccharides, the significant compounds in the root cortex of Bajitian, are account for as much as 18.9 % of dry weight. Because of their high water solubility,

significant activity in anti-depression and certain effect on improving reproductive capacity of Kidney-yang deficiency rats, oligosaccharides have been studied widely and deeply. Four inulin-type oligosaccharides were obtained for the first time in 1995 [8] in the study of anti-stress effect. Nystose (**6**, shown in Fig. 16.2) was used as the standard compound for evaluation of the quality of Bajitian in Chinese Pharmacopoeia (2010). More oligosaccharides, such as inulotriose, inulotetraose, and inulopentaose were isolated from Bajitian later [9].

16.3 Pharmacological Studies

As previously mentioned, Bajitian is one of the most popular and commonly used herbal medicines in TCM, especially for almost all the diseases related to the Kidney-yang deficiency. It has been extensively used as a Yang-tonifying drug for a long time in China. Warming and tonifying the kidney-yang and replenishing vital essence can be good for preventing or treating a wide range of symptoms, including depression, poor digestion, high blood pressure, respiratory problems, immune deficiencies, inflammation and osteoporosis. Modern pharmacological studies have indicated Bajitian to have the following multifarious biological activities: protective effect on bone loss and age-induced bone degeneration, anti-fatigue, antioxidant, hypoglycemic and immunomodulation agents [10]. The principal bioactive constituents of Bajitian are anthraquinones, which were reported to exhibit anti-inflammatory, antinociceptive, antioxidant, antihepatotoxic and antimutagenic, antiosteoporotic [11]. Oligosaccharides, another important constituents, have been shown to possess antidepressant, antistress and angiogenesis promoting effects [12].

16.4 TCM Applications and Dietary Usage

16.4.1 TCM Applications

Bajitian is one of the most commonly used herbal medicines and health-maintaining products. As the best known herb for kidney and related diseases, it shows the treatment and health-care function in the following five aspects: reinforcing kidney to strengthen yang, warming and tonifying the kidney-yang, storing the essence and dominating reproduction, strengthening the tendons and bones, and dispelling wind-dampness. Bajitian could be used on its own or in combination with other herbs based on TCM theory.

Common clinically use of Bajitian preparations including the following forms: (1) Bajitian Oligose Capsule [13]. It is composed of *M. officinalis* oligosaccharide. The capsule is the first anti-depression patented drug in China, selective serotonin reuptake inhibitor, which is developed by Beijing Tongrentang Co., Ltd. Bajitian Oligose Capsule is effective, similar to fluoxetine hydrochloride tablets and safe in

the treatment of mild and moderate depressive episode, superior to the latter treatment of traditional Chinese medical symptoms. It is mainly used for the treatment of depressive disorders caused by deficiency of the kidney, such as depressed mood, panic, insomnia and dreaminess, anxiety and oversensitive, weary and feebleness, sexual hypoactivity, tinnitus and amnesia through tonifying the kidney-yang. (2) Compound Baji Capsule [14]. It composed of sixteen herbal components: *M. officinalis*, *polygonum multiflorum*, *Eucommia ulmoides*, *Cistanche deserticola*, *Epimedium brevicornum* and so on. It is mainly used for the treatment of waist and knee weakness and irregular menstruation. Besides, it is also helpful for osteoporosis. (3) Chuankezhi Injection [15]. Two herbs, *Epimedium brevicornum* and *M. officinalis*, have been used to prepare Chuankezhi Injection. The products was used as a kind of immunomodulator for the treatment of bronchial asthma in clinical. (4) Baji Zhenyang Tablets. It is composed of six herbal components: *Epimedium brevicornum*, *Panax ginseng*, *Acanthopanax senticosus*, *Carthamus tinctorius* and *M. officinalis*. The product is one of the proprietary Chinese medicines for the treatment of male diseases like impotence. (5) Bajitian extract is a very convenient form of administration, which can be made from single Bajitian or mixed with other herbs. The significant advantage of this form is ease of use and readily available for absorption; (6) Preparations made from active components including polysaccharides, oligosaccharides, monotropein, anthraquinones are also in the market as chemical drugs.

16.4.2 Dietary Usages

As one of the most famous herbs and valuable dietary botanical materials, Bajitian has been used in many ways historically due to the effectiveness and sweet taste, such as Bajitian tea, Bajitian wine, Bajitian soup, Bajitian oral liquid, and Bajitian extract. The following dietary forms can be easily made at home.

16.4.2.1 Bajitian Teas [16]

Herbal tea made of Bajitian alone or mixed with other herbs is the most common way. For instance: Bajitian Tea composed of Bajitian (5 g) and black tea (3 g); The tea composed of Bajitian (12 g), Yizhiren (*Alpinia oxyphylla*, 10 g) and Fupenzi (*Rubus chingii*, 12 g) could be helpful for kidney deficiency; BajiShanzhuyu Tea composed of Bajitian (30 g) and Shanzhuyu (*Cornus officinalis*, 30 g), is useful for Nephrotic Syndrome in children with Cushing Syndrome; BajiGouqi Drink composed of Bajitian (15 g), Gouqizi (*Lycium barbarum*, 15 g). To make the herbal tea, softened water or natural water with less mineral and alkaline is recommended in order to reduce the decomposition of active ingredients.

16.4.2.2 Bajitian Wine [17]

Bajitian itself or combined with other herbs can be used to prepare herbal wine for Kidney-yang deficiency and related diseases. There are several typical examples: soaking Bajitian without xylem (60 g), Shudihuang (*Rehmannia glutinosa*, 45 g), Gouqizi (*Lycium barbarum*, 30 g), Zhifuzi (processed *Aconitum carmichaeli*, 20 g), Ganjuhua (*Chrysanthemum lavandulifolium*, 60 g) and chuanjiao (*Zanthoxylum*, 30 g) in 1.5 L of Chinese spirit or vodka for 5 days or more. Drinking 25–50 mL daily is recommended; soaking Bajitian (1800 g) and Niuxi (*Achyranthes bidentata*, 1800 g) in 30 L of Chinese spirit or vodka for one week or more. Drinking 10–20 mL daily is recommended. In addition, Bajitian can also be used to make herbal wines in combination with many other herbs depending on the specific function need. Daily intake amount will be based on the content of herb and alcohol.

16.4.2.3 Bajitian Used in Medicated Foods

Bajitian can be used to make soups with rice or meat. A conventional and typical way is to boil Bajitian or combined with other herbs, such as Tusizi (*Cuscuta chinensis*), Rougui (*Cinnamomum cassia*) with rice or meat, such as chicken, pork, mutton and dog meat together. This nutritious rice porridge or soup can be used for endogenous cold syndrome marked by pallor, cold limbs, lassitude, weakness and soreness in the waist and knees, impotence, and sterility caused by Kidney-yang deficiency.

Red dates, black soya bean, peanuts, and most corns or vegetables can also be cooked with Bajitian to take advantage of the health-maintaining effect of Bajitian. The taste of Bajitian-containing foods can be adjusted based on personal preferences.

16.5 Clinical Evidences

Bajitian is mostly used in combination with *Epimedium davidii* Franch as tonic (i.e. Chuankezhi Injection and Yikang Medicinal Liquor). Clinical and observational studies reported the effect of Bajitian and its related preparations on diseases caused by depressed, immunodeficiency, and impotence. Bajitian may have effect on the function of hypothalamus-hypophysis-gonadal axis, and less reaction of the parasympathetic nerve-M receptor to cure impotence as well as depression. Its water extract showed anti-depression pharmacological activity on 18 patients [18]. For the Chuankezhi Injection, clinical reports showed that the preparation could cure mild and moderate asthma [15]. For Er-xian Decoction [19], clinical observation indicated that the prescription respond to Partial Androgen Deficiency in Aging Male (PADAM), especially for prostatitis patients.

16.6 Safety Evaluation and Toxicity Data

Few clinical reports on the toxicity or side effects are available which is directly related to the use of Bajitain. Animal studies also have shown no noticeable toxicity for various organs through oral administration. Dosage of 250 g/kg QID of Bajitian decoction was given to mice via oral administration; there was no death within 72 h. Its water extract showed no effect on the SOS response (DNA damage response) system of *E. coli* PQ37 in vitro, which indicated Bajitian water extract have no mutagenic or induced mutagenesis effect [20].

Though Bajitian is definitely a relatively safe herbal medicine often used in health-maintaining products and for the treatment of impotence, attention must also be paid when you decide to use this herb personally without doctor's advice, as it is obvious that Bajitian has strong biological activity and cannot be used as a regular food. It's strongly suggested to ask your doctor if it is right for you.

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Chapter 17
Ophiopogon japonicus (Thunb.) Ker-Gawl. 麦冬 (Maidong, Fountain Plant)

Li-mei Lin and Xiao-liang Zhao

17.1 Botanical Identity

The roots of *Ophiopogon japonicus* are moderately thick, usually with tuberous part near middle or tip. Leaves are basal, tufted, sessile, grasslike, generally 10–50 cm × 2–4 mm, 3–7-veined and margin serrulate. Scape is 6–15(–27) cm, much shorter than leaves. Inflorescencea is a reduced panicle, 2–5 cm, several to more than 10-flowered; bracts lanceolate, basal one 7–8 mm. Flowers are solitary or paired, usually nodding; pedicel is 3–4 mm, articulate is near middle. Tepals are white or purplish, lanceolate, ca. 5 × 2 mm. Filaments are very short; anthers are 2.5–3 mm. Style is somewhat narrowly conical, ca. 4 mm, moderately thick, basally widened. Seeds are globose, 7–8 mm in diameter [1].

Ophiopogon japonicus mainly grows in China specifically in the regions Zhejiang and Sichuan, however it is also produced in Guangxi, Hubei, Fujian, Yunnan, Guizhou and Anhui. Maidong on the market are mostly grown products. The demand of Maidong is not only in China, but in Japan and southeastern Asian countries [1].

Maidong is fusiform meaning it slightly tapers at both ends of the herb and is 1.5–3 cm long, 3–6 mm in diameter. The exterior appearance is a color of a yellow tint with irregular and longitudinally wrinkled appearance. The odor of Maidong is slightly aromatic, with a sweet but slightly bitter taste [2].

The herb is collected in the summer, washed clean, sun-dried, and then the roots are removed. These procedures are generally carried out before clinical use. The commonly used processing methods are cleansing, stir-frying, stir-frying with wine,

L. Lin
School of Pharmacy, Hunan University of Chinese Medicine, Changsha 410208, China

X. Zhao (✉)
Experimental Research Center, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: zhaoxiaoliang1218@aliyun.com

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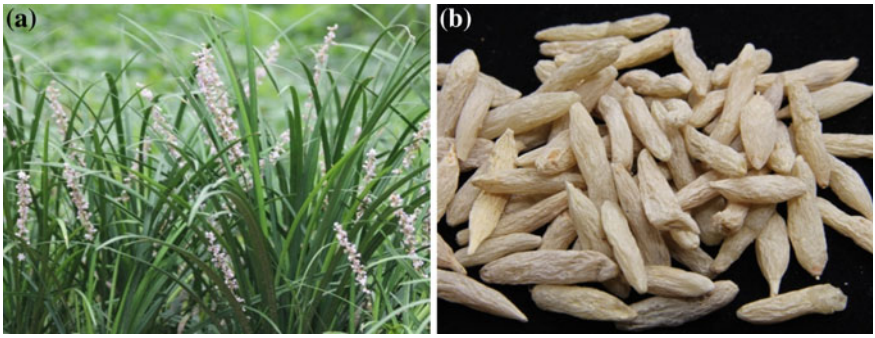


Fig. 17.1 The flowering plant (**a**) and crude drug (**b**) of Maidong

stir-frying with rice, stir-frying with cinnabar, etc. The cleansing method is to eliminate foreign matter, and to soften the herb (Fig. 17.1).

17.2 Chemical Constituents

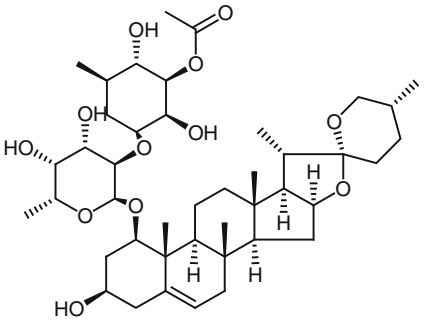
Saponins and flavonoids are two major kinds of active compounds found from the roots of *Ophiopogon japonicus* (Thunb.) Ker-Gawl. [3].

17.2.1 Saponins

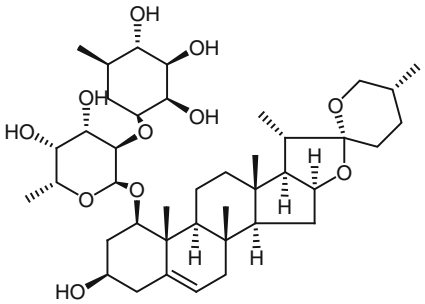
Maidong contains a variety of steroidal saponins, such as ophiopogonin A (1), ophiopogonin B (2), ophiopogonin B′, ophiopogonin C, ophiopogonin C′, ophiopogonin D, ophiopogonin D′ (Fig. 17.2).

17.2.2 Flavonoids

The flavonoids of Maidong are homo-isoflavonoids including 5,7-dihydroxy-8- methoxy-6-methyl-3-(2′-hydroxy-4′-methoxybenzyl)chroman-4-one, 7-hydroxy-5,8-dimethoxy-6-methyl-3-(2′-hydroxy-4′-methoxybenzyl)chroman-4-one, 5,7-dihydroxy-6,8-dimethyl-3-(4′-hydroxy-3′-methoxybenzyl)chroman-4-one, 2,5,7-trihydroxy-6,8-dimethyl-3-(3′,4′-methylenedioxybenzyl)chroman-4-one and 2,5,7-trihydroxy-6,8-dimethyl-3-(4′-methoxybenzyl)chroman-4-one [4]. In addition, ophiopogonone A (1), ophiopogonone B (2), isoophiopogonone B, 6-aldehydo-

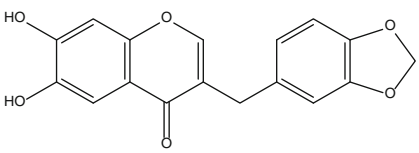


Ophiopogonin A, 1

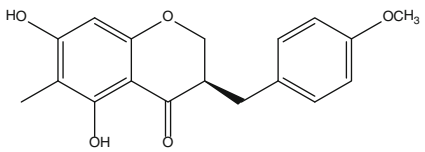


Ophiopogonin B, 2

Fig. 17.2 Typical saponins isolated from Maidong



Ophiopogonone A, 1



Ophiopogonone B, 2

Fig. 17.3 Typical flavonoids isolated from Maidong

isoophiopogonanone A, methylophiopogonanone B, methylophiopogonanone A, 6-aldehydo-isoophi-opogonone A, and 6-aldehydo-isoophiopogonone B have been identified in Maidong [5] (Fig. 17.3).

17.3 Pharmacological Studies

Maidong is widely used for cardiovascular diseases. Maidong can treat myocardial ischemia and myocardial infarction with dose-response relationship [6]. It has been proven to improve myocardial ischemia, and enhance force of cardiac muscle through vitro and vivo test models such as toads, rats and rabbits. The total saponins and total polysaccharides in Maidong can increase nutritional blood flow of cardiac muscle in mice. The total saponins and polysaccharides of Maidong have protective efficacy of myocardial ischemia [7]. Maidong has a positive effect on ventricular arrhythmias triggered by myocardial hypoxia and ischemia induced by coronary artery ligation in dogs [8]. In addition, the n-butanol extract of Maidong can prevent and treat thrombosis by maintaining endothelial physiological function [9]. Lastly, Maidong can increase the immune system [10], treat hypoxia [11] and scavenge free oxygen radical [12].

17.4 TCM Applications and Dietary Usage

17.4.1 TCM Applications

Maidong can nourish *Yin* and promote the production of body fluids, moisten the lungs, and anchor the mind. It can be used to relief dry and phthisical cough, thirst (due to impairment of body fluids, and/or internal heat), restlessness and insomnia, constipation and diphtheria. Shengmai powder composed of Renshen (root of *Panax ginseng*, 9 g), Maidong (root of *Ophiopogon japonicus*, 9 g) and Wuweizi (fruit of *Schisandra chinensis*, 6 g) is a famous prescription for treating diabetes. Maidong Decoction composed of Maidong (root of *Ophiopogon japonicus*, 60 g), Banxia (root of *Pinellia ternate*, 9 g), Renshen (root of *Panax ginseng*, 6 g) and Gancao (root of *Glycyrrhiza uralensis,* 4 g) is always used for treating chronic bronchitis, bronchiectasis and chronic pharyngitis.

17.4.2 Dietary Usages

Maidong possesses sources of various steroidal saponins, homo-isoflavonoids, β-sitosterols, stigmasterols, amino acids, glucoses, polysaccharides, vitamin A, and other trace elements. Apart from its medical function, it can be utilized as an ingredient for healthy foods which prevent disease and preserve health, such as: in tea, soup, porridge, brewing wines and cooking cuisine.

17.4.2.1 Juhua Maidong Tea

Composition: Juhua (flower of *Dendranthema morifolium*) 10 g, Maidong (root of *Ophiopogon japonicus*) 10 g, Jinyinhua (flower of *Lonicera japonica*) 10 g.

Preparation: Put all materials in a teapot, add boiling water and steep for 5 min.

Function: Clearing heat, resolving thirst and relieving inflammation of throat.

17.4.2.2 Moli Maidong Tea

Composition: jasmine flower 4 flowers, Maidong (root of *Ophiopogon japonicus*) 1 g, Shanzha (fruit of *Crataegus pinnatifida*) 2 g and green tea 2 g.

Preparation: Soak all materials in boiling water for 20 min.

Function: To moisten the lungs, tender skin and remove spots on the face.

17.4.2.3 Maidong Wine

Composition: Maidong (roots of *Ophiopogon japonicus*) 30 g and low-alcohol-content wine 2000 ml.

Preparation: Pound Maidong to pieces, then put into bottle with wine and steep for 1 month.

Function: It applies for those who have deficiency of kidney, asthma or constipation.

17.4.2.4 Maidong Milk

Composition: Maidong (root of *Ophiopogon japonicus*) 50 g, milk 200 g and sugar 30 g.

Preparation: Put clean Maidong into a pot and add 50 ml water. Heat it to boil and then simmer for 20 min. Filter Maidong with gauze and keep liquid. Boil the milk, then mix with Maidong juice and sugar.

Function: To nourish Yin, remove heat, produce diuretic and anti-inflammation effect.

17.5 Clinical Evidences

Maidong is usually combined with other traditional Chinese medicines (more than five kinds of TCM) in clinical use, and mostly used in *Traditional Chinese Medicine Patent Prescription*, such as: in Kouyan Keli, Fufang Maidong Wan, Guben Kechuan Pian, Chuanbei Xueli Gao, Shashen Maidong Runfei Keli and Shen Mai Injection.

Treatment of coronary heart disease: Maidong Decoction (1.5 g crude/ml) was oral administration, 10 ml every time, 3 times per day for 3–18 months. Therapeutic effects were evaluated by ECG and symptoms improvement. The total effective rate was 74 % in 50 patients in symptoms improvement. The total effective rate was 40.5 % in 42 patients in ECG improvement.

17.6 Safety Evaluation

Maidong is safe and can be used both as medicine and as food. Clinical study of chronic pharyngitis shows that Shashen-Maidong decoction are no adverse reactions for 97 patients [13].

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Chapter 18
Paeonia lactiflora Pall. 芍药 (Shaoyao, Chinese Herbaceous Peony)

Feng Zhang, Yin Lu, Wenhui Qian and Zifan Pei

18.1 Botanical Identity

Shaoyao, a well-known Chinese herb, has been used for more than two thousand years and was originally prescribed for typhoid. During the Southern and Northern Dynasties (420–581 CE), Shaoyao was recorded as either Chishao and Baishao, as their medicinal uses were not really distinguished and they were both derived from the same wild variety of *Paeonia lactiflora* Pall [1]. Since then, Chinese pharmacopoeia has categorized Shaoyao as two different herbs: Baishao and Chishao. Each variety of herbs has different methods of cultivation and processing as well as different clinical applications; however, they have many biological characteristics in common. In terms of plant origin and biology, Chishao and Baishao are both from *Paeonia* in the Buttercup Family. Chishao is the dry root of *Paeonia lactiflora* Pall. Or *Paeonia veitchii* Lynch. Harvested in spring and autumn, the rhizome and fibrous roots are removed and the roots are dried. Whereas for Baishao, the roots of *Paeonia lactiflora* are harvested and then boiled to remove the cortex, or cortex removed and boiled, and then dried [2]. *Paeonia lactiflora* Pall. is mainly grown in Inner Mongolia, Heilongjiang, Jilin and Liaoning provinces of China, while *Paeonia veitchii* Lynch mainly comes from Sichuan province and most of them are wild plants. In contrast, Baishao is from the provinces of Anhui (Bozhou area), Zhejiang (Hangzhou area) and Shandong (Heze area) and most of them are cultivated (Fig. 18.1).

F. Zhang · Y. Lu (✉) · W. Qian · Z. Pei
Department of Pharmacology, College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China
e-mail: luyingreen@126.com; nucmzf@163.com

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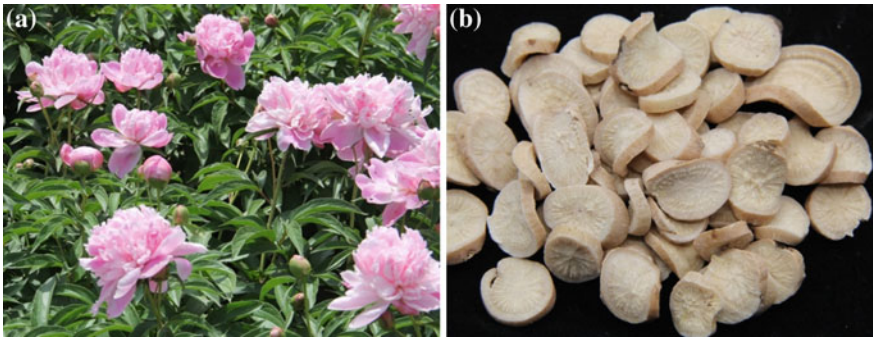


Fig. 18.1 Flowering plant (**a**) of *Paeonia lactiflora* Pall. and crude drug of Shaoyao (**b**)

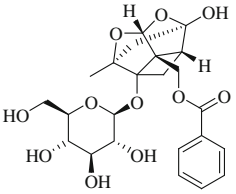
18.2 Chemical Constituents

Researchers have studied the chemical components of Baishao and Chishao systematically for a long time. The main classes of chemical constituents isolated from the two kinds of herbs of Shaoyao are: monoterpene glycosides, polyphenolic compounds, flavonoids, daucosterol, etc. [3]. Paeony monoterpene glycosides mainly include paeoniflorin (**1**), albiflorin, oxypaeoniflorin and benzoylpaeoniflorin (**2**), etc., and are collectively called glycosides of paeony. Another major group of components, polyphenolic compounds are mainly composed of paeonol (**3**), pentagalloyl glucose (**4**) and other analogs. These have been generally accepted as the main bioactive components of the two medicinal herbs of Shaoyao based on modern pharmacological data.

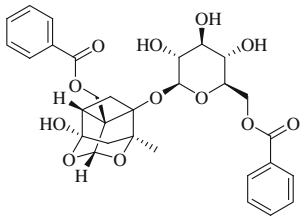
Chemically, Chishao and Baishao are very similar in terms of composition profiles due to the same botanical source. However, as the growth environment and post-harvest processing for the two herbs are slightly different, the contents of the active components may vary [4]. For example, in comparison with the wild unprocessed Chishao, Baishao contains lower levels of gallic acid, peoniflorin, pentagalloylglucose and paeonol, which are likely removed with the peeling of root cortex and the boiling process. However, the content of albiflorin (**5**) in Baishao is much higher compared with that in Chishao. In fact, it is the second principal component after paeoniflorin in Baishao. Representative structures of these constituents are shown in Fig. 18.2.

18.3 Pharmacological Studies

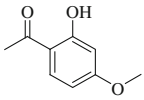
Total glucosides of paeony (TGP) isolated from Baishao is the general name of peony monoterpenes and paeoniflorin. TGP has been reported to have a variety of pharmacological activities including the activities of anti-arthritis [5–8], liver protection [9, 10], antidepressant [11], anti-inflammatory and analgesic [12].



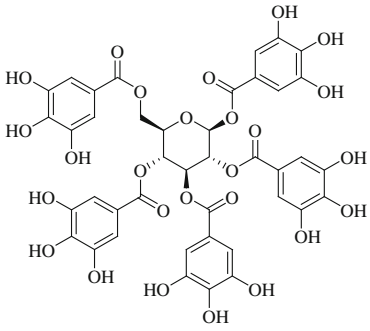
Paeoniflorin, 1



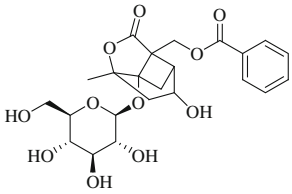
Benzoylpaeoniflorin, 2



Paeonol, 3



1,2,3,4,6-*O*-Pentagalloylglucose, 4



Albiflorin, 5

Fig. 18.2 Chemical structures of major constituents in Shaoyao

For example, studies demonstrated that paeoniflorin could induce the Th1 cells immune tolerance, which then shifted to Th2 and Th3 cells-mediated activities to generate the anti-inflammatory and immune-regulatory effects [5]. TGP was also found to significantly inhibit the progression of adjuvant arthritis, and the inhibitory effects might be associated with its ability to regulate the level of cAMP and reduce the production of IL-1, TNF-α, IL-6 and PGE2 from activated synoviocytes [6]. Paeoniflorin significantly protected against immunological liver injury in mice and the protective mechanism was related to the modulation of TNF-α, IL-6, LBP and CD14 mRNA expression in mouse liver [9]. Furthermore, intragastric administration of TGP at 80 and 160 mg/kg for seven days caused a significant reduction of immobility time in both forced swim and tail suspension tests, yet TGP did not stimulate locomotor activity in the open-field test. TGP treatment antagonized

reserpine-induced ptosis and inhibited the activities of monoamine oxidases in mouse cerebrum, suggesting that the antidepressive effects of TGP were mediated, at least in part, by inhibition of monoamine oxidases [11].

18.4 TCM Applications and Dietary Usage

18.4.1 TCM Applications

Baishao and Chishao are both common TCM herbs and widely used to treat diseases related to immune and cardiovascular systems. According to TCM theory, both Baishao and Chishao are of cold nature, and have Heat-clearing effects. But Baishao is a tonic drug and is adept in nurturing Blood and suppressing the Yang of the Liver. However, Chishao is a Heat-clearing drug and good at removing Heat to cool Blood and eliminating stasis. Also, Baishao tastes bitter, sour, sweet, and slightly cold, and it belongs to the Liver and Spleen channels in TCM system. It has the functions of enriching Blood and regulating menstruation, calming Liver and relieving pain, and retaining Yin and suppressing sweating. It is often used to treat irregular menstruation with deficiencies in Blood and Yin, perspiring during sleep, headache and pain in other body parts due to deficiency of Liver Yin [13]. Chishao, on the other hand, tastes bitter and slightly cold, and belongs to the Liver channel. It removes Heat and cools Blood, eliminates stasis and relieves pain, and is used to treat Blood-Heat and hematemesis, ocular pain and redness. The differentiation on clinical use of these two related herbs is clearly described in TCM: Baishao is for replenishing Blood and retaining Yin; Chishao is good at clearing Heat and removing Blood stagnation [14].

18.4.2 Dietary Usages

18.4.2.1 Shaoyao Wine

It is recorded in General Medical Collection of Royal Benevolence that Shaoyao wine is composed of Shaoyao, Huang Qi (root of *Astragalus membranaceus*), Shengdihuang (root of *Rehmannia glutinosa*) and Aiye (leaf of *Artemisia eargyi*) and made by immersing the herbal materials in the wine for 12 h. To be drunk warm in moderation before meals, it helps with leucorrhea and menstruation for women.

18.4.2.2 Shaoyao Used in Medicated Foods

Siwu and chicken soup: ingredients include chicken, Danggui (root of *Angelica sinensis*), Chuanxiong (rhizome of *Ligusticum chuanxiong*), Shudihuang (prepared root tuber of *Rehmannia glutinosa*), Baishao, Gouqizi (fruit of *Lycium chinense*) and Guizhi (twig of *Cinnamomum cassia*). The soup has been used as a dietary therapy in traditional Chinese Medicine for thousands of years. In addition, it has been prescribed for correcting women's pathophysiological functions, such as blood stasis and abnormal menstruation, by enriching and activating Blood and regulating menstruation.

18.5 Clinical Evidences

In traditional Chinese medicine, Baishao mainly refers to the cultivated boiled plant root with the cortex removed, and is used as antispasmodic and painkiller. In an observational trial with 18 subjects, Baishao showed beneficial effects on epilepsy [15]. Another study [16] showed that when Baishao was combined with other herbs in the formula Shaogan Tongluo decoction, it could relieve gastric convulsion, back and abdominal pain. For Chishao, on the other hand, the TCM uses are mainly for dispersing stasis, activating Blood and clearing Liver Heat. It treats irregular menstruation, abdominal, join, and chest pain. For example, in a clinical trial with Chishao and Honghua (flower of *Carthamus tinctorius*) oral liquid preparation, Chishao was shown to have effects of activating blood, relieving muscle spasm, increasing blood flow, and improving myocardial ischemia in 70 % of the 84 patients studied [17]. Chishao was also reported to be effective in treating hyperbilirubinemia when combined with Dahuang (root and rhizome of *Rheum palmatum*) [18]. It was also used in Dahuang Chishao decoction to clear Heat and activate Blood, remove blood stasis and relieve pain. In a trial involving 62 patients with acute appendicitis, 54 subjects recovered after treatment with the Dahuang Chishao decoction [19].

18.6 Safety Evaluation and Toxicity Data

Acute toxicological data show that oral administration of TGP is highly safe. Oral doses of TGP of more than 2500 mg/kg did not cause toxicity or death. In addition, the LD_{50} values for intravenous injection and intraperitoneal injection in mice were 159 and 230 mg/kg, respectively [20]. Furthermore, Chishao was given at a total dose of 80 g/kg via i.g. 2 times within 24 h in mice, and a majority of the mice showed adverse reactions including hair relaxation, infantile myasthenia, reduced activity, slowing breathing and others [21]. The safety evaluation experiments indicated that Baishao is safer than Chishao. In clinical application, there are also

reports of certain side effects related to Chishao. Therefore, caution should be taken when applying them in dietary therapy or medicated food. Professional advice should be sought before use.

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Chapter 19
Panax ginseng 人参 (Renshen, Ginseng)

Yuqing Zhao

19.1 Botanical Identity

Panax ginseng C.A. Meyer is a perennial herb native to Korea and China. It has been used as a herbal remedy in eastern Asia for thousands of years. Ginseng is 60–80 cm tall, its main root being often 5–6 cm long. The herb is fleshy, bifurcate, aromatic, and grayish white to amber yellow. The surface of the root is wrinkled and furrowed, and tastes at first sweet, with a somewhat bitter after taste. Ginseng stem is straight, and deep red in color; its flower is pink; and its fruit, a small berry, is red. The leaves are clustered together, oval, and thin [1]. Sun-dried ginseng (white ginseng), sliced red ginseng, and ginseng in crude drug form are illustrated in Fig. 19.1.

In China, ginseng is mainly produced in Jilin, Heilongjiang and Liaoning. It traditionally was only harvested widely through China, the cultured one has become the main source supply to the market. This is because of the increasing demand for ginseng and huge shortage for wild material. Ginseng needs to grow for 5–6 years to be harvested, and the wild form may even grow for decades. The cultured ginseng root is harvested in fall between September to October. The wild ginseng root is harvested in summer between May to September.

The ginseng root is used as an ingredient in medicines and health foods. Harvested and dried roots can be stored and marketed as raw material. Further processing is done by taking the raw material, after slicing the roots to 5–10 mm thickness and softening with warm water. The sliced product is dried again naturally, or heated in an oven under controlled temperature. All of these procedures must be handled with careful and gentle caution to keep the ginseng as complete as

Y. Zhao (✉)
School of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang, China
e-mail: zyq4885@126.com

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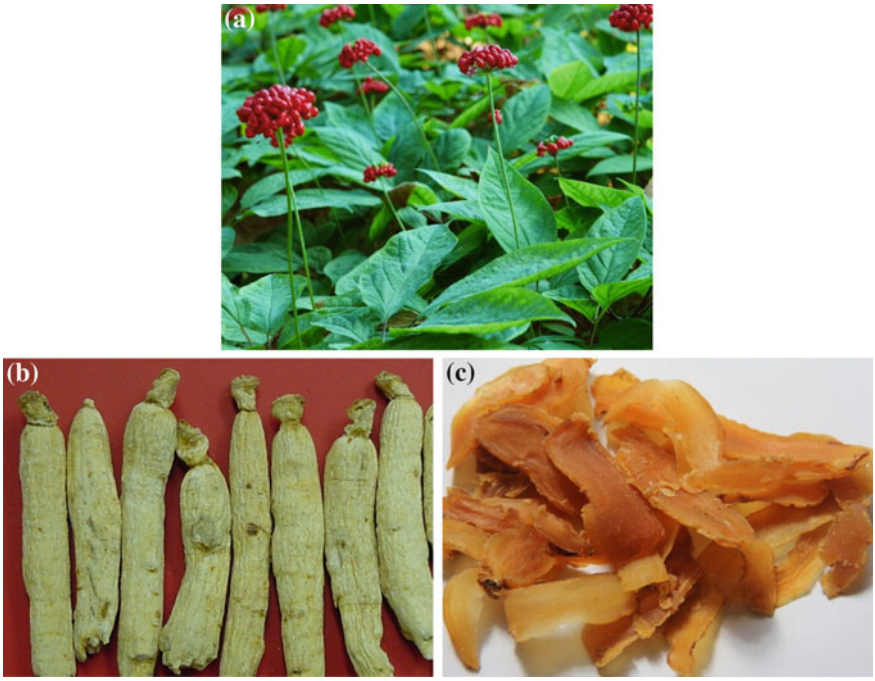


Fig. 19.1 Fruiting plant (**a**), sun-dried ginseng (*white* ginseng, **b**) and sliced *red* ginseng (**c**)

possible. There are also other processing methods for some specific medicinal purposes, including red ginseng and sugar ginseng, etc.

19.2 Chemical Constituents

In general, the active or inactive chemical entities obtained from ginseng species can be classified into four categories as follows.

19.2.1 Saponins

Saponins are glycosides consisting of a sapogenin moiety, which may be a steroid or a triterpene, attached to one or more sugar moieties. Ginseng saponins are generally called ginsenosides and are the main active principles of ginseng. They are often used as marker compounds for the quality control of ginseng and ginseng-containing drugs and commercial products. Ginsenosides can be further classified into the following four types based on the steroidal skeleton and number of hydroxyl groups or sugar moieties attached (Fig. 19.2).

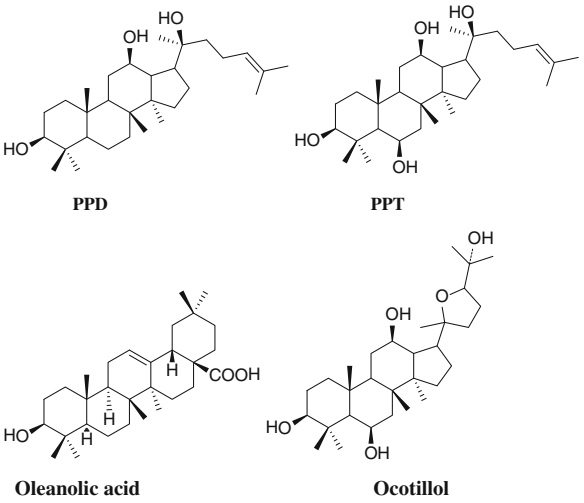
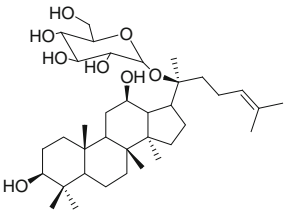


Fig. 19.2 Basic structures of four types of ginsenosides

19.2.1.1 Protopanaxadiol Protopanaxadiols (PPD)

PPD belongs to the dammarane-type ginsenosides, such as ginsenosides Ra_1, Ra_2, Ra_3, Rb_1, Rb_2, and Rb_3, notoginsenoside R_1, R_2, Rs_1, and Rs_2, quinquenoside R_1, malonylginsenoside Rb_1, Rb_2, Rc, and Rd. More than 30 ginsenosides of the PPD type belong to the Rb series. The metabolic pathway of the PPD-type ginsenosides has been extensively investigated, resulting in identification and characterization of several active metabolites. Compound K has been notably identified with a large number of studies showing that compound K has strong antitumor activity [2]. Most of the PPD type metabolic into compound K in human gut and play the final antitumor activity.



Compound K

19.2.1.2 Protopanaxatriol Protopanaxatriols (PPT)

PPT is also dammarane-type ginsenosides, including ginsenosides Re, Rf, Rg_1 and notoginsenoside R_1. The main structural difference between PPT and PPD is the presence of a hydroxyl group or sugar residue at C-6 in the PPT moiety [3].

19.2.1.3 Oleanolic Acid Type

Oleanic acid, including ginsenosides Ro, has a pentacyclic triterpene skeleton.

19.2.1.4 Ocotillol Type

This group has a five-membered epoxy ring at C-20 [4]. Majonoside R_2 from the Vietnamese ginseng is a prototype for this group [5].

19.2.2 Polysaccharides

Ginseng polysaccharides are water-soluble compounds containing various sugar moieties conjugated to uronic acid and include panaxanes A to U. They are acidic polysaccharides and have been shown to possess immunomodulating and anti-proliferative effects. Recent studies have identified an acidic polysaccharide, referred to as "ginsan" with immunostimulatory activity [6].

19.2.3 Polyynes

The polyynes are a group of organic compounds with alternating single and triple bonds. In ginseng, these compounds isolated so far include falcrinol (panaxynol), falcarintriol (panaxytriol), acetic acidor linolenic acid [7].

19.2.4 Flavonoids and Volatile Oil

Besides the compounds mentioned above, some flavonoids and volatile oil also have been investigated and identified from *Panax* genus [7].

19.3 Pharmacological Studies

As described previously, ginseng is one of the most popular herbs used in TCM. Ginseng extracts exhibit multifaceted pharmacological actions in the central nervous system (CNS), cardiovascular system, growth-metabolism system and immune system. Ginseng extracts also possess anti-fatigue, anti-hyperglycemic, anti-cancer, and anti-aging activities as described below.

19.3.1 Effects on the CNS

An early study revealed that ginseng extract caused CNS depression and neuroleptic effects in mice [8]. The extract-induced CNS depression was observed along with a reduction of spontaneous and exploratory movements and the potentiation of hypnotic actions of hexobarbital. It can maintain neuronal membrane system and promote protein synthesis and put off anti-aging effect of neurons. Analgesic and anticonvulsant activities were also confirmed in this study. In addition to this, ginseng extract inhibited conditioned avoidance response in the pole climbing test.

19.3.2 Effects on Cardiovascular System

Ginseng extracts had preservative effects on the cardiovascular systems and prevented myocardial ischemia in animal experiments [9]. Another study [10] confirmed that ginseng extract protects against acute myocardial infarction (AMI) in rats by promoting angiogenesis in the infracted or ischemic area of myocardium [11].

19.3.3 Effects on Growth and Intermediary Metabolism

Ginsenosides from Chinese ginseng have been shown to significantly increase the protein and RNA contents of muscles and liver in rats, as well as accelerate the growth of young pigs. It was suggested that ginsenosides may have direct influence on RNA and protein synthesis [12].

19.3.4 Anti-hyperglycemic Effects

One third of diabetic patients use dietary supplements or alternative medicines [13]. Previous studies indicated that ginseng is an important alternative medicine to treat diabetes and both Chinese and American ginseng roots had anti-hyperglycemic effect [14, 15].

19.3.5 Anti-cancer Effect

The anti-cancer effect of ginseng is an important pharmacological function. Anti-cancer effects of Chinese ginseng extract were found after co-administration of

acidic polysaccharide (from Chinese ginseng) enhanced therapeutic effects, and reduced hematopoietic complications induced by systemic chemotherapy or radiation therapy [13]. Total saponins from *Panax ginseng* protected against cyclophosphamide (a commonly used anti-cancer compound)-induced genotoxicity and apoptosis in bone marrow cells and peripheral lymphocytes in mice [16]. Thus, ginseng extracts can be a new source for anti-cancer drugs.

In animal studies, ginsenosides had many protective activities as discussed above, which can be potentially used to treat human diseases. Ginsenosides Rg_3 and Rh_2 have been reported to have a cell-growth suppressive effect on various cancer cells [17]. Ginsenoside 25-OH-PPD had significant, dose-dependent effects on apoptosis, proliferation, and cell cycle progression and showed preventive effect to cancer cells. Ginsinosides Rh_2 and Rb_1 have also shown activity in reducing ischemic brain injury in rats after oral administration [18].

19.3.6 Anti-aging Effects

A clinical trial showed that *Tongbu* No. 1, a proprietary Chinese medicine formula containing ginseng, improved some symptoms related to aging, improved immune and endocrinal functions, scavenged free radicals and adjusted intestinal flora [19].

19.3.7 Anti-ulcer Effect

Ginseng is used in Chinese medicine to treat gastrointestinal disorders. Research showed that the crude polysaccharide fraction from ginseng exhibited potent anti-ulcer activity against acute gastric lesions in mice [20].

19.3.8 Anti-obesity Effect

Obesity is a serious medical disorder that may cause a myriad of health problems, such as heart disease, hypertension and adult-onset diabetes. Berry, root and leaf extracts of American and Chinese ginseng showed anti-obesity activities in animals. American ginseng extract has also shown to significantly reduce body weight in adult *ob/ob* mice [21–23].

19.4 TCM Applications and Dietary Usage

19.4.1 TCM Applications

Ginseng is one of the most common herbal medicine used in traditional Chinese medicine and health-maintaining products. It has a wide range of therapeutic and pharmacological uses. It has been said to reinforce vital energy, *Yang*-deficiency asthmatics, and spleen-deficiency to treatment and health-maintaining actions. Ginseng could be used as single form or in combination with other herbs based on TCM theory.

Common ginseng preparations clinically used include the following forms: (1) Ginseng monkshood soup. It is composed of two herbal components: 15 g of ginseng and 50 g of cooked Fuzi (roots of *Aconitum carmichaeli Debx*) extracted by boiling in water. The prescription can be taken twice daily for the treatment of *Yang* deficiency asthmatics. (2) 10 g of ginseng, 10 g of Baizhu (rhizomes of *Atractylodes macrocephala Koidz*), 8 g of Fuling (sclerotia of *Poria cocos*), 3 g of Gancao (roots and rhizomes of *Glycyrrhiza uralensis Fisch*), 3 piece of Shengjiang (roots of *Zingiber officinale Roscoe*), a Dazao (fruits of *Ziziphus zizyphus*) also decocted in water. The prescription can be used for treatment of spleen-deficiency.

19.4.2 Dietary Usages

The historically diverse uses of ginseng has given it one of the most famous reputations of herbs, due to its valuable dietary botanical material. These include ginseng tea, ginseng wine, ginseng soup, ginseng candy. The following dietary forms can be easily made at home. Ginseng has been approved as a new resource food, from the legal level can feed medicine combination.

19.4.2.1 Ginseng Wine

Ginseng itself or combined with other herbs can be used to prepare herbal wine. The wine is used to strengthen the weak body and treat the impotence. One example of a recipe includes ginseng (60 g) is soaked in 500 mL of Chinese spirit or vodka for more than a week. Drinking 25–50 mL daily is recommended. Ginseng can also be used to make herbal wines in combination with many other herbs depending on the specific need of functions.

19.4.2.2 Ginseng Used in Medicated Foods

Ginseng can be used to make soups with Old hen or Lingzhi (*Ganoderma lucidum*) and Wuweizi (fruits of *Schisandrae Chinensis Fructus*), etc. These soups can be used for invigorating *Qi*, soothing the nerves, relieving asthma, and strengthening the immune system. The taste of ginseng-contained foods can be adjusted based on personal preferences. Ginseng has many other beneficial ways of use, for example: ginseng tea, ginseng instant tea, ginseng sugar and ginseng fruit.

19.5 Clinical Evidences

As one of the most widely used herbs, many dosage forms of ginseng can be seen in the process of treating diseases. Clinical studies on the effects of ginseng supplements have shown that ginseng added to conventional treatment of diabetes. This has been done by significantly improving glycemic control through lowering postprandial glycemia, without precipitating preprandial hypoglycemia in type 2 diabetics [24].

19.6 Safety Evaluation and Toxicity Data

Researchers have studied safe dosage of ginsenosides used on animals. For example, a low dose (10 μM or 11.09 μg/mL) of Rb_1 showed significantly preventive effect on HUVEC (Human Umbilical Vein Endothelial Cells). For example, proliferation and superoxide anion production in vitro and have found that Rb_1 completely blocked the effect of homocysteine on endothelial cells [25]. Orally administered ginsenoside Re, Rg_1 or Rg_3 of 25 mg/kg in the mouse model resulted in a significant reduction of Alzheimer's Aβ peptide detected in the brains at 18 h post-drug administration. Although results from animal teratogenicity study may not reflect the circumstances in humans, we should be aware of the uses of these ginsenosides alone.

As narrated above, ginseng is definitely a safe herbal medicine often used for the treatment of yang deficience, lower immunity related diseases, and health maintaining purpose. The attention must, however, be paid to the decision to use ginseng personally, and utilize the strong biological activity of the herb in a personal best way with the help of a health professional.

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Chapter 20
Panax notoginseng (Burk.) F.H. Chen 三七 (Sanqi, Notoginseng)

Yuqing Zhao

20.1 Botanical Identity

Panax L. is a small genus of the family Arliaceae. Nearly all species in the genus *Panax* such as American ginseng (*P. quinquefolius* L.), Asian ginseng (*P. ginseng* C.A. Meyer), and Sanqi [*P. notoginseng* (http://www.plant.csdb.cn/taxonpage?sname=Panax%20notoginseng) (Burk.) F.H. Chen] [1] are important herbal medicines. Sanqi is a remedy that has a long history of use in China and other Asian countries. As the biological features, Sanqi is a perennial herb, 60 cm in height, with a short root and stem. Its stem is erect, hairless and glabrous. It has palmate compound leaves with long petiole and 3–4 oval or oblong-obovate, leaflets with serrulation on the edges. Its inflorescence is terminal umbel, with 20–30 cm long peduncles and the flowerets are small, with 5-parted greenish yellow, calyx and 5 petals and stamens. The shape of the fruit is that of a bacca-like drupe, almost kidney-shaped, red in colour when mellow. In each drupe, there are 1–3 flat spherical seeds. The flowering phase is from June to August, and the fruiting period is from August to October. In the wild, the plant is always located in the underlayer of hillside forests and on the slope of foothills or mounds. Its main production locations are in Yunnan, Guangxi and Sichuan province. The root is collected in later autumn or winter after the plant has grown for three years. The plant is processed as follows: The Sanqi root is dug out, then the fibrous roots are removed, insolated until they are half-dried, then they are rubbed slightly and insolated again, and the process is repeated several times, then the roots are transferred to a jute bag, polished by waxing, and sliced up for sale [2].

The roots of Sanqi are used as medicine and dietary supplement purposes. The shape of the root is conical, fusiform or like an irregular block, it is 1.5–5 cm long

Y. Zhao (✉)
School of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang, China
e-mail: zyq4885@126.com

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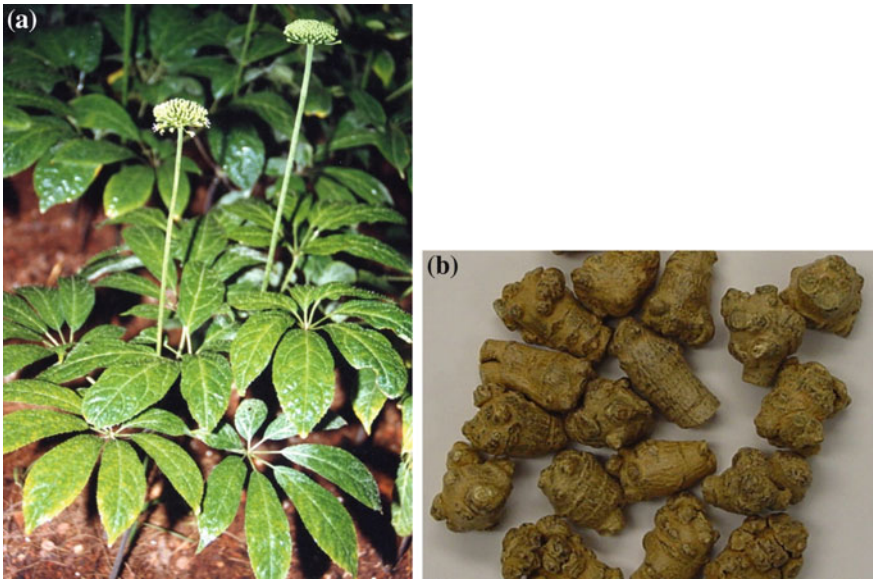


Fig. 20.1 Flowering plant (**a**) and commercial dry roots (**b**) of *P. notoginseng* (http://www.plant.csdb.cn/taxonpage?sname=Panax%20notoginseng)

and 1.2–2 cm in diameter. The surface is greyish yellow or brown-black, with a waxy luster, irregular fine thread and transverse long lenticels. There are several knotty rootlets on the upper side and a residual rootstalk in top end. The root is solid, and the cortex and xylem separate when smashed, showing white or yellow-brown color inside and small brown dots in the cortex. It has a faint scent, bitter, but slightly sweet taste [2]. A growing plant (a) and commercial dry roots (b) are displayed in Fig. 20.1.

20.2 Chemical Constituents

The saponins are major bioactive compounds found in the root of Sanqi. However, Sanqi also contains other constituents such as flavonoids, amino acids, and polysaccharides, etc.

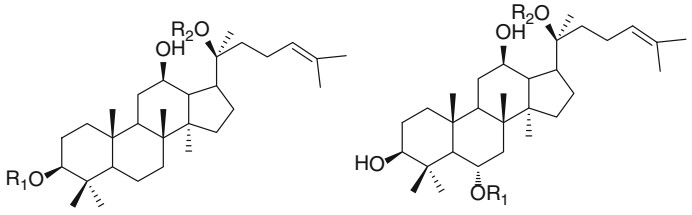
20.2.1 Saponins

Like saponins isolated from American ginseng and Asian ginseng, the saponins from Sanqi are also dammarane-type glycosides. The oleanane-type saponin, which

is present in American ginseng and Asian ginseng, was not found in Sanqi so far. Ginsenosides Rb_1, Rd, Re, and Rg_1 were the first saponins to be isolated and elucidated from Sanqi [3]. Currently, more than 60 dammarane-type saponins have been isolated from the roots, rootlets, leaves, flower buds, fibers, seeds, rhizome, and fruit pedicels of Sanqi. Most of these saponins are notoginsenosides and ginsenosides (see Table 20.1).

20.2.2 Other Constituents

Sanchinan-A, PF3112, PBGA11, PF3111, and PBGA12 were isolated from Sanqi [4]. Choi et al. [5] isolated the *β*-amyloid-induced neurotoxicity-ameliorating constituent quercetin-3-*β*-xylopyranosyl-*β*-D-galactopyranoside from the root of Sanqi. Wei et al. [6] isolated quercetin-3-*O*-sophoroside, kaempferol-3-*O*-(2″-*β*-D- glucopyranosyl)-*β*-D-galactopyranoside, and quercetin-3-*O*-(2″-*β*-D-glucopyranosyl)-*β*-D-galactopyranoside from the leaves of Sanqi. Liu et al. [7] isolated polyacetylene compounds, and Chan et al. [8] isolated trilinolein from the roots of Sanqi.



20.3 Pharmacological Studies

Sanqi is one of the most popular herbs used in TCM. It has acquired a very favorable reputation for the treatment of bleeding, blood stasis, and blood deficiency. Recent studies have shown the alcohol extract of Sanqi provides better hemostatic effects and the shortest bleeding time than no treatment, placebo treatment or treatment with hydrophilic or lipophilic extracts [9]. Although polysaccharides with immunopotentiating activity, proteins with antifungal, ribonuclease and xylanase activity, and a triacylglycerol (trilinolein) with antioxidant activity have been reported, the bulk of pharmacological findings have been based on the saponins or steryl glycosides. Protective actions against cerebral ischaemia

Table 20.1 Major saponins isolated from Sanqi

Type	Name	R_1	R_2	Plant part
Type I	Ginsenoside Rb_1	Glc2 → 1Glc	Glc6 → 1Glc	Root
				Corm
				Leaf
				Flower
				Berry
				Seed
	Ginsenoside Rb_2	Glc2 → 1Glc	Glc6 → 1Ara(p)	Root
				Corm
				Flower
	Ginsenoside Rb_3	Glc2 → 1Glc	Glc6 → 1Xyl	Leaf
				Flower
				Berry
				Seed
	Ginsenoside Rc	Glc2 → 1Glc	Glc6 → 1Ara(f)	Leaf
				Flower
				Berry
				Seed
	Ginsenoside Rd	Glc2 → 1Glc	Glc	Root
				Corm
				Flower
				Seed
	Ginsenoside CK	H	Glc	Leaf
	Ginsenoside Mc	H	Glc6 → 1Ara(f)	Leaf
	Notoginsenoside Fa	Glc2 → 1Glc2 → 1Xyl	Glc6 → 1Glc	Leaf
				Flower
				Berry
				Seed
	Notoginsenoside Fc	Glc2 → 1Glc2 → 1Xyl	Glc6 → 1Xyl	Leaf
				Berry
				Seed
	Notoginsenoside Fe	Glc	Glc6 → 1Ara(f)	Leaf
				Berry
	Gypenoside IX	Glc	Glc6 → 1Xyl	Leaf
				Flower
				Berry
				Seed
	Gypenoside XV	Xyl2 → 1Glc	Glc6 → 1Xyl	Berry
	Gypenoside XVII	Glc	Glc6 → 1Glc	Root
				Flower
				Berry
	Ginsenoside Rg_3	Glc2 → 1Glc	H	Root
				Leaf
	Ginsenoside Rh_2	Glc	H	Leaf

(continued)

Table 20.1 (continued)

Type	Name	R_1	R_2	Plant part
Type II	Ginsenoside F_1	H	Glc	Root
				Leaf
	Notoginsenoside R_1	Glc2 → 1Xyl	Glc	Root
				Corm
	Ginsenoside Re	Glc2 → 1Rha	Glc	Root
				Corm
	Ginsenoside Rg_1	Glc	Glc	Root
				Corm
	Ginsenoside Rg_2	Glc2 → 1Rha	H	Root
				Corm
	Ginsenoside Rh_1	Glc	H	Root
				Corm
				Leaf

and beneficial effects on the cardiovascular system have also been illustrated [10, 11]. Its protective mechanism is partly due to protection against damage by oxygen free radicals [12], and also by binding to the estrogen receptor, as ginsenosides share many of the protective actions of estrogen in various physiological systems [13]. Pharmacokinetic and pharmacodynamic studies have found that intranasal preparation of Sanqi saponins is a promising development [14]. Sanqi extracts were also found to possess the capacity to adjust energy metabolism [15] and cure diabetes [16]. Recent studies found that Sanqi showed anti-tumor effects [17]. and antioxidant, hypolipidaemic, haemostatic, hepatoprotective, renoprotective, and estrogen-like activities have been described [18] (see Table 20.2).

20.4 TCM Applications and Dietary Usage

20.4.1 TCM Applications

Sanqi is one of the most common herbs traditionally used in herbal medicines and health-maintaining products. Sanqi has been used for thousands of years due to its beneficial effects as an anti-inflammatory and its ability to improve blood circulation properties. It has also been shown to possess several interesting pharmacological activities such as anti-aging, anti-tumor, immuno-stimulating and radio resistance activities et al. Sanqi could be used alone or in combination with other herbs based on TCM theory.

Fufang Danshen Pian can remove blood stasis by promoting blood circulation. The main ingredients are Sanqi, Danshen and Borneolum. Sanqi can resolve blood stasis by arresting bleeding and relieving pain. Yunnan Baiyao is exceptionally

Table 20.2 Biological activities of Sanqi

Biological activity	Chemical constituent/fraction
Antidiabetic nephropathy	Crude extract
Antidiabetic macroangiopathy	Crude extract
Hepatoprotective	Saponin
Renoprotective	Saponin
Immunological adjuvant	Saponin
Anti-inflammatory	Saponin
Hypolipidaemic	Saponin
Haemostatic	Saponin
Anti-atherosclerotic	Saponin
Cardioprotective	Saponin
Negative chronotropic and inotropic	Saponin
Improving early post-burn cardiac function	Saponin
Antithrombotic	Saponin, trilinolein
Anti-arrhythmic	Saponin, trilindein
Immunomodulatory	Polysaccharides, saponin
Antitumour	Extract, Ginsenoside Rb_1
Fibrinolytic	Notoginsenoside R_1
Enhancing sperm motility	Polysaccharide fraction Ginsenosides Rb_2 and Rc
Hypoglycaemic	Ginsenoside Rg_1
Estrogen-like	Ginsenoside Rg_1
Antioxidant	Trilinolein, aqueous extract

effective in the treatment of fracture, injury, etc. The chief active ingredient consisted of Sanqi.

Sanqi can remove blood stasis and stop bleeding. Ejiao (*Colla Corii Asini*) can nourish blood and stop bleeding. A mixture containing 10 g of Danggui (roots of *Angelicae Sinensis*), 12 g of Ejiao, 10 g of Sanqi powder and 5 g of Gancao (roots and rhizomes of *Glycyrrhiza uralensis Fisch*) can be decocted in water. The decoction can be taken twice daily for the treatment of metrorrhagia [19]. Both Sanqi (roots of *Panax Notoginseng*) and Baiji (tubers of *Bletilla striata*) are hemostatic drugs. A mixture containing 5 g of Baiji powder, 5 g of Sanqi powder and 20 g of Oujie (*Nodus Nelumbins Rhizomatis*) can be decocted in water and then the decoction can be taken twice daily for the treatment of hemoptysis [20].

20.4.2 Dietary Usages

Sanqi is characterized as a functional food in China [21]. Based on the US Dietary Supplement Health and Education Act (DSHEA) of 1994, Sanqi tea or capsules are

being sold as over-the-counter dietary supplements in the US health food market [22]. These include Sanqi tea, Sanqi wine, Sanqi soup, Sanqi paste, Sanqi powder, Sanqi pill, and Sanqi extract. The following dietary forms can be easily made at home.

20.4.2.1 Sanqi Wine

A mixture containing 10 g of Sanqi, 50 g of Lingzhi (*Ganoderma lucidum*) and 10 g of Danshen (roots and rhizomes of *Salvia miltiorrhiz*) can be ground into a powder. After the addition of 750 g of Chinese spirits, the mixture should be sealed and stirred once a day for 2 weeks. Then the herbal wine obtained can be taken twice daily at a dose of 10 mL, which can tonify *qi*, promote blood circulation and soothe nerves.

20.4.2.2 Sanqi Used in Medicated Foods

Ejiao can be crushed and fried until it turns yellow, and then ground into a powder. About 30 g of Raw Dihuang (roots of *Rehmannia glutinosa*) can be sliced and boiled for 10 min. After the addition of 50 g of japonica, the mixture can be boiled into rice porridge. Finally, 30 g of Ejiao, 3 g of cooked Sanqi powder and a moderate amount of sugar can be added to the porridge. This prescription can be taken once a day as a breakfast replacement, which has many functions such as nourishing *Yin* and clearing heat, cooling blood and stopping bleeding.

20.5 Clinical Evidences

In order to study the therapeutic effect and possible mechanism of total saponins from Sanqi for treatment of rheumatoid arthritis (RA), and to observe its influence on RA immune related inner environment, eighty-four patients were randomly assigned to two groups. All were treated with the routine therapy with Leflunomide, diclofenac sodium, and prednisone for 28 days, but the total saponins were given for the 43 patients in the treatment group additionally. Clinical efficacy and change of indexes including immnuoglobulins (IgG, IgA, IgM), platelet counts, complement (C)3, C-reactive protein (CRP), rheumatoid factor (RF), haptoglobin (HPT), ceruloplasmin (CER), and alpha1-acid glycoprotein (AAG) were observed. Clinical symptoms including the joint swelling index, joint pain index, joint tenderness index, time of morning stiffness and VAS were revealed significant improvement in both groups after treatment, and the effect in the treatment group was better ($P < 0.05$ or $P < 0.01$). PLT, HPT, CER, CRP, AAG, IgG, IgM, IgA, C3, and RF were lowered in both groups ($P < 0.01$), but the lowering in PLT, AAG, CER, and CRP in the treatment group was more significant than that in the control group

respectively ($P < 0.05$ or $P < 0.01$). Through regulating the disordered immunity and improving the effect of anti-inflammatory and analgesia, the total saponins from Sanqi can significantly improve the condition of patients and enhance the therapeutic effect in treating RA [23].

20.6 Safety Evaluation and Toxicity Data

In order to evaluate the toxicity of the total saponins from Sanqi on the liver and kidney, thirty-two Wistar rats with body weight of 140–180 g were randomized to intramuscularly inject with either injection solution, the total saponins (450 mg/kg) for 3 days or the total saponins (50 or 150 mg/kg) for 28 days. The results showed rats administered with the total saponins (450 mg/kg) experienced a significant reduction in body weight and showed abnormal escalation of aspartate aminotransferase, alanine aminotransferase, urea nitrogen and creatinine levels. The degeneration and necrosis of both hepatic cells and epithelia cells of renal tubule of the rats were found by histopathological examination [24].

As described above, the total saponins from Sanqi have significant nephrotoxicity and hepatotoxicity. There may also be some pharmacologically inactive constituents of Sanqi that are more likely than the active components to produce allergies. It's strongly suggested to ask your doctor if it's proper for you.

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Chapter 21
Panax quinquefolius L. 西洋参 (Xiyangshen, American Ginseng)

Yuqing Zhao

21.1 Botanical Identity

American ginseng *(Panax quinquefolius* L.) is an herbaceous perennial plant in the ivy family, commonly used as herbal medicine. Its forked root and leaves were traditionally used for medicinal and tonic purposes. American ginseng is recorded in The Pharmacopeia of People's Republic of China as a common crude drug [1].

Similar to ginseng, American ginseng grows about 25 cm in height with a short, main root and stem. Its stem is cylindrical. It has palmate compound leaves with long petiole and 3–4 oblong-obovate leaflets [2]. Its inflorescence is terminal umbel with 5–13 cm long peduncles and the flowerets are small, with 5-parted green Calyx almost bell-shaped and 5 petals and stamens. The petals are green-white. The fruit shape is bacca-like drupe, becoming a red colour when mellow. The flowering phase is from May to June, while the fruiting period is from June to September.

The root is used medicinally. The shape of the main root is conical or fusiform, 2–6 cm long and 0.5–1 cm in diameter. The surface is light brown with tense thin lines on cover. There are denser fine threads on the upper side, with the appearance of a growth ring. The root is light, and the colour of the cross section is white-yellow. It is slightly fragrant and tastes bitter, but slightly sweet.

American ginseng is native to America and Canada and cultured in China as well. American ginseng produced in Wisconsin is thought to be the best variety, with the highest reputation. In China its main production locations are the Beijing, Jiangxi and Shandong areas. The root is plucked in autumn after 3–6 years of cultivation. The processing is as follow: fibrous roots are removed, insolated until they are half-dried, slightly rubbed and then insolated again; this process is repeated several times, then the roots are transferred to a jute bag and polished by waxing.

Y. Zhao (✉)
School of Traditional Chinese Medicine, Shenyang Pharmaceutical University, Shenyang, China
e-mail: zyq4885@126.com

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Fig. 21.1 Dried American ginseng (**a**) growing in Wisconsin and sliced crude drug (**b**) of American ginseng produced in Huairou, Beijing

Compared with the American ginseng cultivated in China, the local American ginseng looks dark and mealy; it tastes sweet and fresh, and the cross section is flatter with a fine texture and shaped like a Chrysanthemum. Dried American ginseng (a) grown in Wisconsin and the sliced crude drug (b) of American ginseng produced in Huairou, Beijing are shown in Fig. 21.1.

21.2 Chemical Constituents

The constituents isolated and characterized from American ginseng include saponins, essential oils, polysaccharides, peptides, polyace-tylenic alcohols, and fatty acids [3].

21.2.1 Saponins

Saponins are the major bioactive compounds of American ginseng. More than 60 saponins including dammarane-type, ocotillol-type, and oleanane-type have been isolated from the roots, leaves, stems, flower buds, and berries of American ginseng. Dammarane ginsenosides such as ginsenosides Rg_3, Rg_5 and Rk_1 are formed through transformation by steaming and heating and are metabolized into metabolites such as compound K and ginsenoside Rh_1 by intestinal microflora. Ginsenosides differ from one another by sugar type, number, and linkage position [4]. The content of saponins in American ginseng is 6.4–7.3 %.

The major saponins are dammarane-type ginsenosides [5], which include two classifications: 20(*S*)/20(*R*)-protopanaxadiol (PPD) and 20(*S*)/20(*R*)-protopanaxatriol (PPT). Protopanaxadiol-type ginsenosides (PPD) contain ginsenosides Rb_1, Rc, Rb_2, Rb_3, Rd, Ra_0, F_2, quinquenosides R_1 and gypenoside X, XI and VII. Protopanaxatriol-type ginsenosides (PPT) found in American ginseng are the ginsenosides Rg_1, Rg_2, Re, Rg_3, F_3, and Rh_1. The basic structures of these types of saponins are illustrated in Fig. 21.2.

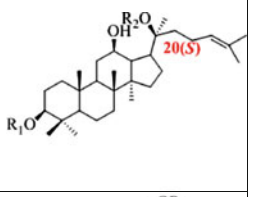
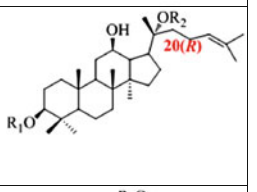
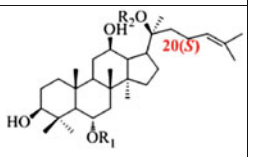
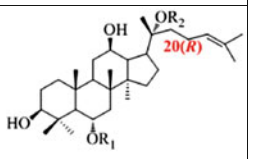
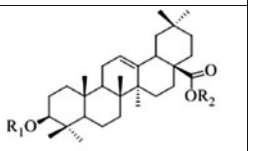
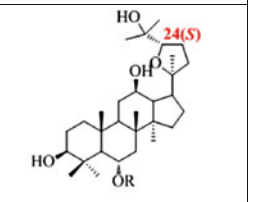
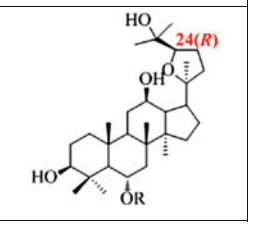
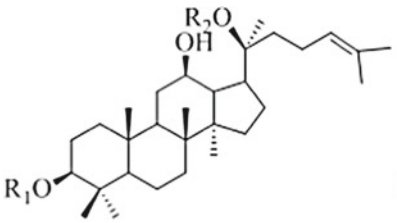
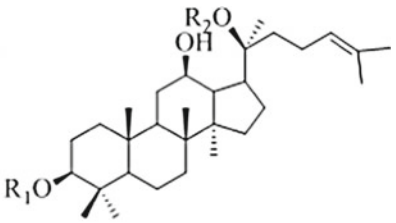
dammarane-type	20(*S*)-PPD	
	20(*R*)-PPD	
	20(*S*)-PPT	
	20(*R*)-PPT	
Oleanane-type		
Ocotillol-type	24(*S*)	
	24(*R*)	

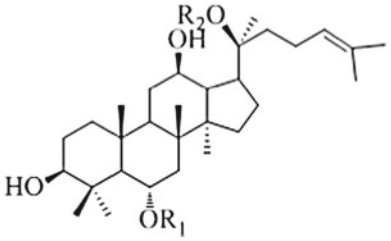
Fig. 21.2 Three types of saponins isolated from American ginseng



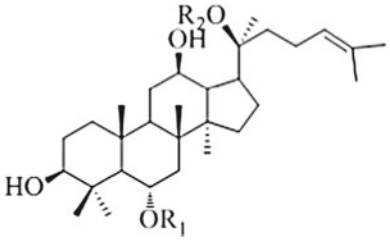
Ginsenoside Rb_1, 1,
R_1=Glc2→1Glc, R_2=Glc6→1Glc



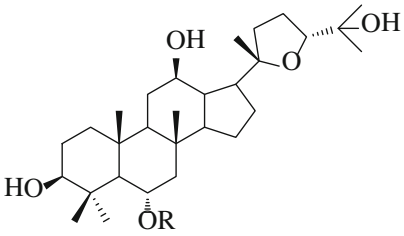
Ginsenoside Rc, 2,
R_1=Glc2→1Glc, R_2=Glc6→1Ara(f)



Ginsenoside Rg_2, 3,
R_1=Glc2→1Rha, R_2=H



Ginsenoside Re, 4,
R_1=Glc2→1Rha, R_2=Glc



Pseudoginsenoside F11, 5, R=Glc2→1Rha

Fig. 21.3 Representative saponins isolated from American ginseng

In general, ginsenosides Rb_1, Re, Rd, Rc, Rg_1 and Rb_3, the six major saponins, make up more than 70 % of total ginsenoside content in American ginseng [6, 7]. In addition, the minor ginsenosides: four ocotillol-type ginsenosides, two oleanane-type ginsenosides, and three dammarane saponins with a modified steroid skeleton, were isolated from *P. quinquifolium* [8]. Minor saponins modified in C-20 side-chain were also isolated.

Among the ginseng saponins, Rb_1 (shown in Fig. 21.3) is the highest in American ginseng. There is also a large amount of Rc, Rg_2 and Re (shown in Fig. 21.3), which have anti-hyperlipidemic functions. An important and iconic parameter used for distinguishing between Asian ginseng and American ginseng is the presence of ginsenoside Rf in Asian ginseng but pseudoginsenoside F11 (shown in Fig. 21.3) in American ginseng [9].

21.2.2 Polysaccharides

Many kinds of polysaccharides were also isolated from American ginseng. Immunomodulating glycans, such as water-soluble COLD-FX (CVT-E002), were isolated from the roots of American ginseng [10]. Hypoglycemic glycans, such as quinquefolans A, B and C, were isolated from the roots of *P. quinquifolium* [11]. The polysaccharides can be hydrolyzed and found to contain glucose, galactose, arabinose, rhamnose, and mannose.

21.3 Pharmacological Studies

As we know, American ginseng is one of the most popular tonics used in TCM. In the all kinds of modern pharmacological studies, American ginseng has been reported to have a wide range of pharmacological effects [12] such as antioxidant properties [13], anti-lipid peroxidation, hypoglycemic activity, anti-fatigue, inhibition of platelet aggregation, reducing blood coagulability, anti-bacteria, anti-virus and anti-tumor, etc. The pharmacological properties of American ginseng are mainly attributed to ginsenosides, the active constituents which are found in the extracts of ginseng and American ginseng. Ginsenosides were proven to have beneficial effects on central nervous system, cardiovascular system, anti-diabetic [14] and anti-cancer activities. It also showed immunomodulatory activities and an ability to guard against acute respiratory illness. The activity of CVT-E002 [15], an aqueous extract containing mainly oligosaccharides and polysaccharides from American ginseng, as an immunobooster on murine spleen cells and peritoneal macrophages, was studied in vitro. It could be an excellent candidate agent for improving immunomodulatoty activity.

The previous studies demonstrated that the polysaccharides fraction from American ginseng berry extract has significant anti-hyperglycemic activity. The polysaccharides may have clinical utility in treating type 2 diabetic patients according to many studies [16].

American ginseng has also been shown to significantly alter the activity of hypothalamic catecholamines involved in the facilitation of copulatory behavior and hormone secretion.

21.4 TCM Applications and Dietary Usage

21.4.1 TCM Applications

American ginseng, bitter and cool, is one of the most common herbs traditionally used in herbal medicines and health-maintaining products. It can clear the evil-heat and promote the body-fluid production [17]. And it is suitable for the treatment of

febrile disease with prostration of both *Qi* and *Yin*. It effectively treats prostration syndrome manifested as shortness of breath, lassitude, thin and feeble pulse.

American ginseng is used to relieve the syndrome of both *Qi* and *Yin* deficiency. For lassitude, lack of strength, shortness of breath, dyspenea, spontaneous sweating with warm and sticky sweat, dysphoria and thirst due to consumption of primordial *Qi* and *Yin* fluid, it has good therapeutic efficacy when used in combination with Maidong (roots of *Ophiopogon japonicus*), Wuweizi (fruits of *Schisandrae Chinensis Fructus*). For palpations, angina pectoris, insomnia and dream-disturbed sleep, it is combined with Gancao (roots and rhizomes of *Glycyrrhiza uralensis Fisch*) and Maidong as well.

American ginseng not only tonifies lung-*Qi*, but also nourishes lung-*Yin*, clearing lung heat. Therefore, American ginseng in combination with Yuzhu (rhizomes of *Polygonatum odoratum*) and Maidong, can be used to treat a chronic cough with little phlegm, dry throat and lassitude caused by lung-*Qi* and lung-*Yin* deficiency.

American ginseng can also be used to remit thirst due to *qi* deficiency and consumption of fluid in febrile diseases. In this case, it is usually used in combination with fresh Shengdihuang (roots of *Rehmannia glutinosa*), fresh Shihu (stems of *Dendrobium nobile Lindl*), and Maidong.

21.4.2 Dietary Usages

Because of the good record of American ginseng as one of the most famous herbs and valuable dietary botanical materials, it has been used in many ways historically. These include tea, wine, and soup, etc. The following dietary forms can be easily made at home.

21.4.2.1 American Ginseng Teas

Herbal tea made of American ginseng alone or mixed with other herbs is the most common way to use American ginseng. There are many combination methods, such as American Ginseng tea composed of American ginseng (3 g) and green tea (5 g); American Ginseng drink composed of American ginseng (15 g), Yin-er (15 g) (*Tremella fuciformis Berk*), and some rock candy, etc.

21.4.2.2 American Ginseng Porridge

American ginseng can be used to make porridge with Anemarrhenae Rhizoma, Fritillaria or rice [18]. A mixture containing 5 g of American ginseng, 50 g of Zhimu (rhizomes of *Anemarrhena asphodeloides Bunge*), 50 g of Beimu (bulbs of *Fritillaria Bulbus*), and 50 g of rice can be ground into powder. After addition of

some water, the mixture was boiled until it was well done. The porridge can be taken twice daily to moisten lungs and arrest cough.

21.4.2.3 American Ginseng Used in Medicated Foods

In some cases, American ginseng can heal loss of appetite and reduce fatigue. A mixture containing 10 g of American ginseng, 10 g of Baizhu (rhizomes of *Atractylodes macrocephala Koidz*), and 10 g of Fuling (sclerotia of *Poria cocos*) can be decocted in water. The prescription can be taken twice daily. It can be used by patients regularly.

About 30 g of American ginseng, 250 g of Longyanrou (fruits of *Dimocarpus longan Lour*), 150 g of Maidong and 120 g of Fried jujube kernel can be concentrated into cream. Eating 50–60 g daily divided into two servings is recommended. It can be used in cases of coronary heart disease and angina.

21.5 Clinical Evidences

As the most widely used herb, many dosage forms of American ginseng can be seen on the market. There are thousands of clinical related reports or observational studies published on the effects of American ginseng and its related preparations for type II diabetes [19]. Some studies demonstrated that capsules made from 3 g of American ginseng could reduce postprandial glycemia (PPG) in individuals with type 2 diabetes. Further work showed that American ginseng reduced PPG irrespective of dose and time of administration. No more than 3 g of American ginseng was required at any time in relation to the challenge to achieve reductions. As the reductions included glycemia at the 2 h diagnostic end point, there may be influences for diagnosis and treatment of diabetes [20]. To our surprise, American ginseng is able to reduce the anticoagulant effect of warfarin in trials [21]. Thus, when prescribing warfarin to patients, physicians may ask them about their use of ginseng. American ginseng can be also used to cure the postoperative gastric emptying delay. This treatment is called alimentotherapy. When porridge is made with a mixture of American ginseng and pericarpium citri reticulatae, we can get a satisfactory therapeutic effect.

21.6 Safety Evaluation and Toxicity Data

Based on many toxicologic studies, there is no evidence to show obvious toxicity or side effects of American ginseng. In an acute oral toxicity test [22], the LD_{50} of total saponins from American ginseng for male and female mice were 5.84 (4.30–7.94) g/kg and 5.01 (3.44–7.30) g/kg, respectively. According to the “Food Safety and

Toxicology Evaluation Procedures and Methods", the result indicated the nontoxicity of American ginseng. In another toxicological study on *Panax quinquefolius* saponin, one-time dosing of 1.5 and 0.75 g/kg for 60 days didn't influence the growth [23], blood routine examinations, liver function, renal function, and main organs of rats. In addition, in dosages of i.g. (intragastrical administration) 2.0 and 1.0 g/kg for 60 days, it did not significantly change the electrocardiogram, hematological examinations, hematiological biochemical criterins and main organs in dogs.

All in all, American ginseng is a relatively safe herbal medicine often used for enhancing the central nervous regulation and health maintaining purpose. Attention must also be given to when you decide to use American ginseng personally without a doctor's advice because it is obvious that American ginseng has strong biological activity and cannot be used as a regular food item. The "ginseng abuse syndrome", which is a group of symptoms arising from prolonged and excessive ginseng intake, has been reported. Cases of induced headaches and female endocrine disorders after dosing of American ginseng are being researched. Therefore, it is strongly necessary for patients to consider clinical use and recommendations from doctors.

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Chapter 22
Platycodon grandiflorum (Jacq.) A. DC. 桔梗 (Jiegeng, Balloonflower)

Muxin Gong and Xuran Lu

22.1 Botanical Identity

Platycodon grandiflorum (Jacq.) A. DC., a herbaceous perennial plant known as Balloonflower, is the only species of the Bellflower Family. It distributed in most provinces of China, Korean, Japan, the Russian Far East and Siberia [1]. It is the legal source recorded in the Pharmacoepia of People's Republic of China [2] and all historical records of Chinese herbal works.

The name Balloonflower is based on the unopened flower buds which creates the appearance of little balloons. The whole plant is smooth, 40–50 cm high, with the white milk in the body. Its root is hypertrophic and succulent, long conical or cylindrical, and brown or gray-brown. The stems are upright and branched on the upper part. Sessile leaves are in the central and lower part of stem. The shape of these leaves is ovate or lanceolate, with irregular sharp jagged edges. The upper leaves are small and narrow. Solidary flower or several are hydrophobic racemes of birth, calyx bell-shaped, lobes 5. The corolla is wide bell-shaped, blue-purple, white or yellow with 5 lobes. Stamens 5, alternate with corolla lobes. Under the ovary, oval shape, stigma 5 crack, densely covered with soft white hair [3] (Fig. 22.1a).

The root is used as medicine, and is also called Platycodon root. It is collected in summer and autumn, dried under the sunshine and cut into pieces as raw material [2]. Platycodon root is long oval and sometimes has branches. There are many base marks in half-moon shape on the apex. The whole root is 6–30 cm long and 0.5–2 cm in diameter. The surface is white or yellow-white. There are thin stripes, irregular longitudinal wrinkles, horizontal lenticels and fibrous root marks on the surface of upper roots. It is hard, friable and easily broken. The cross-section is white to off-white, slightly granular, with radial fissures called "Chrysanthemum

M. Gong (✉) · X. Lu
School of Traditional Chinese Medicine, Capital Medical University, Beijing, China
e-mail: gongmuxin@126.com

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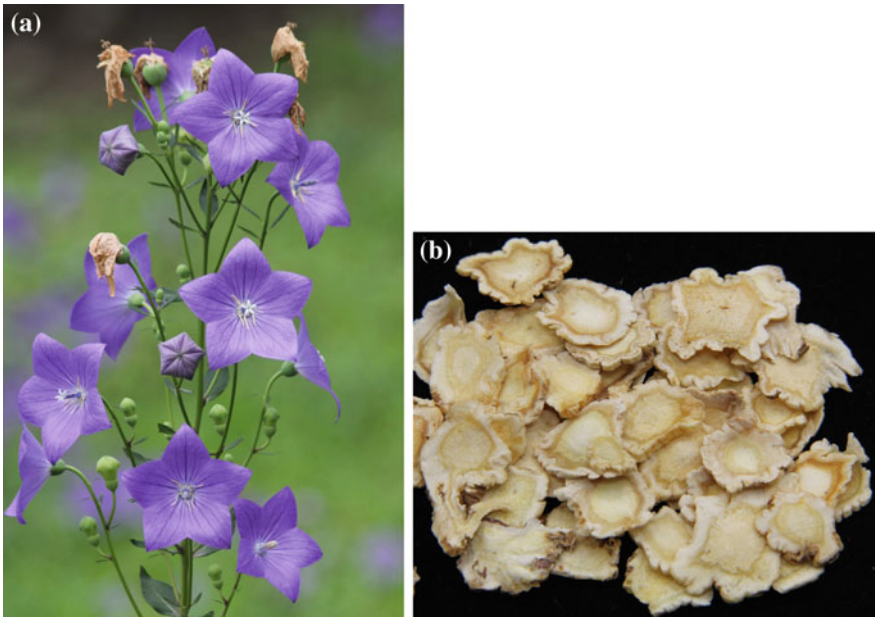


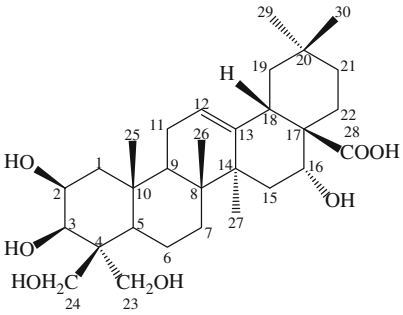
Fig. 22.1 Flowering plant (**a**) and processed slices (**b**) of Jiegeng

heart". The cambium ring is clear, light brown, white to off-white. The xylem is canary yellow, has no-smell and taste slightly sweet followed by bitterness [4] (Fig. 22.1b).

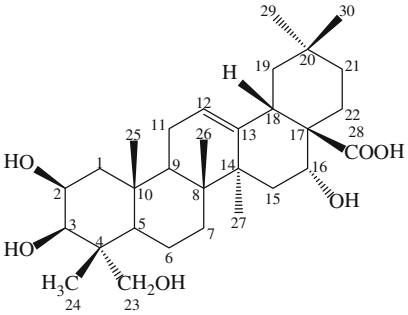
22.2 Chemical Constituents

Saponin is the major class of bioactive compounds of Jiegeng, which belongs to oleanane-type triterpenoid derivatives. So far, more than seventy saponins have been isolated. According to the C-24 structural characteristics, they can be classified into three types. Those three types are, platycodic acid-type (CH_2OH at C-24), platycodigenic acid-type (COOH at C-24) and polygalacic acid-type (CH_3 at C-24). Platycodic acid-type and polygalacic acid-typeare the main types of saponins in Jiegeng with their aglyconesare platycodigenin (**1**) and polygalacic acid (**2**). Glycosyl such as D-glucose, L-arabinose, L-rhamnose, D-xylose and D-apioseas well as their derivatives usually connect at C-3 and C-28 of platycodigenin, and form bisdesmosidic saponins. Among them, Platycodin D (**3**) is of high content and the first found compound with a D-apiose [5]. As rare sugar chains of medicinal plants, apiose in platycodon saponins usually links to C-28 sugar chains (Fig. 22.2).

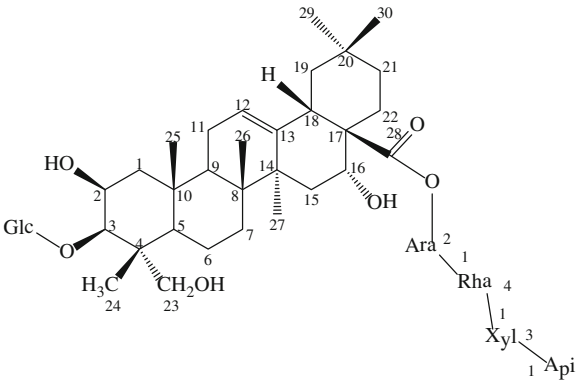
In addition, there are flavonoids (such as platyconin), alcohol glycosides, sterols, saccharan, phenolic acids, vitamins and other components found in the whole plant.



Platycodigenin, 1



Polygalacic acid, 2



Platycodin D, 3

Fig. 22.2 Structures of main aglycones and platycodin D in Jiegeng

22.3 Pharmacological Studies

Modern research has mainly found that due to the various saponins of Jiegeng, its pharmacological actions are very broad.

22.3.1 Antitussive and Expectorant Activities

The aqueous extract and total saponins from Jiegeng showed high antitussive activities and low toxicity in rats and guinea pigs [6]. Platycodin D and platycodin D_3 also showed expectorant activities [7].

22.3.2 Anti-inflammatory Activities

Platycodon saponins have high anti-inflammatory activities for several inflammation animal models. In addition, platycodon saponins can inhibit prostaglandin E pathways and resist the LPS-induced NO increasing in mice peritoneal macrophages. It can also inhibit the PGE_2 production induced by rat cancer promoter 12-*O*-tetradecanoylphorbol 13-acetate (TPA) [8]. Through the inhibition of inflammatory cytokines and Syk-dependent signaling cascades, saponins isolated from Jiegeng could be used for allergy therapy [9].

22.3.3 Hepatoprotective Activities

Platycodon saponins showed many activities such as anti-hepatic fibrosis, anti-hepatic lipid peroxidation, protecting liver cells, promoting the metabolism of material and energy to accelerate the repair of liver injury, improving the liver microcirculation and inhibiting liver cancer cells, and so on. Jiegeng is potentially useful as a therapeutically potent natural ingredient for the prevention of chronic alcohol-induced oxidative stress and liver damage [10]. Six triterpenoid saponins have been identified as active components exerting anti-HCV (Hepatitis C virus) activity [11].

Moreover, Jiegeng also showed antipyretic, antinociception, hypotensive, hypoglycemic, anti-ulcer, anticholinergic, antioxidant, anticancer, anti-obesity and other activities. Platycodin-enriched diets can lower the cholesterol contents of the blood circulation system and the whole body, and thus reduce the risk of cardiovascular diseases through mechanisms independent from cholesterol absorption or synthesis [12].

22.4 TCM Applications and Dietary Usage

22.4.1 TCM Applications

Jiegeng was first recorded in *Shennong Bencao Jing*, which was the earliest book on materia medica in the world and was completed in BC100. It can promote expectoration and discharge of pus to relieve cough, sore throat, flank pain, diarrhea and abdominal pain. Jiegeng also has the effect of promoting blood circulation and removing blood stasis. Jiegeng was usually used in the following prescriptions.

22.4.1.1 Jiegeng Decoction

Jiegeng has the effects of expectorant, apocenosis, relieving sore throat and cough. The representative prescription is Jiegeng Decoction recorded in *Shanghan Lun*, which is composed by Jiegeng (3 g) and Gancao (root and rhizome of *Glycyrrhiza uralensis*, 6 g).

22.4.1.2 Yinqiao Powder

Yinqiao Powder is another representative for relieving sore throat and cough recorded in *Wenbing Tiaobian*, composed of Lianqiao (fruit of *Forsythia suspensa*, 9 g), Jinyinhua (flower of *Lonicera japonica*, 9 g), Jiegeng (6 g), Bohe (herb of *Mentha haplocalyx*, 6 g), Zhuye (leaf of *Phyllostachys nigra*, 4 g), Gancao (5 g), Jingjiesui (spica of *Schizonepeta tenuifolia*, 5 g), Dandouchi (fermented seed of *Glycine max*, 5 g) and Niubangzi (fruit of *Arctium lappa*, 9 g).

22.4.1.3 Xuefu Zhuyu Decoction

Being combined with drug invigorating the circulation of blood, Jiegeng can relieving pain, attending chest blood stasis syndrome. The representative prescription recorded in *Yilin Gaicuo* is Xuefu Zhuyu decoction, which is composed by Danggui (root of *Angelica sinensis*, 9 g), Dihuang (root of *Rehmannia glutinosa*, 9 g), Taoren (seed of *Prunus persica*, 12 g), Honghua (flower of *Carthamus tinctorius*, 9 g), Zhiqiao (unripe fruit of *Citrus aurantium*, 6 g), Chishao (root of *Paeonia lactiflora*, 6 g), Chaihu (root of *Bupleurum chinense*, 3 g), Gancao (6 g), Jiegeng (4.5 g), Chuanxiong (rhizome of *Ligusticum chuanxiong*, 4.5 g) and Niuxi (root of *Achyranthes bidentata*, 9 g), treating for headache, cerebrovascular diseases, coronary heart disease and dysmenorrheal.

22.4.1.4 Shenling Baizhu Powder

Platycodon root can help stop diarrhea. The representative prescription is Shenling Baizhu Powder, which is composed by Renshen (root and rhizome of *Panax ginseng*, 100 g), Fuling (sclerotium of *Poriacocos*, 100 g), Baizhu (rhizome of *Atractylodes macrocephala*, 100 g), Shanyao (rhizome of *Dioscorea opposita*, 100 g), Baibiandou (seed of *Dolicho lablab*, 75 g), Lianzi (seed of *Nelumbo nucifera*, 50 g), Yiyiren (seed kernel of *Coix lacryma-jobi* var. *meyuan*, 50 g), Sharen (fruit of *Amomum villosum*, 50 g), Jiegeng (50 g) and Gancao (root and rhizome of *Glycyrrhiza uralensis*, 100 g) [2].

22.4.2 Dietary Usages

Jiegeng is not only a traditional Chinese medicine but also a good functional food, which can be made into delicious dishes. Jiegeng is a nutritious food since it contains a lot of protein, amino acid, vitamin C and vitamin B, calcium, zinc, potassium, iron and other trace elements, as well as a large number of unsaturated fatty acids such as linoleic acid. It has the effects of hypertension resistance, reducing hyperlipemia, stimulating blood circulation and antiatheroselerosis. Also, it is good for the elimination of toxin in the human body because of its high content of crude fiber. It is used as a common vegetable in northeast China, Japan, Korea and other countries. In recent years, the tender stems and leaves have become a special vegetable. The following dietary forms can be easily made at home.

22.4.2.1 Jiegeng Gruel

Jiegeng 10 g, rice 100 g. Add some water to soak Jiegeng, 5–10 min later boil and use the juice to cook rice to porridge for facilitating expectoration and suppressing cough. It is suitable for treating cough due to lung heat, yellow thick sputum, or dry cough and hard to spit up sputum.

22.4.2.2 Jiegeng Tea

Jiegeng 10 g, Gancao 20 g. Boil two herbs after soaking for 5–10 min. Use as a daily dose. It is suitable for treating suppurative lung diseases.

22.4.2.3 Jiegeng Mushroom Soup

Fresh stems and leaves of Jiegeng 200 g, waterishlogged mushroom 100 g, clear soup 1000 g, cooking oil, salt, sesame oil, green onion and monosodium glutamate appropriate amount. Wash and blanch Jiegeng, then cool it in cold water, drain excessive liquid, cut into 2 cm-long sections, slice mushroom, heat the cooking oil, put it into the green onion. Add clear soup and mushroom pieces, bring soup to a boil, then add Jiegeng, salt, monosodium glutamate, boil for 3 min and drizzle in the sesame oil.

22.4.2.4 Runfei Zhike Tea

The Runfei Zhike Tea has an effect of moistening lung and resting cough. Jiegeng 6 g, Xuanshen (root of *Scrophularia ningpoensis*) 6 g, Maidong (root of *Ophiopogon japonicus*) 3 g, Wumei (fruit of *Prunus mume*) 3 g and Gancao (root and rhizome of *Glycyrrhiza uralensis*) 3 g. Put all of them into a vacuum cup, add boiling water and cover the cup with the lid for 15 min [13].

22.5 Clinical Evidences

As a therapeutic medicine, Jiegeng is mostly used for treating upper respiratory disease in combination with other herbs. There are many clinical related reports or observational studies published on the effects of Jiegeng and its related prescriptions for upper respiratory disease and other diseases. Clinical reports show that the modified Jiegeng Decoction could effectively relief the symptom of chronic pharyngitis in 90 cases [14], which was better than Wanying capsule which was the positive control group. Jiegeng is also often used as guide herb for treating cardiovascular disease and has a good effect [15].

22.6 Safety Evaluation and Toxicity Data

Acute toxicity: The LD_{50} of mice fed Platycodon decoction is 24 g/kg, the LD_{50} of mice administered crude saponins intraperitoneally is 2.23 mg/kg, while LD_{50} is 14.1 mg/kg for rats and 23.1 mg/kg for guinea pig. The minimum lethal dose of platycodinin mice administered subcutaneous injection is 7.70 mg/kg [16]. Platycodin showed hemolytic activity, and the hemolytic index is the 1:1000. Generally, platycodin cannot be injected in order to avoid tissue necrosis or hemolysis. Platycodin administered orally will decomposition in the gastrointestinal tract then without hemolysis.

According to Chinese Pharmacopeia, the daily dosage of Jiegeng is 3–9 g. A massive dose platycodin taken orally can excite vomiting center to cause nausea and vomiting. "Chinese Dictionary" contains: Jiegeng administered orally can stimulate the release of allergens. It is reported that the dose of 15 g can cause a serious skin allergy [17].

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Chapter 23
Polygonatum cyrtonema Hua 黄精 (Huangjing)

Ta-si Liu and Bei Xu

23.1 Botanical Identity

Huangjing, is the rhizome of several perennial *Polygonatum* species in the family of Liliaceae. Presently there are about 40 species of the genus *Polygonatum* have been found in the world, most are distributed in north temperate region. There are 31 species in China. Among them, *Polygonatum kingianum* Coll. et Hemsl., *Polygonatum sibiricum* Red. and *Polygonatum cyrtonema* Hua are the major and legal sources of Huangjing listed in the Pharmacopeia of People's Republic of China. *Polygonatum sibiricum* Red. is mainly distributed in Hebei, Inner Mongolia and Shanxi provinces. *Polygonatum kingianum* Coll. et Hemsl. and *Polygonatum cyrtonema* Hua are mainly cultivated in Guizhou, Yunnan, and Guangxi provinces. The height of Huangjing plant is between 40 and 100 cm, stems erect, cylindrical, single. The leaf shapes like bamboo leaf and the color of the flowers is white [1].

The rhizome is harvested in spring and autumn, dried and used as crude Huangjing [1]. For further processing, the raw material is mixed with yellow wine (rice wine), put in gallipot and be airtight, heated by using steam or water-barrier until the yellow wine is exhausted. It is further steamed until thoroughly moist, and turned black, sliced, then dried. This is commonly used in TCM according to traditional practices [1] (Fig. 23.1).

T. Liu (✉) · B. Xu
Hunan University of Traditional Chinese Medicine, 410208 Changsha, China
e-mail: liutasi@126.com

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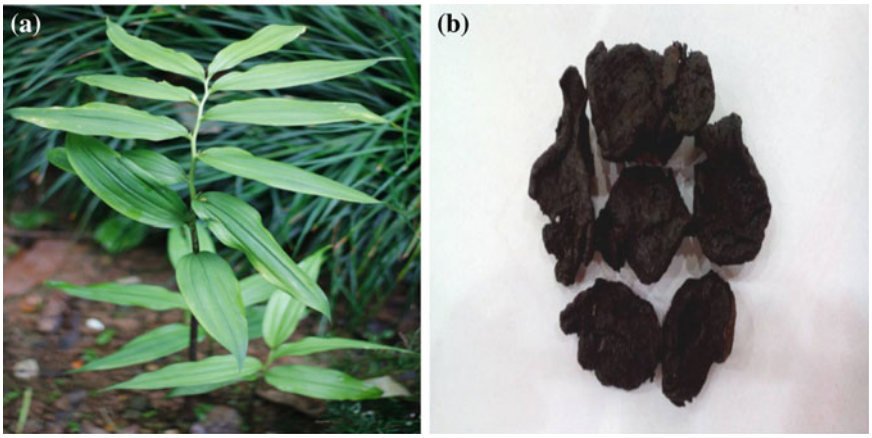


Fig. 23.1 The plant (**a**) and processed rhizome slices (**b**) of *Polygonatum cyrtonema* Hua

23.2 Chemical Constituents

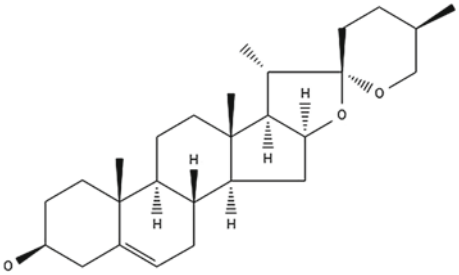
Polygonatum polysaccharide and oligosaccharides are the major classes of bioactive constituents found in Huangjing. In addition, steroidsaponins, flavonoids, alkaloids, lignins and amino acids have also been reported [2].

23.2.1 Poly- and Oligosaccharides

Huangjing contains three polysaccharides, the polygonatum polysaccharide I, II and III, with molecular weight larger than 200,000 Da. The sugar composition includes glucose, mannose and galacturonic acid. It was also revealed to have three oligosaccharides, oligosaccharides I (MW 1630 Da, comprises 8 fructose units and 1 glucose), oligosaccharides II (862 Da, 4 fructose units and 1 glucose) and oligosaccharides III (474 Da, 2 fructose units and 1 glucose). The total polysaccharide content was reported to be 11.74 % in Huangjing [3–5].

23.2.2 Steroidsaponins

Steroidsaponins found in Huangjing includes dioscin, diosgenin, digitoxin, smilagenin, etc., with dioscin as the dominant one. The structures of representative steroidsaponins are shown in Fig. 23.2 [6–9].



I R=-β-D-Glc-[(2→1)-α-L-Rha]-(4→1)-β-D-Glc-(3→1)-β-D-Glc

II R=-β-D-Glc-[(4→1)-α-L-Rha]-(2→1)-α-L-Rha

III R=-β-D-Glc-[(2→1)-α-L-Rha]-(4→1)-β-D-Glc

Fig. 23.2 Representative steroid saponins isolated from Huangjing

23.3 Pharmacological Studies

Huangjing is a common herb used in TCM, especially for treating diseases related to cardiovascular system. Modern pharmacological studies have revealed that Huangjing have the following bioactivities, such as enhancing immune function, anti-aging, regulating blood sugar and blood lipids, anti-inflammatory, antiviral, anti-fatigue, detoxification, improving learning and memorizing abilities, etc. [10–12].

Polysaccharide was shown to have beneficial effects on hyperglycemia through inhibiting the action of the adrenaline in hyperglycemia mice. It showed anti-aging potential through reducing the oxygen free radicals of the brain, strengthening radical scavenging capacity and improving the antioxidant function. Animal studies provided some pieces of evidence. For example, in one study, rats were treated with 300, 600, 1200 mg/kg respectively by intragastric administration, 10 ml/kg per day for 30 days. Then the activities of serum SOD, GSH-Px and the content of MDA were measured. The results showed that polysaccharides can significantly reduce the skeletal muscle MDA level, and enhance the activity of SOD and GSH-Px [13].

It also showed the activities of enhancing the immunologic functions, antibacterial, and anti-tumor. In addition, total saponins in Huangjing showed to have improved memory acquired disorder caused by scopolamine.

23.4 TCM Applications and Dietary Usage

23.4.1 TCM Applications

Huangjing could reinforce Qi and nourish Yin, invigorate the function of Spleen, moisten Lung, and benefit the Kidney. It is commonly used for dry cough, deficient

spleen and stomach, dizziness, weak lower back and knees, and pulmonary tuberculosis. Now it is also widely used in treatment of diabetes [14, 15], hyperlipidemia, hypertension, chronic hepatitis, headache, etc. Huangjing could be used in single form or in combination with other herbs based on TCM theory.

In clinical applications, commonly used Huangjing preparations include the following forms:

1. Huangjing tablets: it is only composed of Huangjing with function of nourishing Qi and blood.
2. Danggui Huangjing extract: it is composed of two herbal components: Danggui (roots of *Angelica sinensis*) and Huangjing, with functions of nourishing blood Yin and benefiting Liver and Spleen. It is used for weak people with these symptoms such as eating less, dry mouth, dry throat, sallow and emaciated.
3. Huangjing syrup: it is composed of Huangjing, Yiyiren (seed of *Coix lacryma-jobi* var. *ma-yuen*.), Nanshashen (root of *Adenophora tetraphylla*). This drug is suitable for people who are physically weak, fatigue, palpitations, shortness of breath, cough without phlegm, dry mouth.
4. Kelening capsule: it consists of Huangjing, Huangqi (root of *Astragalus membranaceus*), Shengdihuang (root tuber of *Rehmannia glutinosa*), Taizishen (root tuber of *Pseudostellaria heterophylla*), Tianhuafen (root of *Trichosanthes kirilowii*). The product is used for patients of non-insulin-dependent diabetes [16].

23.4.2 Dietary Usages

As a dietary herb, Huangjing is commonly used to prepare medicated foods such as: Huangjing tea, Huangjing wine, Bingtang Huangjing soup and Huangjing porridge.

23.4.2.1 Huangjing Tea

This tea can be made of Huangjing alone or with other herbs. Here are a few examples: Huangjing Tea (Huangjing 15 g); Huangjing Gouqi Tea (Huangjing 15 g; Gouqizi (fruit of *Lycium barbarum* L.), 10 g; and green tea 3 g); Yuzhu Huangjing Tea (Huangjing 15 g; Yuzhu (rhizome of *Polygonatum odoratum*), 15 g); Heshouwu Huangjing Tea (Heshouwu (rhizome of *Polygonum multiflorum*), 15 g; Huangjing, 15 g). You can put them into a cup with gauze bag, add boiling water, keep for 10 min, then use as tea.

23.4.2.2 Huangjing Wine

Huangjing alone or combined with other herbs can be used to prepare wine. For example, Huangjing (20 g) is cut into slices and put in a small bag, then soaked it in

500 g wine for 30 days. Taking 15–20 ml daily is recommended for its benefit to spleen and sleep disorders [17].

23.4.2.3 Huangjing Used in Medicated Foods

In daily life, Huangjing can be used to prepare Bingtang Huangjing soup and Huangjing porridge. For making Bingtang Huangjing soup, Huangjing (30 g) is soaked in cold water, added rock sugar (50 g), then cooked for 1 h. As for Huangjing porridge, Huangjing (15–30 g) and rice (100 g) are put together and boiled till fully cooked. It is claimed to have anti-aging and anti-oxidant effects.

23.5 Clinical Evidences

Huangjing is a commonly used Yin-tonifying medicine in TCM. In clinic, Huangjing is mostly used in combination with Yuzhu (rhizome of *Polygonatum odoratum*), Maidong (root of *Ophiopogon japonicus*) and some other Yin-tonifying herbs. Huangjing decoction was reported to lower blood glucose in a study involving 94 subjects with type II diabetes. In that report, 48 subjects were given Huangjing decoction orally, while the control group was treated with metformin. The total effective rate was 81.25 % in Huangjing group, compared to 56.52 % in the control group indicating a significant effect [18].

23.6 Safety Evaluation and Toxicity Data

Few clinical report on the toxicity or side effect is available that could be directly related to the use of Huangjing. The maximum tolerance dose in mice with oral ingestion of Huangjing was 2.04 g/20 g (102.4 g/kg, or equivalent to 409.6 times of clinically recommended dose, that is 15 g crude herb daily). At this dose, animals were found to be generally in good condition, showing normal activity, food intake, urination, and fur condition, all indicators of non-toxic symptoms [19].

In summary, Huangjing is a fairly safe herb and is used to regulate blood glucose and blood lipids, as well as to enhance immune function. Nevertheless, one must seek doctors' advice when considering using this herb.

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Chapter 24
Polygonatum odoratum (Mill.) Druce 玉竹 (Yuzhu)

Ta-si Liu and Ying-Jiao Liu

24.1 Botanical Identity

Yuzhu, a perennial herb in the family of Liliaceae, has traditionally been used as a tonic and thus frequently applied as a food supplement. It belongs to the *Polygonatum* genus [1], with dried rhizome as the medicinal part. At present, the commercial product is prepared from cultivated material grown in Hunan, Henan, Jiangsu, Liaoning and Zhejiang provinces. As the typical botanical traits, *Polygonatum odoratum* (Mill.) Druce often grows in open coniferous forests, in woodland edges, on shaded slopes, and along streams and rivers, at the elevations of about 500–3000 m. Yuzhu is a perennial herb growing up to 20–65 cm high, stem tipped to one side. The fleshy roots are of 0.5–1.3 cm in diameter, yellowish white, densely fibrous roots. Leaves are 7–12, alternate, elliptic-oblong to ovate, upper surface green, under surface grey, vein bump. Flowers are axillary, usually 1–3 in clusters, white [2].

Yuzhu is usually processed with steam and air dried after being harvested in the fall between September and October of third year plant, with hair-like roots removed. The partially dried rhizomes are sorted by size, dried in the sun to soften, rubbed repeatedly until the drug is devoid of hard core, and then dried in the sun thoroughly. *P. odoratum* grows wildly and is cultivated in the southern area of China, known as Yuzhu, especially in Hunan province. In addition to China, it grows in Thailand and Vietnam. It can also be found growing throughout the southern United States [3] (Fig. 24.1).

T. Liu (✉) · Y.-J. Liu
Hunan University of Traditional Chinese Medicine, 410208 Changsha, China
e-mail: liutasi@126.com

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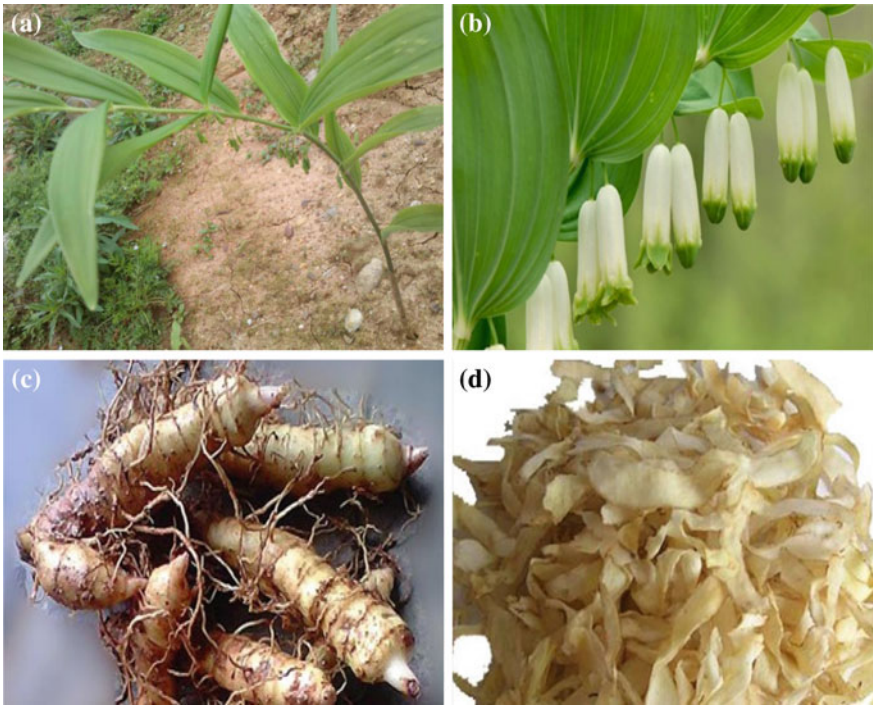


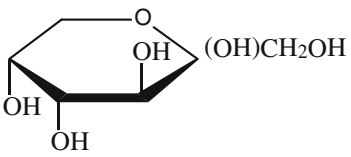
Fig. 24.1 The whole plant (**a**), flowering plant (**b**), fresh rhizomes with roots (**c**) and processed products (**d**) of Yuzhu

24.2 Chemical Constituents

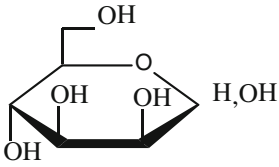
Yuzhu, a typical representative herb of the Liliaceae family, is an important traditional Chinese herbal medicine which contains a variety of biologically active compounds. Various steroidal saponins and polysaccharide have been isolated from this plant.

24.2.1 Polygonatum Odoratum Polysaccharide

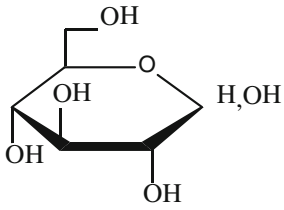
Polygonatum odoratum polysaccharide is the main bioactive component, and the content is 6.51–10.27 % [4]. The monosaccharide composition includes D-fructose (1), D-Mannose (2), D-Glucose (3), D-Galacturonic acid (4) (shown in Fig. 24.2), with molar ratio of 6:3:1:1.5. It also contains Polygonatum fructans A, B, C, D, with composition of glucose and fructose [5]. *Polygonatum odoratum* lectin, a novel mannose-binding lectin with anti-viral and apoptosis inducing activities, was also isolated from rhizomes of *Polygonatum odoratum* (Mill.) Druce [6].



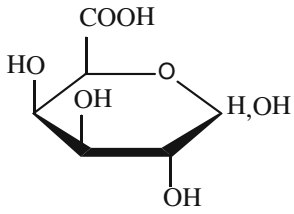
D-Fructose, 1



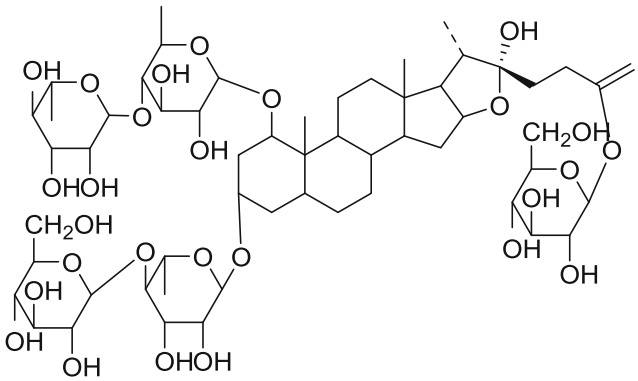
D-Mannose, 2



D-Glucose, 3



D-Galacturonic acid, 4



Convallamarin

Fig. 24.2 Representative polysaccharide monomers and convallamarin isolated from Yuzhu

24.2.2 Steroidal Saponins

Steroidal saponins are considered Yuzhu's bioactive ingredients, with its total steroidal saponins content at 0.22–0.36 % [7]. Yuzhu contains a number of steroidal saponins, namely convallamarin (5) (shown in Fig. 24.2), convallarin, odospiroside, polyspirostanol, polysipirostanoside, polyfuroside. Now four steroidal saponins POD I–IV had been isolated [8, 9].

24.3 Pharmacological Studies

Yuzhu is a common Chinese medicinal herb and is considered to be an immune conditioning agent with a long history of indigenous use for relieving dryness by quenching thirst and promoting secretion of fluid, reducing blood lipids, glucose, improving myocardial ischemia, and have been widely used in traditional Chinese medicine for treatment of diverse diseases such as diabetes.

Polygonatum odoratum polysaccharide can improve mouse superoxide dismutase activity, enhance radical scavenging, inhibit lipid peroxidation, and reduce MDA content, thereby reduced injury to body tissues, enhanced immune function [10], anti-neoplastic activities [11] and anti-aging [12]. The methanol and n-butanol extracts of Yuzhu were reported to reduce blood glucose in diabetic mice, and have tendency of improving glucose tolerance [13, 14]. Yuzhu has certain benefits to diabetes, heart disease, and leukemia.

Flavonoids are well known as antioxidants, and may influence the intracellular redox status. In a rat study comparing antidiabetic effects of saponin rich and flavonoid rich fractions from Yuzhu, the former was found to be more effective in reducing blood glucose, the flavonoid rich fraction was more effective in enhancing superoxide dismutase (SOD) activity and reducing malondialdehyde (MDA) level [15].

24.4 TCM Applications and Dietary Usage

Yuzhu has important application in the frame of a healthy diet, while remains to be a traditional Chinese herb.

24.4.1 TCM Applications

In traditional Chinese medicine, the properties of Yuzhu ascribed to jade bamboo, are sweet with slight bitter after taste, nontoxic, warming, nourishing the Yin (vital essence), lubricating dryness, stopping thirst, enhancing wisdom, improving circulation, and producing good complexion, with the lungs, kidney, stomach and spleen being its target organs. Clinical studies gave favorable reports of its application in decoction and effects on lowering the blood pressure via vasodilation and for hyperlipidemia:

1. Nourish Yin and release the exterior: JiajianWeirui Tang (Modified Polygonatum Decoction) with Yuzhu 9 g, Congbai (*Allium fistolosum*) 9 g, Jiegeng (root of *Platycodon grandiflorum*) 5 g, Baiwei (root of *Cynanchum atratum*) 3 g, Dandouchi (fermented seed of *Glycine max*) 9 g, Bohe (herb of *Mentha haplocalyx*) 5 g, processed Gancao (root of *Glycyrrhiza uralensis*) 5 g, and two pieces of Dazao (fruit of *Ziziphus jujuba*) to be taken as a decoction [16].

2. Replenish Qi and nourish blood, anti-neoplastic [11]: Renshen (root of *Panax ginseng*) 10 g, Huangqi (root of *Astragalus membranaceus*) 25 g, Baizhu (rhizome of *Atractylodes macrocephala*) 15 g, Fuling (sclerotium of *Poria cocos*) 15 g, Wuweizi (fruit of *Schisandra chinensis*) 10 g, Dangshen (root of *Codonopsis pilosula*) 15 g, Danggui (root of *Angelica sinensis*) 10 g, Yuzhu (rhizome of *P. odoratum*) 15 g, Heshouwu (root tuber of *Polygonum multiflorum*) 15 g, Yinyanghuo (leaf of *Epimedium brevicornu*) 15 g, Nvzhenzi (fruit of *Ligustrum lucidum*) 15 g, Suanzaoren (seed of *Ziziphus jujuba* var. *spinosa*) 10 g, Sanqi (root of *Panax notoginseng*) 2 g, Baihuasheshecao (herb of *Hedyotis diffusa*) 25 g.
3. Atrophic gastritis [17]: Yuzhu 30 g, Danshen (root of *Salvia miltiorrhiza*) 30 g, Tanxiang (core material of trunk of *Santalum album*) 5 g, Sharen (fruit of *Amomum villosum*) 10 g, shanzha (fruit of *Crataegus pinnatifida*) 10 g.

Yuzhu concentrated decoction [18]: It is prepared by extracting freshly rhizome with boiling water and subsequently filtering the water extracts 250 g/bottle.

24.4.2 Dietary Usage

Because of the sweet fragrance and taste, as well as health-improving activity, Yuzhu has been widely used as an ingredient or supplement in many food products including functional foods, flavours, drinking water, and tea preparations. As Yuzhu is nontoxic, it can be used quite freely in making soup in combination with several herbs and spareribs, fish, or chicken.

Yuzhu porridge [19]: Yuzhu 30 g, crystal sugar 20 g, rice 100 g. It can offer adjutant therapy to people who are with weakness of spleen and stomach.

Yuzhu tea: Grinding Yuzhu 10 g into powder and then brewing with boiling water. The functions include nourishing Yin and moistening dryness, promoting fluid production.

Yuzhu wine: Yuzhu 100 g, wine 720 g. Yuzhu is cut into pieces then mixed with sugar and wine and stored in cold and dark place. It has functions of filling kidney essence and helping on fatigue.

24.5 Clinical Evidences

The term for diabetes in ancient China was Xiaoke Zheng or Xiaodan Zheng resulted from lung heat, excessive fire in the stomach, deficiency of kidney Yin or both of Yin and Yang. According to those, treatment strategies for diabetes in Chinese medicine were to eliminate heat by nourishing Yin, moistening dryness and promoting fluid production. Yuzhu is an important yin-nourishing herb and has long been used, since then, to improve health status of patients with Xiaoke zheng.

Recent evidence revealed its bioactive components saponins and flavonoids might prevent or reduce body damage or diabetic complications from diabetes [15].

Polygonatum odoratum polysaccharide can enhance the radical scavenging, inhibit lipid peroxidation, reduce MDA content, thereby reduce the injury of body tissues, enhance the immune function and anti-aging.

24.6 Safety Evaluation and Toxicity Data

Yuzhu is used in supplements for many food products including tea. Azetidine-2-carboxylic acid (ACA) in Yuzhu is a potent toxin that could be incorporated into proteins in place of proline leading to protein dysfunction. Quantification of ACA in *Polygonatum* species can contribute to establish safety in food industry. Unlike the ACA toxicity in animals, the toxicity of ACA in humans is not yet clearly understood [20].

However, some reports indicated that Yuzhu has little toxicity, which was demonstrated by the LD_{50} of Yuzhu injection in mice of 112.5 g/kg, and in rabbit showing no toxicity with stem and leaf decoction, root extract or decoction for intravenous injection at 10 g/kg [21].

In a word, Yuzhu is definitely a relatively safe Chinese herbal medicine often used in the treatment of diabetes and healthcare purpose. But each herbal medicine has its potential side-effects, so the attention must also be paid when you decide to use this herb personally without doctor's advice. It's suggested to seek doctor's advice prior of use.

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Chapter 25
Polygonum multiflorum Thunb. 何首乌 (Heshouwu, Tuber Fleeceflower Root)

Raorao Li and Hui-Min Gao

25.1 Botanical Identity

Heshouwu, also called Chishouwu or tuber fleeceflower root, is the dried root of *Polygonum multiflorum* Thunb. [1], a perennial twining vine plant in the family of Polygonaceae. It is one of the most popular Chinese herbal medicines. The root is collected in autumn and winter while the lower leaf of the plant turns yellow and the upper leaf becomes fragile. Once collected, it is then washed clean.

Traditionally, Heshouwu was recorded as two classes: one is Chishouwu, which is collected from the root of *P. multiflorum* Thunb., with the characteristic of reddish-brown root epidermis, and the other is Baishouwu. However, the origin plant of Baishouwu remains unclear up to now. The ongoing argument is focused on *Cynanchum bungei* Decaisne [2], or *P. multiflorum* var. *angulatum* S.Y. Liu (Lingzhi Heshouwu in Chinese). Only Chishouwu is discussed here.

P. multiflorum Thunb. is widely distributed in many places in China, such as *Hebei*, *Shanxi*, *Jiangsu*, *Zhejiang*, *Anhui*, *Fujian*, *Shandong*, *Hubei*, *Hunan*, *Guangdong*, *Guangxi*, *Gansu*, *Sichuan*, *Yunnan*, *Guizhou*, etc. This plant lives in warm and humid places where the average temperature ranges from 16.0 to 21.5 °C in a year and air relative humidity is 70–80 %. The optimal soil water content is 25–30 %. It can be cultivated in the duct, tanabe, the edge of forests and farmlands [3].

In recent years, Heshouwu is widely used not only as the raw material for the pharmaceutical manufacture, but also as an important ingredient in food products, health products and cosmetics. The increased demand for Heshouwu has led to the shortage of the wild resources, and some GAP planting bases appeared across the country, such as *Guizhou* and *Sichun* planting bases [3].

R. Li · H.-M. Gao (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: huimin_gao@126.com

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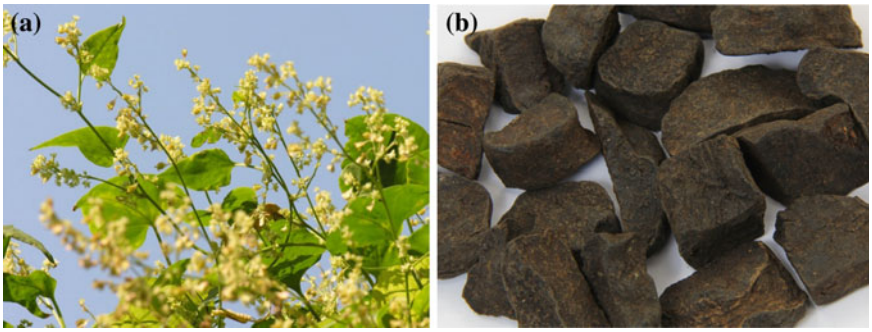


Fig. 25.1 Flowering plant (**a**) and crude drug (**b**) of Heshouwu

Heshouwu slices are obtained by the following procedure: the crude material was washed, macerated shortly, softened thoroughly, cut into thick slices or sections, and then dried. For some special therapeutic actions, these slices will be further processed with black bean juice by stewing or steaming. Namely, *Polygoni Multiflori Radix Praeparata*, was obtained by stewing Heshouwu slices together with black bean juice in a suitable non-ferrous container till the juice is exhausted or steaming till the appearance of a brown colour occurred (Fig. 25.1).

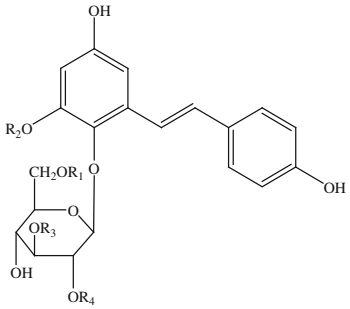
25.2 Chemical Constituents [1, 4]

Heshouwu, root of *P. multiflorum,* contains a variety of constituents including stilbene glycosides, anthraquinones, phenolics, flavonoids, phospholipids, carbohydrate compounds and other types of compounds. Among them, stilbene glycosides and anthraquinones are two main types of effective compounds.

25.2.1 Stilbene Glycosides

The contents of this type of compounds are over 2.6 % in the root of *P. multiflorum*. 2,3,5,4′-tetrahydroxystilbene-2-*O*-*β*-*D*-glucoside, which is also called stilbene glycoside (TSG, **1**), is used as an index component for the quality evaluation of Heshouwu because of the high amounts in the crude material and potent bioactivity. 2,3,5,4′-tetrahydroxystilbene-2,3-di-*O*-*β*-*D*-glucoside (polygonimitin C, **2**), 2,3,5,4′-tetrahydroxystilbene-2-O-(6″-*O*-*α*-*D*-glucopyranosyl)-*β*-*D*-glucopyranoside (**3**) and 2,3,5,4′-tetrahydroxystilbene-2-O-(6″-*O*-acetyl)-*β*-*D*-glucopyranoside (**4**) are also isolated from this plant (Fig. 25.2).

Fig. 25.2 Stilbene glycoside isolated from *P. multiflorum*



TSG, 1, R_1=R_2=R_3=R_4=H

polygonimitin C, 2, R_1=R_3=R_4=H, R_2=*β-D*-glc

3, R_1=*α-D*-glc, R_2=R_3=R_4=H

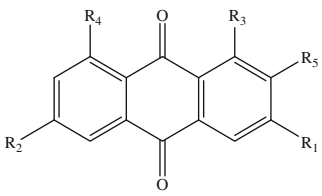
4, R_1=acetyl, R_2=R_3=R_4=H

25.2.2 Anthraquinones

Anthraquinone is another major type of compounds, such as main constituents emodin (**5**) and chrysophanol (**6**), minor constituents rhein and citreorosein, as well as trace compounds physcion (**7**), aloe-emodin, 2-acetyl-emodin, emodin-1,6-dimethylether, questin, emodin-8-O-*β-D*-glucoside, physcion-8-O-*β-D*-glucoside, chrysophanol-8-O-*β-D*-glucopyranoside, emodin-3-ether and etc (Fig. 25.3).

The content of free anthraquinone in the decoction of *P. multiflorum* is slightly higher than that in crude one, but the content of conjugated anthraquinone in the crude drug is obviously higher than that in the decoction. This is resulted from the chemical change induced by the decoction.

Fig. 25.3 Anthraquinones isolated from *P. multiflorum*



Emodin,5,R_1=CH_3, R_2=OH, R_3=OH, R_4=OH, R_5=H

Chrysophanol,6,R_1=CH_3, R_2=OCH_3, R_3=OH, R_4=OH, R_5=H

Physcion,7,R_1=CH_3, R_2=H, R_3=OH, R_4=OH, R_5=H

25.2.3 Phospholipids

Phospholipids are rich in the root of *P. multiflorum*, with the content of about 0.15–0.30 %. Lecithin, lipositol, phosphatidic, phosphatidic acid and cardiolipin are representative of this type of constituents. Lecithin is the highest compound with the amount of about 30–40 % in total phospholipids.

25.2.4 Carbohydrate Compounds

The monosaccharides, *D*-glucose and *D*-fructose, are detected in the crude material, but not *D*-galactose, lactose, *L*-rhamnose and xylose. The disaccharide, sucrose is also detected. In the processing procedures, the content of *D*-glucose is gradually increased, whereas the content of *D*-fructose, sucrose and the total sugars are reduced. In the first 16 h, the significant content changes of these compounds is observed [5].

25.2.5 Other Compounds

There are many other kinds of compounds in *P. multiflorum*, such as flavonoids, polyphenols composition, trace elements and minerals, etc.

25.3 Pharmacological Studies [1]

The multi-channel, diverse, multi-target pharmacologic effects of Heshouwu is associated with its chemical substances.

Stilbene glycosides have the potent antioxidant activity and can scavenge reactive oxygen species, which is also deduced as one of the reasons that Heshouwu displayed the liver-protection effect. In addition, stilbene glycosides can give a certain action of antagonism to the increase of lipid peroxidation and monoamine oxidase as well as higher level of alanine aminotransferase and aspartate aminotransferase when liver was damaged. Stilbene glycosides can also significantly decrease the levels of free fatty acids in serum.

Anthraquinones can lower blood pressure and have anti-atherosclerotic, antibacterial, laxative and other pharmacological effects. Anthraquinone glycosides from the root of *P. multiflorum* have significant antitumor effects and can reduce toxicity induced by cyclophosphamide [6].

The enriched phospholipids, the main raw material for red blood cell and other cell membrane, can promote development of red blood cell and possess lots of

bioactivities, such as immune regulation, antioxidation, anti-aging and etc. Flavonoids can regulate blood sugar and improve the cardiovascular system. Polyphenols have antioxidant effects and the trace minerals can supply the body with the necessary nutrients.

25.4 TCM Applications and Dietary Usage

25.4.1 TCM Applications [7]

Heshouwu is one of the most commonly-used herbal medicines. According to the Traditional Chinese medical theory, its action is to remove toxin, disperse abscesses, interrupt malaria, and moisten the intestines to relax the bowels. It is indicated for the treatment of sore and abscess, scrofula, itching caused by rubella, weak constitution caused by long-term malaria and constipation caused by intestinal dryness.

The prepared slice, that is *Polygoni multiflori radix praeparata*, is used to tonify liver-kidney, replenish essence and blood, blacken hair, strengthen sinew and bone, resolve turbidity and lower lipid. It is indicated for blood deficiency and sallow complexion, dizziness and tinnitus, premature graying, soreness and weakness in the low back and knees, numbness of the limbs, flooding and spotting, vaginal discharge and hyperlipidemia.

25.4.2 Dietary Usages [8]

As one of the famous herbs and valuable dietary botanical materials, Heshouwu has been used in different ways for a long time, such as Heshouwu wine, Heshouwu tea, Heshouwu soup and so on. The prepared Heshouwu was used in all the following dietaries. The following drinking or eating forms can be easily made in home ordinarily.

25.4.2.1 Heizhima Shanyao Heshouwu Powder

The dried Heizhima (Seed of *Sesamum indicum* L., 250 g) is baked and powdered. Shanyao (rhizome of *Dioscorea opposite* Thunb., 250 g) is washed, cut into pieces, baked to dryness, and then powdered. The prepared Heshouwu (root of *P. multiflorum*, 250 g) is baked to dryness and then powdered. Three powdered herbal medicines above were mixed. The mixture is suspended with water and stewed before eating. The serving size is 25 g. Twice in one day. The powder is very nutrient for patients suffering from the anemia due to deficiency of liver and kidney, whose symptom is as followed: the face color is pale or sallow, dizziness,

hypodynamia, intolerance to cold, cold hands and feet as well as aching in the waist and knees.

25.4.2.2 Pig Liver Steamed with Prepared Heshouwu

The prepared Heshouwu (20 g), slices of pig liver (250 g), Gouqizi (fruit of *Lycium barbarum*, 10 g), ginger pieces, welsh onion segment are mixed and steamed, and at the end, a teaspoon of salt, refined white sugar, sesame oil, soy sauce and rice wine are added, separately. It is better to eat this food when it is hot, otherwise, the liver tastes hard and fishy. This food is suitable for blood deficiency and sallow complexion, dizziness and tinnitus, premature graying, soreness and weakness in the low back and knee, numbness of the limbs, flooding and spotting, vaginal discharge and hyperlipidemia.

25.4.2.3 Hen Steamed by Prepared Heshouwu

The food material is composed of prepared Heshouwu (30 g), a hen, a teaspoon of salt, ginger piece and 50 ml cooking wine. The prepared Heshouwu powder packaged by a little cloth bag, is put into the belly of the cleaned hen, and then the hen is stewed till it is boiled up. Some salt, ginger pieces and cooking wine are to be added before the cooking is finished. The food is helpful for patients have dizziness, insomnia, rectal prolapse, uterine prolapse, and etc.

25.4.2.4 Heshouwu Cishen Soup

Heshouwu (root of *P. multiflorum*, 5 g), Cishen (*Stichopus japonicus*, 150 g) and pork belly (50 g), are put together with a little Jiang (rhizome of *Zingiber officinale*) into a pot with 600 g of broth, and heated by a strong fire. Afterwards, the soup is stewed by a small fire for 30 min and then bean sprouts (10 g) are added. The soup should be stewed for another 10 min. At the end, some condiments can be added according to individual preference. This soup can improve physical weakness, weight loss and fatigue, that is due to the loss of essence and blood. It is also suitable for premature white hair and beard owing to blood deficiency.

25.5 Quality Evaluation and Assurance [7]

According to current Chinese Pharmacopoeia (2010 version), the content 2,3,5,4′-tetrahydroxystilbene-2-*O*-*β*-D-glucoside ($C_{20}H_{22}O_9$) should not be less than 1.0 % in the dried crude material. The content of total anthraquinones in the dry root of *P. multiflorum* is about 1.1 %.

The content of conjugated anthraquinone, in the dry root of *P. multiflorum*, should not be less than 0.10 % referring to emodin and physcion. In the processed slices, the content of conjugated anthraquinone should not be less than 0.05 %.

25.6 Clinical Evidences

Heshouwu is consumed either in its raw form, or as an extract after processing. It appears to be efficacious in the treatment of premature greying of hair, lumbago, spermatorrhea, leucorrhea and constipation, or as an anti-aging product. The following case reports in human regarding Heshouwu or its preparations are related with insomnia and Alzheimer's disease. A large-scale pharmaco-epidemiologic study was conducted to evaluate the frequency and patterns of CHM use in treating insomnia, based on the traditional Chinese medicine outpatient claims from the National Health Insurance in Taiwan for the year 2002. There were 16134 subjects who visited TCM clinics for insomnia in Taiwan during 2002 and received a total of 29801 CHM prescriptions. Shou-wu-teng (stem of *P. multiflorum*) was the most commonly prescribed single Chinese herb [9]. The clinical effect of compound *P. multiflorum* extract on Alzheimer's disease was also observed. 120 of 209 AD patients, were treated with compound *P. multiflorum* extract as a treatment group, 60 were treated with *P. multiflorum* extract as a Chinese herb control group, and 29 were treated with Naofukang as a western medicine control group. After the 12 week treatment, the scores for Mini-Mental State Examination (MMSE) and Ability of Daily Living Scale (ADL) were improved in all groups. Compound *P. multiflorum* extract has effect on AD, and it is superior to *P. multiflorum* extract or Naofukang [10].

25.7 Safety Evaluation and Toxicity Issue

There were some clinical reports on the toxicity and side effects directly related with Heshouwu and related preparations. The major clinical adverse reactions were different degrees of liver injury [11], mostly mild or moderate acute hepatitis. A minority of patients had severe acute hepatitis, mainly as jaundice, abnormal liver function, liver pain and elevated ALT buckle, and so on.

The adverse reactions were related to the following factors: dose, improper drug compatibility, the mode of administration as well as the physique of patients and the processing methods by analyzing case reports [1]. The first one is long-term large dose to take the crude material or the Shouwu tablets. In recent years, people who want to lose weight and make hair black, take too much the crude drug, or its preparations, which resulted in the increasing reports on the adverse effect induced by overdosed *P. multiflorum*. The possible toxic substances were deduced to be related to its anthraquinones, which has similar adrenocorticotropic hormone-like

effect and has a certain toxicity on the liver. The second factor is improper drug compatibility and the mode of administration. For example, the compatibility of Heshouwu (root of *P. multiflorum*) and Laifuzi (seed of *Raphanus sativus* L.) will lead to occurrence of adverse effect. In addition, the injection has a higher risk than oral administration. The third factor is related to allergic reaction of Hesohuwu for some patients with the special physique, especially those with family history of hereditary metabolic liver enzyme defect. The last one is involved in the improper processing method, because the crude material is more toxic than the processed slices.

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Chapter 26
Pueraria lobata (Willd.) Ohwi 葛根 (Gegen, Kudzu)

Minhui Li

26.1 Botanical Identity

Gegen, the root of *Pueraria lobata* (Willd.) Ohwi, a perennial liana in the family Leguminosae, is used as traditional Chinese medicine with various medicinal activities. Puerarin was first recorded in *Shennong Bencao Jing*. It has the efficacy of relieving muscles analgesia, reducing fever and promoting eruptions, helping produce saliva and slake thirst, invigorate vital function, antidiarrheal and so on [1]. Gegen is a robust climbing vine with tuberous roots that can be measured up to 2 m long by 18–45 cm diameter. The stem is up to 30 m long with leaves that are alternate and trifoliate. The standard petal is broadly ovate, often with a yellow blaze near its base; lateral wing petals are more or less obovate and keel petals are nearly straight [2, 3].

Gegen can be harvested wildly. The problem of insufficient resources in development and utilization has not been found, because Gegen is widely distributed in China with the exception of Tibet and Xinjiang provinces in which there are many cultured species. It also wildly spreads over some states of the USA. Gegen is harvested as a 2–3 year plant in autumn and winter. The tuberous roots of Gegen are often cut into thick slices or pieces when they are fresh, then dried [4, 5]. From April to August, the total content of isoflavonoid is lowest, then, increases gradually from October to December. In January of the following year, the content of isoflavonoid reaches to maximum, so it is the best time to harvest [6] (Fig. 26.1).

M. Li (✉)
Baotou Medical College, Baotou 014060, Inner Mongolia, China
e-mail: li_minhui@aliyun.com

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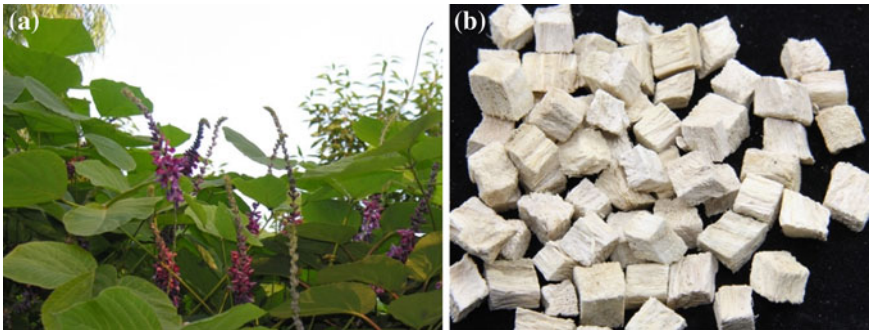


Fig. 26.1 The flowering plant (**a**) and crude drug (**b**) of Gegen

26.2 Chemical Constituents

The major active constituents in the roots of *P. lobata* are isoflavones and their glycosides. So far, about 30 isoflavones have been isolated from Gegen including puerarin (daidzein 8-C-glucoside) (**1**), daidzein (**2**), daidzin (daidzein 7-*O*-glucoside) (**3**), genistein (**4**), formononetin (**5**), 3′-hydroxypuerarin (**6**), 3-methoxypuerarin (**7**) and so forth (shown in Fig. 26.2). Puerarin and daidzein are two kinds of active isoflavones. Furthermore, puerarin, as a main, effective and characteristic marker compound of this genus, is used as a standard compound for quality evaluation of the crude drug Gegen and related pharmaceuticals. Gegen is the main material for extracting puerarin in the medicinal industry in China [6, 7].

Saponins with the structures of oleanene-type triterpenes and their glycosides are identified from kudzu roots, but the contents are low. More than 19 saponins have been isolated so far, such as kudzusaponins $SA_{1–4}$, soyasaponin A_3 and kudzusaponins $A_{1–5}$ (shown in Fig. 26.3) [6].

There are also many other chemical constituents found in Gegen, including but-2-enolides, methyl palmitate, 2-methoxyethyl acetate, acetylcarbinol, butanoic acid 5-methylhydrantoin, tuberosin, choline chloride, acetyl cholinechloride, D-mannitol, glycerol 1-monotetracosanoat and etracosanoid acid-2,3-dihydroxypropyl ester etc. [6, 7].

26.3 Pharmacological Studies

Modern pharmacological studies have revealed that Gegen shows various biological activities including anti-hypertensive, anti-pathogenic, anti-diabetic, anti-platelet, anti-inflammation and anti-apoptotic. It also can alleviate upper respiratory tract diseases, trigeminal neuralgia, lumbar muscle strains, tension headaches, arthralgia, ischemic stroke, rheumatoid arthritis, dysentery, and nettle rash.

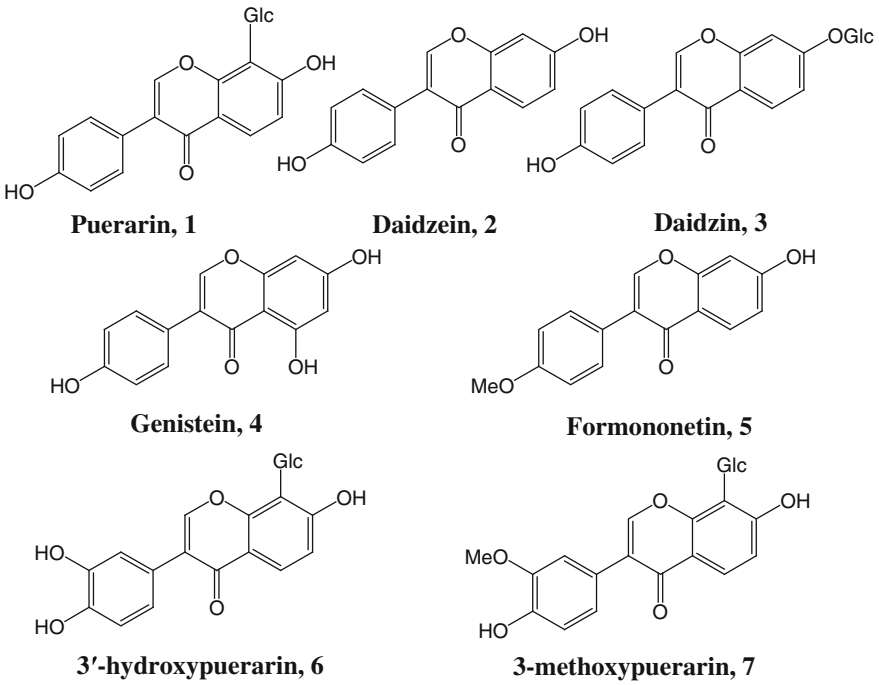
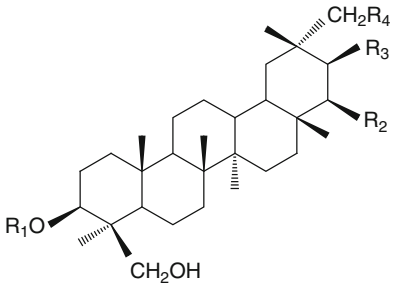


Fig. 26.2 Representative isoflavones and their glycosides isolated from Gegen

26.3.1 Cardiovascular Diseases

According to previous researches, Gegen has been utilized as a traditional medicine in China for thousands of years to enhance the body fluid through its antipyretic effect, and most recently used in TCM formulae for treating cardiovascular diseases. Modern researches demonstrate that the isoflavone puerarin is the most important active component which plays a major role in the cardiovascular systems, such as anti-hypertension, vasodilation, anti-ischaemia and positive chronotropic. Puerarin also has an effect on the cerebrovascular system, and is used to treat cerebral vasodilation, apoptosis, protection of cerebral ischaemia and reperfusion.

Researches manifest that it is possible for puerarin to improve sodium nitroprusside-induced relaxation in the porcine coronary artery by means of the cyclic AMP-dependent pathway [8]. Puerarin has a good effect on cerebral vasospasm, either prophylaxis, treatment or prognosis. The mechanism may be correlated with increasing the plasma levels of NO and PGI_2 (prostacyclin I_2) and the cerebral blood flow, decreasing TXA_2 (thromboxane A_2) in plasma and improving cerebral perfusion [9].



	R_1	R_2	R_3	R_4
Kudzusaponins SA_1	$GlcA^2$-gal	OH	OH	H
Kudzusaponins SA_2	$GlcA^2$-gal	O-ara	OH	H
Kudzusaponins SA_3	$GlcA^2$-gal^2-rha	O-ara	OH	H
Kudzusaponins SA_4	$GlcA^2$-glcA	O-ara	OH	H
Soyasaponin A_3	$GlcA^2$-gal^2-rha	OH	OH	H
Kudzusaponins A_1	$GlcA^2$-ara^2-rha	O-xyl	OH	OH
Kudzusaponins A_2	$GlcA^2$-gal	OH	OH	OH
Kudzusaponins A_3	$GlcA^2$-gal^2-rha	OH	OH	OH
Kudzusaponins A_4	$GlcA^2$-gal	OH	OH	OH
Kudzusaponins A_5	$GlcA^2$-glc	OH	OH	OH

Fig. 26.3 Chemical structures of saponins isolated from kudzu. *Glc* glucose, *gal* galactoside, *rha* rhamnose, *ara* arachidonic acid

26.3.2 Diabetic and Diabetic Complications

Puerarin has been used to treat diabetes mellitus in China for many years. Puerarin can lower the blood glucose level in a dose-dependent and significantly enhance glucose uptake into the insulin sensitive cell [10, 11]. In the case of hyperglycemia in diabetes mellitus, puerarin may inhibit high glucose-induced vascular smooth muscle cell proliferation by means of disturbing PKC beta 2/Rac1-dependent ROS (reactive oxygen species) pathways, consequently making for the attenuation of neointimal formation [12].

The impacts of puerarin on diabetic and diabetic complications are also displayed through inhibition of diabetic ocular complications [13], inhibition of diabetic vascular complications [12] and amelioration of diabetic nephropathy [14].

26.3.3 Phytoestrogenic Activity

Puerarin's structure is similar to that of mammal's estrogen, and commonly regarded as phytoestrogen [15]. Injection of puerarin (0.7 mg/kg) for 14 days up-regulated the number of uterine glands in immature ovariectomized rats; Injection of puerarin (7 mg/kg) for 98 days (140 days in total) significantly increased the percentage of cornified cells in mature female rats, which indicates that puerarin has an estrogenic activity [16]. Estrogenic effects of soybean isoflavones show bidirectional regulation of balance function in vivo. During pregnancy and puberty, the reproductive organs of female rat offspring and serum estrogen levels will be significantly affected when their diets contain 400 mg/kg soybean isoflavone. For the non-pregnant female rats fed diets with soybean isoflavone, there is no significant effect on F1 generation [17].

26.3.4 Treatment of Excessive Alcohol Intake

Some data suggest that Gegen may be a useful adjunct in reducing alcohol intake in a naturalistic setting and there is no report about any side effects [18]. Furthermore, the mechanism of alcohol intake reduce is not clear and this effect has not related to psychomotor and cognitive effects [19]. Alcohol consumption patterns are influenced by puerarin administration and puerarin medication may be treatment for the excessive consumption of alcohol [20].

26.3.5 Others

It also can alleviate upper respiratory tract diseases, trigeminal neuralgia, lumbar muscle strains, tension headaches, arthralgia, ischemic stroke, rheumatoid arthritis, dysentery and nettle rash.

26.4 TCM Applications and Dietary Usage

26.4.1 TCM Applications

Gegen has been traditionally used in TCM for treating CVDs (Cardiovascular diseases) and T2DM (Type 2 Diabetes Mellitus). The properties and taste are pungent, sweet and cool. It may enter into the spleen and stomach meridians. According to Chinese Pharmacopoeia 2010, Gegen is used to release heat by eliminating pathogenic factors in muscles, let out skin eruptions, promote the

production of body fluid, relieve thirst, invigorate vital function and relieve diarrhea, diabetes and hypertension, with a recommended dose of 10–15 g [4]. Yufengningxin tablet is the preparation of pueraria flavonid solid extract and its main ingredient is puerarin with the function of spasmolysis acetanilide and increasing cerebral and coronary blood flow [1].

On the basis of all previous records, Gegen was first documented in the Divine Husbandman's Classic of Chinese Materia Medica (*Shennong Bencao Jing*) for the relief of fever, diarrhoea and emesis. It was also mentioned in the treatise on fevers, *Shang Han Lun*, which described the use of Gegen Tang, a decoction prepared from kudzu roots, for the treatment of neck stiffness, lack of perspiration and aversion to wind. Gegen was also used as an anti-intoxicating agent to treat alcohol-related problems, and was recommended as an anti-lipotropic agent by Li Shi-Zhen in 1200 AD [1].

Gegen could be used in a single form or in combination with other herbs in traditional Chinese medicine. Water extract of Pueraria Radix shows the effect on the activity of hepatic antioxidant enzymes and lipid profile in ethanol-treated rats, which could contribute to alleviating the adverse effect on ethanol ingestion by enhancing the lipid metabolism as well as the hepatic antioxidant defense system [21]. Gegen Qinlian Decoction, one of the ancient China's classical prescriptions, is composed of four Chinese medicinal herbs: Gegen (*P. lobata*), Huanglian (*Coptis chinensis*), Huangqin (*Scutellaria baicalensis*) and Gancao (*Glycyrrhiza uralensis*). The decoction is the original dosage form of Gegen Qinlian Decoction, but now there are another five dosage forms listed, including tablet, capsule, oral liquid, granule and pellet. Gegen Qinlian Decoction is used widely to remedy bacillary dysentery, ileotyphus, pyretic, virus, spasmolysis, hypoxia and arrhythmia [22]. Tongmai Granules, a combination of three herbs Gegen (*P. lobatae*), Danshen (*Salvia miltiorrhiza*) and Chuanxiong (*Ligusticum chuanxiong*), is available to invigorate the blood and dispel bloodstasis, avoiding arising poor blood circulation [21].

In addition, Gegen can be combined not only with Chaihu (*Bupleurum chinense*), Huangqin (*S. baicalensis*) and Baizhi (*Angelica dahurian*) to treat exterior syndrome caused by exogenous attack, but also with Shengma (*Cimicifuga foetida*), Jingjie (*Schizonepeta tenuifolia*) and Niubangzi (*Arctium lappa*) to treat measles at early stage [5].

26.4.2 Dietary Usages

26.4.2.1 Gegen Wine

Gegen is always compatible with other herbs to make healthy herbal wines. When Gegen is combined with stickyrice, black soya bean, organic honey and other black foods to prepare herbal wine, it has the function of preventing cardiovascular diseases and cancer, enhancing immunity, hair care, anti-hypertensive and

anti-diabetic. Another method is to take Shanzha (fruits of *Crataegus pinnatifida*), Gegen (roots and rhizomes of *P. lobata*) and Gouqi (fruits of *Lycium barbarum*) as raw materials to prepare wine. In this way, it can not only keep the flavour of wine, but also retain the health care function of hawthorn, puerarin and medlar, such as increasing appetite, promoting digestion, protecting heart-head blood-vessel, preventing hypertension, anti-aging and immune adjustment [23].

26.4.2.2 Gegen Tea and Gegen Drink

Herbal tea or herbal drink made of Gegen alone or mixed with other herbs is the most common use for Gegen. Different composition of tea or drink has different function. Wulong Jiangzhi tea, composed of Heshouwu (rhizomes of *Polygonum multiflorum*), Zexie (rhizomes of *Alisma orientale*), Gegen (roots and rhizomes of *P. lobata*), Qiancao (roots and rhizomes of *Rubia cordifolia*), Sangjisheng (Leafy stems and branches of *Taxillus chinensis*) and Jueming (seeds of *Cassia obtusifolia*), is used to nourish liver and kidney, promote blood circulation, remove meridian obstruction and prevent hyperlipemia. Another kind of Gegen tea, made from Gegen (roots and rhizomes of *P. lobata*), Jueming (seeds of *C. obtusifolia*), Yiyi (kernel of *Coix lacryma-jobi*), Suanzao (fruits of *Ziziphus jujube*), Juhua (flowers of *Dendranthema morifolium*) and Damai (kernel of *Hordeum vulgare*), can be better used for anti-hypertensive, anti-hyperlipidemia, detox and dispelling the effect of alcohol. There are many kinds of Gegen drinks on the market, for example, Jieliang Baojian tea drink composed of juice of Moli (flowers of *Jasminum sambac*, 40 %), Jinyinhua (flowers of *Lonicera japonica*, 5 %), Juhua (flowers of *D. morifolium*, 20 %), Gegen (roots and rhizomes of *P. lobata*, 20 %) and other additive; Gegen Lugen Juhua Qingshuang drink, made from Gegen (roots and rhizomes of *P. lobata*, 20 %), Lugen (roots and rhizomes of *Phragmites communis*, 30 %), and Juhua (flowers of *D. morifolium*, 20 %); Gegen drink, composed of juice of Gegen (roots and rhizomes of *P. lobata*, 150 mL/L), sucrose (80 g/L), citric acid (2 g/L) and honey (2 g/L), [24] is also a popularly sold on the market.

26.4.2.3 Other Gegen Foods

Because of its advantages of low toxicity, wide safe range and rich resource, Gegen has been produced into many kinds of health products, such as Puerarin oral liquid, Gegen bread, Gegen noodles, Gegen ice cream, Gegen canned, Gegen powder and Gegen sausage [24].

26.5 Clinical Evidences

As a traditional Chinese drug, Gegen is widely applied in clinical practice, and is remarkably effective in cardiovascular diseases, cerebrovascular diseases, hyperlipidaemia, migraine, retinal artery occlusion and sudden deafness [5, 6].

26.5.1 Cardiovascular Diseases

According to some reports, the extracts of Danshen (*Salvia miltiorrhiza*) and Gegen work on coronary artery disease [25]. When the drug has been given to the patients daily for 24 weeks, contrary to the placebo group, there is a mild decrease in plasma LDL and an improvement in brachial flow-mediated dilation and carotid intima-media thickness in the treatment group. When the patients are given Gegen Qushi decoction composed of Gegen (roots and rhizomes of *P. lobata* 18 g), Dangshen (roots of *Codonopsis pilosula* 20 g), Baishu (roots and rhizomes of *Atractylodes macrocephala* 15 g), Fuling (sclerotium of *Poria cocos* 15 g), Shenqu (medicated leaven, 15 g), Baikouren (fruit of *Amomum kravanh* 6 g), Ganjiang (each of roots and rhizomes of *Zingiber officinale* 3 g) and Muxiang (roots of *Vladimiria souliei* 3 g), Sharen (fruits and seeds of *Fructus Amomi* 5 g), Qingpi (immature pericarp of *Citrus reticulata* 5 g), Chenpi (ripe pericarp of *Citrus reticulata*, 5 g), Fuling (sclerotium of *P. cocos* 10 g), Zexie (rhizomes of *A. orientalis* 10 g), Danshen (roots and rhizomes of *S. miltiorrhiza* 10 g) and yujin (roots of *Curcuma wenyujin* 10 g) [26] with stage I or stage II hypertension twice daily, the result shows that the decoction significantly reduces serum total cholesterol and total glyceride level and improves hypertensive symptoms. In addition, the puerarin injection with conventional medicines is a superior treatment option for unstable angina pectoris than the use of conventional medicines alone.

26.5.2 Cerebrovascular Diseases

It was reported that Gegen Qinlian decoction composed of Gegen (roots and rhizomes of *P. lobata*, 30 g), Huanglian (roots and rhizomes of *Coptis chinensis* 5 g), Huangqin (roots of *Scutellaria baicalensis* 20 g), Zhigancao (roots and rhizomes of *Glycyrrhiza uralensis* 5 g), Zhuling (sclerotium of *Polyporus umbellatus* 12 g), Fuling (sclerotium of *Poria* cocos 12 g), Zexie (rhizomes of *A. orientalis* 20 g), Baishu (roots and rhizomes of *A. lancea* 12 g) and Guizhi (bark of *Cinnamomum cassia* 8 g) had an evident treating effect on cerebral infarction [27].

26.5.3 Hyperlipidaemia

An investigation concludes that Gegen has a positive effect on patients with hyperlipoproteinaemia. The experimental result gives an indication that the efficacy of Gegen decoction combined with fenofibrate is much superior than that of using fenofibrate alone in decreasing the total triglyceride and increasing the HDL level. By contrast with Maitong pill, Gegen Qushi decoction is much better in improving lipid profile for patients with hyperlipoproteinaemia [1].

26.6 Safety Evaluation and Toxicity Data

Gegen belongs to the homology of medicine and food, which has few clinical reports on the toxicity or side effects. Puerarin and glycosides from Kudzu root are distributed in the body fast and widely, and eliminate fast, too. So there is no puerarin and glycosides accumulated and no metabolic saturation phenomenon. According to the animal experiment evaluating the acute toxic effect, Gegen preparation has been consecutively applied on animals for two months, with a result that there is no influence on their behavior, blood picture, liver and kidney function, and no significant deviation from the normal histological textures of the liver, kidney, pancreas and spleen tissues observed [28].

There is a study indicating that the LD_{50} of crude isoflavone extract of kudzu root is 5.97 g/kg (i.p.) in rats and has no effect on mutation and abnormality, whereas the intravenous LD_{50} of puerarin in mice is 700–800 mg/kg. The dosage of puerarin in the prescription is up to 56 g, thus Gegen is a kind of wild plants with low toxicity and high quality. Based on intramuscular and intravenous administration of puerarin at 50 mg/kg/d for 50 days in a rat and 10 mg/kg/d for 30 days in a dog, it can be seen that there is no morphological changes and damages on the functions of the major organs [6].

In clinical studies, when the patients had been given 3 g aqueous extract of dried root of Gegen and Danshen (*Salvia miltiorrhiza*, 7:3, w/w) for 24 weeks, there was no significant side effects, but the patients who received puerarin injection intravenously experienced adverse events such as fever, headache and dizziness. In recent years, there appear more and more reports on the side effects of puerarin injection, for instance, fever is the most reported reaction. Therefore, more attention should be paid to puerarin injection in clinics to control the time and amount of the drug, and to avoid mixture with other medicine in same ampoule bottle [6, 29].

As discussed above, as a relative safe traditional herbal medicine, Kudzu root has a relatively low toxicity and side effects, not only can treat different kinds of diseases, such as hypertension, pathogenic, diabetic, platelet, inflammation and apoptotic, but also can be applied as a valuable dietary botanical material. Although Gegen is relatively safe, people should not use it arbitrarily and should act appropriately to the situation while paying attention to its toxicity.

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Chapter 27
Rehmannia glutinosa Libosch. 地黄 (Dihuang, Rehmannia)

Pengfei Li and Mingsan Miao

27.1 Botanical Identity

Rehmannia glutinosa Libosch is a perennial plant in the Scrophulariaceae Family. It grows in several provinces in China, including Henan, Shandong, Shanxi, Hebei, Liaoning, Inner Mongolia, Jiangsu, Zhejiang, Hunan, Hubei, and Sichuan provinces. Wild *R. glutinosa* grows on the hillside and roadside wasteland. The best crude drug (root tuber of *R. glutinosa*) is from Huaiqing region (now Wen county, Meng county, Boai county, and Qinyang county of Henan province in China), and called Huaiqing Dihuang, which is one of four highly regarded Huaiqing TCM herbs. The root tuber is harvested in autumn and, with the fibrous roots removed, is used as a fresh product (Xiandihuang). It is also dried and commonly used as Shengdihuang. In TCM application, a prepared Dihuang (Shudihuang) is also widely used. The preparation process involves steaming or stewing with wine and, traditionally, the process would be repeated nine times (Fig. 27.1).

27.2 Chemical Constituents

The main bioactive constituents of Dihuang are carbohydrates, iridoid glycosides and amino acids [1].

P. Li · M. Miao (✉)
Science and Technology Department, Henan University of Traditional Chinese Medicine, Zhengzhou 450008, Henan, China
e-mail: miaomingsan@163.com

P. Li
e-mail: lpf0224@126.com

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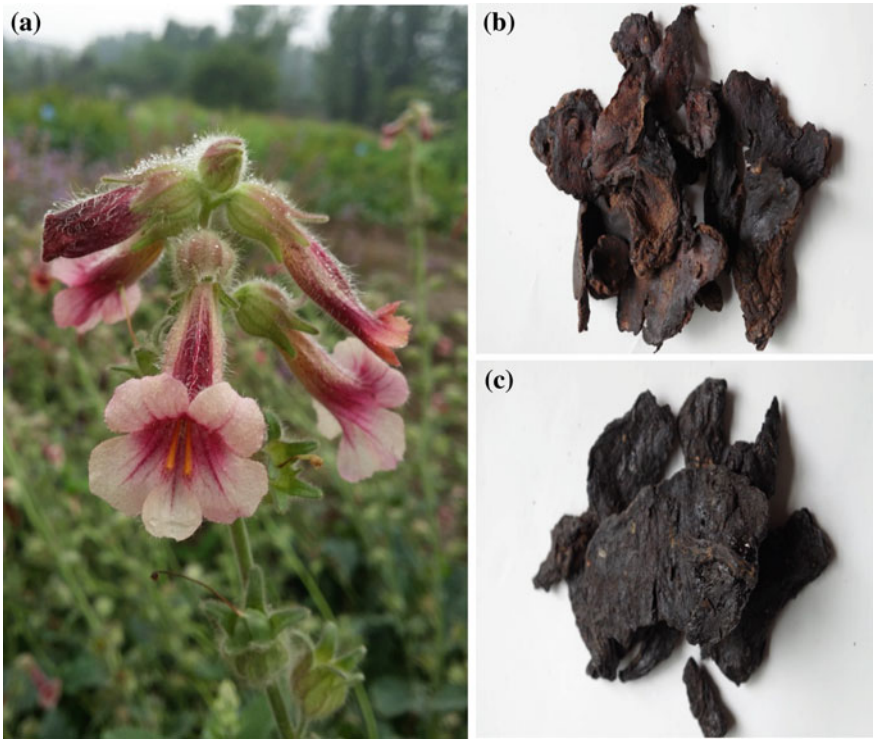


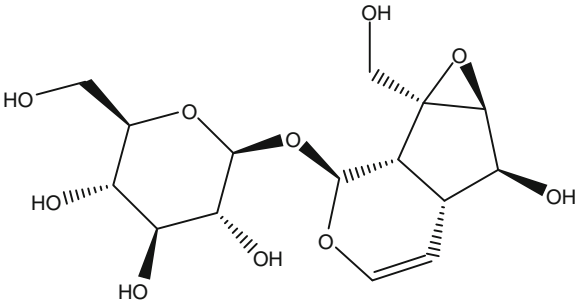
Fig. 27.1 Flowering *Rehmannia glutinosa* (**a**), dried slices (Shengdihuang, **b**), and prepared Dihuang (Shudihuang, **c**)

27.2.1 Carbohydrates

Eight carbohydrates have been isolated and identified from Dihuang: stachyose, raffinose, glucose, sucrose, fructose, mannotriose, verbascose and galactose [2]. The stachyose content is up to 64.9 % of total sugar in fresh Dihuang [3], while it is significantly reduced to 5.98 % in Shengdihuang [4].

27.2.2 Iridoid Glycosides

Dihuang contains rehmaionoside A, catalpol (1) and rehmaionoside D, with catalpol as the main iridoid glycoside at a level up to 2–10 % of dry materials [5, 6]. Catalpol content of fresh Dihuang is decreased by 10.6 % after being stored in sand for six months, 21.6 % after refrigeration (4–8 °C) and 66.5 % after freezing (−8 to 2 °C) [7] (Fig. 27.2).



Catalpol, 1

Fig. 27.2 Chemical structure of representative iridoid glycoside from Dihuang

27.2.3 Other Components

7-Isoquinolinol, 5-hydroxy-2-pyridinemethanol, 6-methyl-3-pyridinol and salidroside have been isolated from Shengdihuang [8]. Four phenollic glycosides were also reported from methanol extract of *Rehmanniae* callus: forsythiaside, acteoside, 3,4-dihydroxy-β-phenyl-(1 → 6)-4-*O*-caffeoyl-β-D-glycopyranoside and 3, 4-dihydroxy-β-phenyl-*O*-β-D-glucopyranosyl-(1 → 3)-*O*-caffeoyl-β-D-glycopyranoside [9].

27.3 Pharmacological Studies

27.3.1 Anti-oxidant and Anti-aging

The water decoction of Dihuang has radical scavenging activity against superoxide and hydroxy free radicals, and protects renal tissue, thus showing to have anti-aging potential [10]. The anti-oxidative activity was found to be enriched in the ethyl acetate extract of Shengdihuang [11]. Shudihuang can improve SOD and NOS activities in rat brain tissue, and decrease MDA and LPO contents and the cell population of SA-B-gal positive expression, implying that Shudihuang can improve the antioxidant ability of brain tissue, and slow the aging process of brain cells [12].

27.3.2 Enhancing Immunity

The Shengdihuang decoction was shown to improve the immune function and regulate endocrine production in mice [13]. *Rehmannia glutinosa* polysaccharide (RGP), as a major class of component of Dihuang, was shown to up-regulate the expression of CD40, CD80, CD83, CD86 and MHC II molecules of BMDCs, down-

regulate pinocytosis and phagocytosis activities, enhance the immunity of host, and induce IL-12 and TNF-α production of BMDCs [14]. The water extract and crude polysaccharide also showed to significantly promote the thymus and spleen lymphocyte proliferation in mice, and improve the levels of interleukin-2, interferon gamma, interleukin-4 and interleukin-5, in a dose-dependent manner [15].

27.3.3 Lowering Blood Glucose

The water extract of *Rehmannia glutinosa* Libosch (high dose 2.4 g/kg day, medium dose 1.2 g/kg day and low dose 0.6 g/kg day) can increase the mRNA and protein expressions of prionsulin, and decrease fasting plasma glucose level of rats with type 2 diabetes mellitus [16]. Oligosaccharides (contain 60 % tetrasaccharides, 20 % trisaccharides, and others as monomers) of Dihuang were found to lower blood glucose level of normal and alloxan-induced diabetic rats, with a possible adrenal-dependent mechanism acting on the neuroendocrine system [17]. The Shudihuang, however, did not show a hypoglycemic effect on alloxan-induced diabetic rats, but it prevented the occurrence and development of diabetic complications [18].

27.3.4 Anti-mutation and Anti-cancer

Catalpol, the main iridoid glycoside in rehmannia, acts on dNTPs competitively at the binding site of Taq DNA polymerase, implying potential anti-cancer activity [19]. The carbohydrate stachyose was also shown to have significant inhibitive effect on HepG-2 and SGC-7901 tumor cells and enhance the anti-tumor effect of cytoxan [4]. The polysaccharides from prepared rehmannia were reported to inhibit the micronucleus, chromosome aberration, and sister chromatid exchange rates in mice that were induced by cyclophosphamide, indicating potential anti-mutagenic and anti-tumor effects [20].

27.3.5 Neuroprotection and Other Effects on Nervous System

In cerebral ischemic model of gerbils, catalpol was injected intraperitoneally immediately after reperfusion with the dose of 5.0 mg/kg. It was found that catalpol significantly reduced brain damage caused by ischemia-reperfusion, decreased neuronal death and decreased infarct size [21]. Prepared rehmannia has been shown to shorten the time for the D-galactose induced aging rats to find platform in the Morris water maze test, therefore demonstrating its improvement on ability of learning and memory [12].

27.3.6 Promoting the Recovery of Hematopoiesis

The polysaccharide component RGP can promote proliferation and differentiation of CFU-S, CFU-CM, CFU-E and BFU-E in bone marrow of normal and senescence accelerated mice, and also increase peripheral leukocytes [22]. Dihuang was also found to significantly enhance bone marrow to generate granulocyte progenitor cells. Shudihuang prepared by yellow wine stewing enhanced capacity of proliferation of erythroid progenitor cell in the blood deficient models of mice which were induced by intraperitoneal injection of cyclophosphamide or by limiting diet and chronic bleeding [23].

27.4 TCM Applications and Dietary Usage

27.4.1 TCM Applications

The application of Dihuang in Chinese medicine has a long history. It has mainly been used for relieving fever and controlling bleeding. Xiandihuang has heat-clearing effect, facilitates generation of body fluid, and plays a hemostatic role. Shengdihuang cools blood, clears heat, nourishes *Yin* and also generates body fluid. Both of them can be used for treating epistaxis, hematemesis, and purpura. Shudihuang has the property of nourishing *Yin* and enriching blood, benefiting essence of life and filling marrow. It is mainly used to treat blood, liver and kidney deficiencies, with symptoms such as palpitation, irregular menstruation, uterine bleeding, soreness of waist and knee, hot flashes, night sweats, nocturnal emission, thirst, vertigo and tinnitus, etc.

For example, Daochi San, which is composed of Shengdihuang 6 g, Mutong (cane of *Clematis Armandii*) 6 g, Gancao (root of *Glycyrrhiza uralensis*) 6 g, can be used for the treatment of irritability, fever, mouth ulcers and acute urinary tract infections. Qingwei San is composed of Shengdihuang 6 g, Danggui (root of *Angelica sinensis*) 6 g, Mudanpi (root bark of *Paeonia suffruticosa*) 9 g, Huanglian (root of *Coptis chinensis*) 6 g, Shengma (root of *Cimicifuga foetida*) 9 g; can be used for sore gums, bleeding gums, bad breath, stomatitis and trigeminal neuralgia, etc. Liuwei Dihuang Wan is composed of Shudihuang 24 g, Shanzhuyu (pulp of *Cornus officinalis*) 12 g, Shanyao (rhizome of *Dioscorea opposita*) 12 g, Zexie (tubers of *Alisma orientalis*) 9 g, Mudanpi (root bark of *Paeonia suffruticosa*) 9 g, Fuling (sclerotium of *Poria cocos*) 9 g. It has been used for treatment of soreness of waist and knee, hot flashes, night sweats, nocturnal emission, vertigo and tinnitus.

27.4.2 Dietary Usages

As Dihuang contains a large number of amino acids, trace elements and carbohydrates, it can be used not only as an herb, but also as food. In literature, it has been used in different forms, including Dihuang porridge, Dihuang drink, Dihuang wine, etc.

27.4.2.1 Dihuang Porridge

Ingredients are 15 mL Shengdihuang juice, 2 mL Shengjiang juice (fresh rhizome of *Zingiber officinale*), 50 g rice and brown sugar. First, the rice porridge is prepared, then Shengdihuang juice and Shengjiang juice are added, and then it is cooked with brown sugar. The porridge is for nourishing blood, treating anemia, Qi deficiency and abdominal pain after delivery.

27.4.2.2 Dihuang Wine

60 g DiHuang is mixed with 500 mL grain spirits and soaked for one week. The tincture can relax muscles and tendons, nourish blood and has been used for treatment of numbness and limb pain because of anemia.

27.5 Clinical Evidences

There are many studies on Dihuang, but most of them are on TCM formulae that contains the herb.

For example, in a type 2 diabetes study, 118 patients with type 2 diabetes were divided randomly into a control group and an experimental group. The control group was given Metformin, while the experimental group used a combination of Dihuang, Huangqi (root of *Astragalus membranaceus*) and Danshen (root of *Salvia miltiorrhiza*). After treatment for 2 months, the total rate of effectiveness was 84.7 %, with 69.5 % as highly effective (the fasting blood glucose level reduced by 2.8 mmol/L, glucose level at 2 h after meal reduced by 4.5 mmol/L) and 15.3 % as effective (the fasting blood glucose level reduced by 1.1–2.8 mmol/L, glucose level at 2 h after meal reduced by 2.2–4.5 mmol/L) in the control group, while the total effective rate for the experimental group was 89.8 %, with 76.3 % as highly effective and 13.6 % as effective [24].

Using a modified Liuwei Dihuang formula decoction to treat 30 in-patients with cerebral infarction at convalescence was revealed to be very effective (total effective rate 80 %) [25].

A study using Dihuang along with irbesartan for treatment of chronic glomerulonephritis showed that the combination use was more effective in reducing proteinuria [26].

Shudihuang, when used with Nvzhenzi (fruit of *Ligustrum lucidum*), Shejincao (herb of *Lycopodium japonicum*), Chishao (root of *Paeonia lactiflora*) combined with madopar, to treat Parkinson's patients, was shown to have a total effective rate of 88.5 %, higher than that in the control group that only used madopar (65.4 %) [27].

27.6 Safety Evaluation and Toxicity Data

In an acute toxicity study on catalpol from Dihuang, at the maximum dose of 1000 mg/kg, the mice showed no obvious symptoms of poisoning and no death after administration for two weeks [28].

Rats were continuously fed Shudihuang (doses of 4.05 g/kg, 2.70 g/kg and 1.35 g/kg) for 60 days. It was revealed that long-term use of Shudihuang would have some impact on cholesterol metabolism of rats, by increasing blood cholesterol level likely through regulating its synthesis and decomposition [29].

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Chapter 28
Rhodiola crenulata L. 红景天 (Hongjingtian, Red-Spotted Stonecrops)

Tao Guo

28.1 Botanical Identity

The plants of the genus *Rhodiola* are widely distributed in the Himalayan, western and northern regions of Asia. There are approximately 90 species recorded in the world, and more than 70 species that are found in China, mainly in plateau areas, such as Yunnan, Sichuan, Qinghai, and Tibet [1]. Among them, Hongjingtian (*Rhodiola crenulata* L.), is an important and representative species of *Rhodiola* genus. It was first recorded in the Pharmacoepia of the People's Republic of China in 1985 [2]. It's traditional medicinal part is the golden root. As the typical botanical characters, *R. crenulata*, is a perennial herbaceous plant. Overground rhizome is short, nearly cylindrical. The leaves are alternate, sessile, having an oval-lanceolate or oblong-ovate shape with a length of 7–35 mm and a width of 5–18 mm. Flowers are red. The black flowering branch grows to heights of 5–20 cm. It usually blooms in June to July, and the fruit is usually ripe by August to September [2, 3].

R. crenulata is mainly distributed in southwest China, including Yunnan and Sichuan provinces as well as the Tibet Autonomous Region. The wild-growing plants are found predominantly in harsh and hilly environments where it is exposed to various stresses including high altitude, insufficient oxygen, extreme cold and intense ultraviolet radiation [4]. *R. crenulata* was approved as a new food resource by the Chinese Ministry of Health in 1991. Overexploitation of the wild *R. crenulata* for commercial purposes has caused a serious reduction of the native populations over the past three decades [5]. This serious situation aroused Chinese government and researchers extensive attention. Hereafter, GAP planting base located at Linzhi

T. Guo (✉)
School of Life and Engineering, Lanzhou University of Technology, Lanzhou 730050, China
e-mail: gt010010@sina.com

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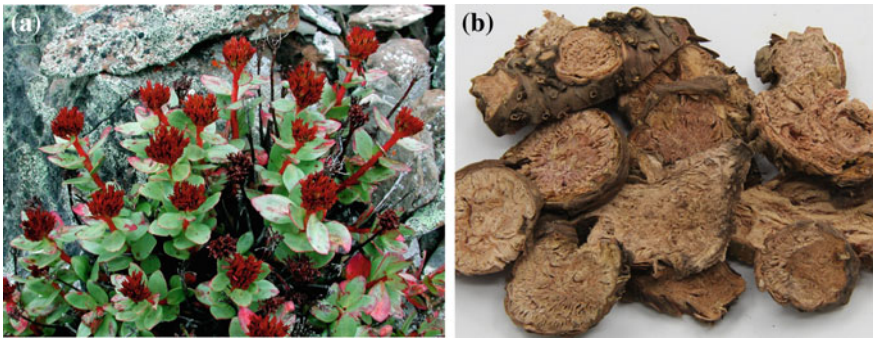


Fig. 28.1 Flowering plant (**a**) and processed slices (**b**) of Hongjingtian

area of Xizang Autonomous Region was built by Qizheng Tibet Medicine Factory in 2006. This action not only ensured the industrial supply and played a modeling role with the higher and identical quality, but also prevented *R. crenulata* becoming an endangered species (Fig. 28.1).

28.2 Chemical Constituents

Previous phytochemical studies have reported the isolation of almost 100 compounds from this genus, including phenols and their corresponding glycosides, cyanophoric glycosides, terpenoids, flavonoids, and lignan. Among them, phenols and their corresponding glycosides, monoterpenoid glycosides, and cyanophoric glycosides were considered as characteristic constituents of *Rhodiola* [1]. Similarly, as in *R. crenulata.* On the other hand, there are about 20 flavonoid compounds isolated from *R. crenulata*, by now, and they are also identified as a class of important bioactive composition.

28.2.1 Phenols and Their Corresponding Glycosides

As a major class of bioactive compounds found from a long time ago, phenols and their corresponding glycosides are one of representative components and used as standard compounds for quality evaluation of the crude drug Hongjingtian and related pharmaceutical or natural health product preparations containing Hongjingtian. To date, about 40 phenanthraquinones have been isolated from Hongjingtian [6, 7]. Some active compounds obtained from the pant are shown in Fig. 28.2. They are gallic acid (**1**), 3-*O*-methyl gallic acid (**2**), 4-*O*-β-D-glucopyranosyloxy-3,5-dimethoxy-benzoic acid (**3**), protocatechuic acid (**4**), vanillic acid (**5**), vanillic acid 4-*O*-β-D-glucopyranoside (**6**), 4-hydroxybenzoic acid (**7**),

4-hydroxybenzoic acid 4-*O*-β-D-glucopyranoside (**8**), caffeic acid (**9**), 1-*O*-β-D-(6″-*O*-galloyl) glucopyranoside (**10**), tyrosol (**11**), 2-phenylethyl β-D-glucopyranoside (**12**), salidroside (**13**), 2-phenylethyl *O*-α-L-arabinopyranosyl- β-D-glucopyranoside (**14**), coniferoside (**15**), dihydroconiferin (**16**), lcariside D2 (**17**), 4-hydroxybenzyl β-D-glucopyranoside (**18**), triandrin (**19**), and vimalin (**20**). Salidroside possessed many bioactivities [8, 9] including the functions of enhancing glucose uptake and increases protein O-GlcNAc levels, resisting tumour growth, and showing hepatoprotective activity against tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, and so on.

28.2.2 Monoterpenoid Glycosides and Cyanophoric Glycosides

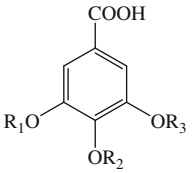
Monoterpenoid glycosides and cyanophoric glycosides are two other major classes of bioactive compounds in *R. crenulata*, and together with phenols and their corresponding glycosides, are considered as characteristic constituents of *Rhodiola*. For example sarmentosin is an active principle for the treatment of hepatitis B in China [10]. Clinical trials of sarmentosin showed a good effect in lowering serum glutamate-pyruvate transaminase (Fig. 28.3).

28.2.3 Flavonoids

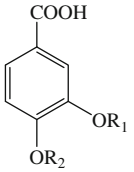
More and more evidence show that flavonoids are also important bioactive components in Hongjingtian. Such as crenulatanoside A, which shows strong inhibitory activity against α-glucosidase with an IC_{50} value of 96.8 μM and may be useful in the prevention and treatment of diabetes [1].

28.3 Pharmacological Studies

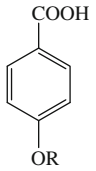
Root extracts of *Rhodiola* have been classified as a plant-derived "adaptogen" defined by Russian researchers as a compound able to maintain a physiological norm upon exposure to stress [11]. *R. crenulata* was first used by Tibetans for maintaining body health and treating various diseases in AD 760. As a traditional herbal remedy, its roots ("Golden Root") have been used as a health food, antidepressive, and antifatigue and to reinforce immunity, improve memory and learning, scavenge active-oxygen species, and relieve altitude sickness. Modern pharmacological studies confirmed that the treatment with *R. crenulata* extract can activate the synthesis and re-synthesis of ATP in mitochondria and stimulate reparative energy processes after intense exercise in the rat skeletal muscles [12]. Root extract of *R. crenulata* can strengthen myocardial contractility, speed up



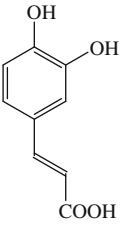
Gallic acid, 1, R_1=R_2=R_3=H
3-O-methyl gallic acid, 2, R_1=R_3=H, R_2=CH_3
4-O-¦Â-D-glucopyranosyloxy-3,5-dimethoxy-benzoic acid, 3, R_1=R_2=CH_3, R_3=Glc



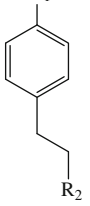
Protocatechuic acid, 4, R_1=R_2=H
Vanillic acid, 5, R_1=CH_3, R_2=H
Vanillic acid 4-O-¦Â-D-glucopyranoside, 6, R_1=CH_3, R_2=Glc



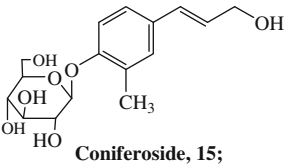
4-hydroxybenzoic acid, 7, R=H
4-hydroxybenzoic acid 4-O-¦Â-D-glucopyranoside, 8, R=Glc



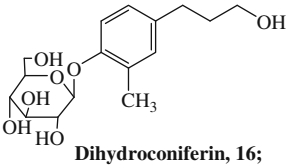
Caffeic acid, 9;



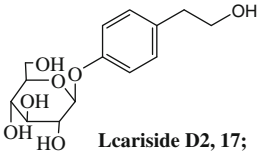
1-O-¦Â-D-(6'' -O-galloyl) glucopyranoside,10, R_1=OH, R_2=Glc-galloyl
Tyrosol, 11, R_1=OH, R_2=H
2-phenylethyl ¦Â-D-glucopyranoside, 12, R_1=H, R_2=Glc
Salidroside, 13, R_1=OH, R_2=Glc
2-phenylethyl O-¦Á-L-arabinopyranosyl- ¦Â-D-glucopyranoside, 14, R_1=H, R_2=Glc-Ara



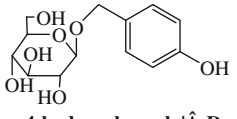
Coniferoside, 15;



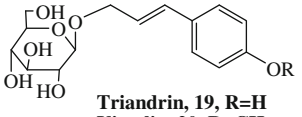
Dihydroconiferin, 16;



Lcariside D2, 17;



4-hydroxybenzyl ¦Â-D-glucopyranoside, 18;



Triandrin, 19, R=H
Vimalin, 20, R=CH_3

Fig. 28.2 Some representative phenols and their corresponding glycosides isolated from Hongjingtian

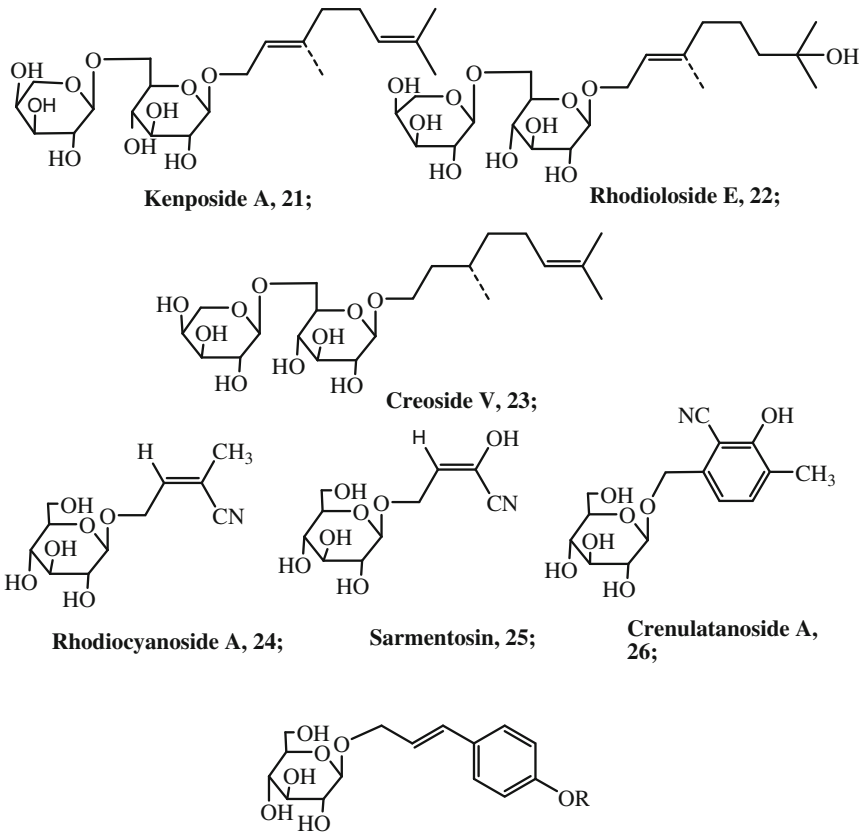


Fig. 28.3 Some representative monoterpenoid glycosides and cyanophoric glycosides isolated from Hongjingtian

myocardial contraction, and reduce the mean pressure of arteries. Interestingly, *R. crenulata* has the bi-directional function of accommodating the central nervous system and endocrine system, and keeps the body in an excellent state of balance. [13]. In additon, *R. crenulata* can reinforce immunity [14], lower blood glucose [15], and prevent progression and metastasis of breast cancer [11].

28.4 TCM Applications and Dietary Usage

28.4.1 TCM Applications

Hongjingtian is an important crude herb used in Chinese medicine and Tibetan medicine with primarily anti-hypoxia, antimicrowave radiation, anti-fatigue activities, and can improve work efficiency, postpone body caducity, prevent and cure

diseases of ageing. Hongjingtian could be used as single form or in combination with other herbs based on TCM theory.

According to TCM understanding, Hongjingtian can replenish Qi (vital energy), clear the Lung system, nourish the Heart system, enhance mental functioning. Common Hongjingtian preparations clinically used include the following forms: (1) Hongjingtian capsule: It is a preparation of *R. crenulata* extract, and used for relieving stress, maintaining energy, improving fatigue and altitude sickness. (2) Hongjingtian oral liquid is a patent medicine, it can significantly improve Qi and Blood deficiency and enhance normal intelligence and physical power. Particularly, it is suitable for workers and athletes in poor circumstances to keep healthy. (3) Compound Hongjingtian oral liquid is mainly composed of Hongjingtian (root and rhizome of *R. crenulata*), Huangqi (root of *Astragalus membranaceus*), and Gouqizi (fruit of *Lycium chinense* Mill), accompanied by honey and sorbic acid as excipient. Clinically, it is used to strengthen the Spleen, nourish the Kidney, and nourish the Heart to calm the Mind. (4) Hongjingtian Injection is used clinically for promoting blood circulation and removing blood stasis. It is effective in treating patients with acute ischemic stroke or coronary heart disease with stable exertional angina.

28.4.2 Dietary Usages

Hongjingtian is not only used as a traditional Chinese herbal drug, but also as a valuable dietary botanical material. It has been used in many ways, such as Hongjingtian tea, Hongjingtian capsule, Hongjingtian wine, and Hongjingtian gruel. The following dietary forms can be easily made at home.

28.4.2.1 Hongjingtian Tea

Herbal tea made of Hongjingtian alone or combined with other herbs is the most common way to use Hongjingtian.

Preparation: 10 g Hongjingtian (root of *R. crenulata*) is washed and cut into pieces, alone or with Gouqizi (fruit of *Lycium barbarum*, 10 g) and Dazao (fruit of *Ziziphus jujuba* 2–3 g) together put into a cup or water pot, proper amount of boiling water is added and then let stand for about 15 min. Drink it like an ordinary tea. The tea was often used as adjuvant therapy of diabetes, anemia, elderly heart failure and liver disease.

It has been demonstrated that treatment of type 2 diabetic patients with *R. crenulata* tea for 12–24 months significantly lowered blood glucose concentration, accompanied by improvement of dysfunctions of liver and kidneys [16].

28.4.2.2 Hongjingtian Capsule

30 g of Hongjingtian powder (root of *R. crenulata*) are mixed with a proper amount of flour together, and then filled into capsules. Each capsule contain about 0.2 g crude drug. It is orally taken using warm boiled water. The recommended dose is two at a time, twice daily.

The drug is used to nourish and strengthen the body for physical weakness.

28.4.2.3 Hongjingtian Wine

Hongjingtian alone or combined with other herbs can be used to prepare herbal wine for improving neurasthenia, insomnia, forgetfulness, fatigue and other symptoms. One example is to soak Hongjingtian (5 g) in 250 mL of Chinese liquor for more than a week, drinking not more than 50 mL daily is recommended.

28.4.2.4 Hongjingtian Gruel

Hongjingtian gruel is a very popular food in Qinghai-Tibet Plateau. A common cooking way is to boil 6 g of *R. Crenulata* root slices with water for 10–15 min, and remove the residue. Add 50 g sticky rice to the decoction and boil the porridge. The taste could be adjusted with sugar. This rice porridge can be mainly used for preventing and curing diseases of ageing.

28.5 Quality Evaluation and Assurance

Unique active ingredients like tryosol, salidroside, rosavin, pyridrde, rhodiosin and rhodionin are found in most of the *Rhodiola* species, but vary in amounts, and so these ingredients are now regarded as the standards for quality evaluation. Salidroside and tyrosol are the two most important bioactive components from *R. crenulata* and frequently used as references for quality evaluation of the preparations of raw material [6]. As recorded in China Pharmacopoeia, the content of salidroside is not less than 0.5 % in raw material. However, it is well known that multiple constituents are responsible for the therapeutic effects of TCM, thus it seems necessary to determine bioactive components as much as possible to ensure the quality of *R. crenulata*. In recent years, some methods for multi-component analysis have been founded as a credible solution for the analysis of a complex system in *R. crenulata* [17]. But, these methods are not adopted and only as a laboratory research work (Fig. 28.4).

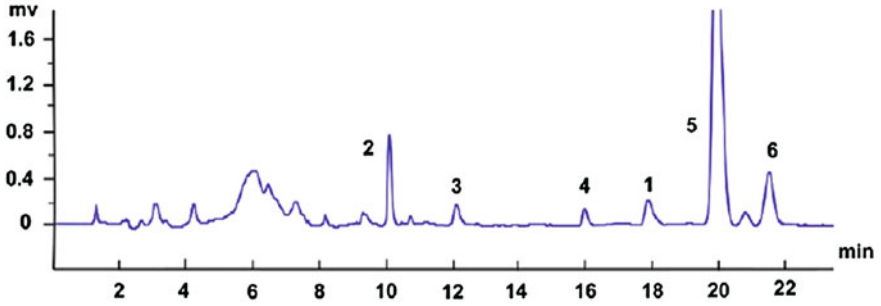


Fig. 28.4 Typical HPLC chromatogram of crude extract of *R. crenulata*. *Note* 2-(4-hydroxyphenyl)-ethyl-*O*-β-D-glucopyranosyl-6-*O*-β-D-glucopyranoside (*1*), icariside D_2 (*2*), p-hydroxyphenacyl-β-D-glucopyranoside (*3*), picein (*4*), salidroside (*5*), tyrosol (*6*). *Experimental conditions* column, Phenomenex C_{18} column (250 × 4.6 mm, 5 μm); mobile phase, methanol-water (15:85, v/v); flow rate, 1.0 mL/min; detection wavelength, 275 nm; column temperature, 25 °C

28.6 Clinical Evidences

Hongjingtian recorded in the Pharmacopoeia of the People's Republic of China (2010 Edition, Vol. I) has been used orally or topically to treat lung disorders, bleeding, burn, soft tissue injuries, impotence, and diabetes. Hongjingtian is partly used in compound preparation clinically. It is mainly combined with Duzhong (bark of *Eucommia ulmoides* Oliver), Huangqi (root of *Astragalus membranaceus*), Chuanxiong (rhizome of *Ligusticum chuanxiong*), Yinxingye (leaf of *Ginkgo biloba*), et al. Some compound preparations are patent medicines and the formula ingredients are not clear. It was reported that Hongjingtian injection for the treatment of angina pectorisis was safe and effective in randomized and double-blind 233 cases of clinical research, and there were no significant difference in blood parameters, liver and kidney function tested [18]. In another clinical investigation, it was found that Hongjingtian capsule can remarkably improve symptoms of deficiency of Spleen and Kidney, and increase values of SOD, COR and HDL-C and lower LPO indicators [19].

28.7 Safety Evaluation and Toxicity Data

It is well known Ginseng and Manyprickle acathopanax roots can strengthen the body and are good health-protecting medicines, but because of some side effects they should not be used for a long time. *Rhodiola* species have benefits similar to those of Ginseng and Manyprickle acathopanax roots, but they are thought to have no side effects [20].

Experience gained during clinical tests showed evidence of no toxicity and side effects complications related to administration of *R. crenulata* extract. Animal

studies also did not show noticeable teratogenic effects for pregnant rats through oral administration of compound Hongjingtian oral liquid [21]. By now, No other toxicity from animal studies on *R. crenulata* have been reported. On the other hand, for *R. rosea*, another species of *Rhodiola*, there are many safety evaluation and toxicity data from clinical and animal studies. It is proved to be very safe. For example, it was found that there wasn't significant toxicity and teratogenicity compared with control group when it was administered in rats by oral with dose of 80 g/kg (80 times as the actual intake) [22].

The harmless character of Hongjingtian preparations in clinical provides the possibility of using them not only in medicine, but in the food industry as well- in particular as additives. It is certainly a relative safe herb often used for the treatment of cardiovascular diseases and health maintaining purpose. It has been used as the new source of food in China. But, Hongjingtian has strong biological activity after all, and can't be abused. The current study reports about *R. crenulata* is still relatively few, more related research for *R. crenulata* is needed to support the current practice.

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Chapter 29
Salvia miltiorrhiza Bonge 丹参 (Danshen, Red Sage)

Yanze Liu

29.1 Botanical Identity

Danshen, a perennial herb in the family of Labiataceae, is one of the most popular Chinese herbal medicines and frequently used as the material of dietary supplements. The medicinal part is the root with red skin and so called Dan (means red in Chinese) Shen (means valuable as ginseng). Although there are 700–900 species of genus *Salvia* in the world, only a few species with similar botanical features are used as Danshen. *Salvia miltiorrhiza* Bunge is the major and legal source recorded in The Pharmacopeia of People's Republic of China [1] and all historical records of Chinese herbal works. As the typical botanical traits, *Salvia miltiorrhiza* grows between the height of 30–60 cm. Leaves are simple or divided, depending on their position on the stem. Flower petals are purple or blue, and are held within a dark green to brown calyx. Another variety called White Flower Danshen has the same botanical features, but the flowers are white [2].

Danshen traditionally was harvested wildly but the cultured variety is becoming the main source of supply as more and more Danshen-derived commercial products are in the market and there has been shortage for wild material. The root is harvested in later fall between November and December of the second year plant. Cleaned and dried root can be stored and marketed as raw material. For further processing, the raw material is sliced 5–10 mm in thickness after being softened by warm water. Sliced product will be dried again naturally or heated in the oven under controlled temperature. All of these procedures must be careful and gentle to keep the red skin as complete as possible because of the active components called phenanthraquinone,

Y. Liu (✉)
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, 100193 Beijing, China
e-mail: yzliu@implad.ac.cn

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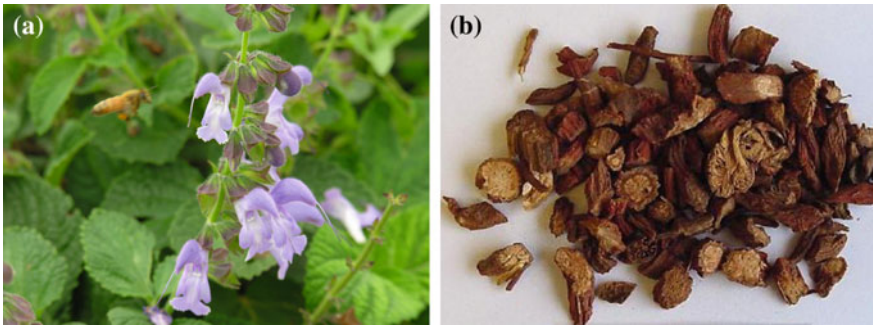


Fig. 29.1 The flowering plant (**a**) and crude drug (**b**) of Danshen

which are present in the red skin. There are also other processing methods for some specific medicinal purposes, including fried Danshen, alcoholic Danshen, vinegared Danshen, charcoaled Danshen, and turtle blood treated Danshen etc. [3] (Fig. 29.1).

29.2 Chemical Constituents

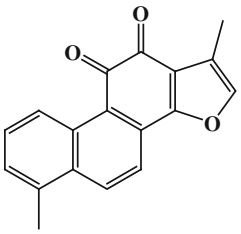
Phenanthraquinones and phenolic acids are two major classes of bioactive compounds found in the root of *Salvia miltiorrhiza* Bonge [4–6].

29.2.1 Phenanthraquinones

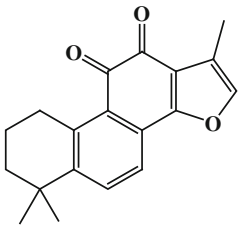
As a major class of bioactive compounds found a long time ago, phenanthraquinones are mainly contained in the skin of Danshen, making the root a red to dark-red color. Tanshinone I (**1**), tanshinone II_A (**2**), and cryptotanshinone (**3**) (shown in Fig. 29.2) are representative components and used as standard compounds for evaluation of the quality of crude drug Danshen and related pharmaceutical or natural health product preparations containing Danshen. So far, about 40 phenanthraquinones have been isolated from Danshen [4, 6].

29.2.2 Phenolic Acids

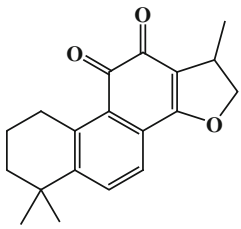
Phenolic acids [4, 6] as one of two major classes of bioactive compounds in Danshen were found in the 1980th, much later than hydrophobic phenanthraquinones. Due to their high water solubility and significant activity in expanding coronary blood vessel, phenolic acids have become a new angle to further



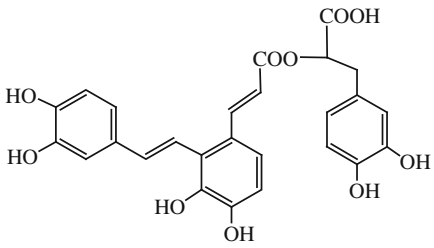
Tanshinone I, 1



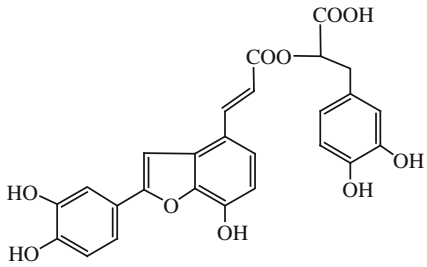
Tanshinone IIa, 2



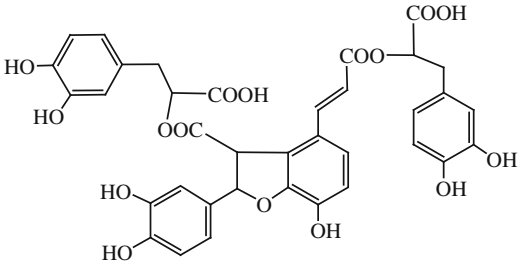
Cryptotanshinone, 3



Salvinolic acid A, 5



Salvinolic acid C, 6



Salvinolic acid B, 4

Fig. 29.2 Representative phenanthraquinones and phenolic acids isolated from Danshen

understand the mechanism of Danshen for its effects on cardiovascular diseases. Salvianolic acid B (**4**) is a major phenolic acid with strong activity, originally existed in the root of crude Danshen, while phenanthraquinones only presented in the skin of Danshen root as red pigment. As seen from the Fig. 29.2, the structures of salvianolic acids A (**5**), B (**4**), and C (**6**) are closely related and easily to be hydrolyzed or decomposed in the presence of water, heat, acid/base, and oxygen etc. It's reminded and suggested that the attention must be carefully paid to make preparations or dietary forms from Danshen.

29.3 Pharmacological Studies

As described previously, Danshen is one of the most popular herbs used in TCM, especially for almost all the diseases related to the circulatory system. Maintaining good blood circulation can also be beneficial to prevent or treat a lot of other diseases. Modern pharmacological studies have indicated [5, 7] Danshen to have the following bioactivities, such as anti-atherosclerosis, anti-inflammation, anti-hypertension, neuro-protection through anti-inflammatory effects, expanding the coronary blood vessels, improving peripheral circulation, anti-hepatic fibrosis, anti-bacterial, anti-viral, and anti-tumor, etc. Tanshinones were shown to have beneficial effects to cardio-cerebral vascular diseases with multiple mechanisms. It also showed the activities of anti-tumor, anti-inflammation, anti-bacterial, and modulating effect on female hormones. Salvianolic acid B as a major phenolic acid with significant bioactivities in the aspects of anti-oxidation, brain-cardio protective function, and against liver fibrosis, has been developed as a new chemical drug.

29.4 TCM Applications and Dietary Usage

29.4.1 TCM Applications

Danshen is one of the most common herbs traditionally used in herbal medicines and health-maintaining products. As the most famous herb for heart and related diseases, it exerts therapeutical and health-maintaining actions in the following three aspects: promoting blood circulation and dissolving the stasis, cooling blood and removing swelling, and nourishing blood and calming consciousness. Danshen could be used as single form or in combination with other herbs based on TCM theory [8].

Common Danshen preparations clinically used include the following forms: (1) Compound Danshen Tablets [9, 12]: It is composed of three herbal components: *Salvia miltiorriza*, *Panax notoginseng*, and Borneol (Dryobalanops aromatic Gwaertn. f.). There are hundreds of manufacturers making this product based on the same formula legally in China while there has been no patent protection in decades even thought the quality varies among these products. It is mainly used for the treatment of chest tightness, the precordial tingling, and angina pectoris through its function of promoting blood circulation and dissolving the stasis, and pain relief through adjusting *Qi*; (2) Compound Danshen Dripping Pill is a relatively new preparation with significantly reduced dosing [10, 11]. Although hundreds of clinical reports have been published, the dosage level and efficacy are still debatable [12]; (3) Danshen Injection and Compound Danshen Injection: Danshen can be used to prepare Danshen Injection by itself or combining it with other herbs, the most used is Jiangxiang (*Dallbergia odarifera*). The products have been used clinically for the treatment of angina pectoris, myocardial infarction, and cerebral

anoxia through vein injection. It is available in liquid or freeze-dried powder forms for injection delivery; (4) Danshen Extract and Instant Danshen Powder is a convenient form of administration, which can be made from single Danshen or mixed with other herbs. The significant advantage of this form is the ease of use and it is readily available for absorption; (5) Preparations made from active components including salvianolic acids A, B, tanshinone II_A, and total salvianolic acids are also on the market as chemical drugs.

29.4.2 Dietary Usages

Because of the good record of Danshen as one of the most famous herbs and valuable dietary botanical materials, it has been used in many ways historically. These include Danshen tea, Danshen wine, Danshen soup, Danshen paste, Danshen powder, Danshen pill, and Danshen extract. The following dietary forms can be easily made at home [2, 3].

29.4.2.1 Danshen Teas

Herbal tea made of Danshen alone or mixed with other herbs is the most common way to use Danshen. Some examples are: Danshen Tea composed of Danshen (9 g) and green tea (3 g); Danshen-Rock Candy Water composed of Danshen (15 g) and rock candy (30 g); Danshen Shouwu Tea composed of Danshen (15 g), Heshouwu (*Fallopia multiflora*, 15 g), and Beishashen (*Glehnia littoralis*, 15 g); Danshen Yuzha Drink composed of Danshen (15 g), Yuzhu (*Polygonatum odoratum*, 15 g), and Shanzha (*Crataegus pinnatifida*, 15 g); and Danshen Drink composed of Danshen (15 g), Tanxiang (*Santalum album*, 5 g) and Sharen (*Elettaria cardamomum*, 5 g), etc. To make the herbal tea, use softened water or natural water with less mineral and alkaline as this is recommended in order to reduce the decomposition of phenolic acids.

29.4.2.2 Danshen Wine [13]

Danshen itself or combined with other herbs can be used to prepare herbal wine for irregular menstrual and coronary diseases. One example is soaking Danshen (60 g), Honghua (*Carthamus tinctorius*, 15 g), and rose (*Rosa rugosa*, 15 g) in 500 mL of Chinese spirit or vodka for more than a week. Drinking 25–50 mL daily is recommended. Danshen can also be used to make herbal wines in combination with many other herbs depending on the specific need of functions. Daily intake amount will be based on the content of Danshen, other herbs, and alcohol.

29.4.2.3 Danshen Used in Medicated Foods

Danshen can be used to make soups with corn powder, rice, or sticky rice. A typical way is to boil Danshen or with other herbs, such as Honghua (*Carthamus tinctorius*), and Danggui (*Angelica sinensis*) for 20–25 min. After removing the residue of crude drug by filtration, the corn powder, rice, or sticky rice is added to continuously boil until fully cooked. This rice porridge can be used for irregular menstrual problems and coronary vascular disease.

Mushroom, steak, peanuts, and most vegetables can be boiled together with Danshen. Beautiful red color, nutrient, and health-maintaining effect of Danshen can be utilized simultaneously. The taste of Danshen-contained foods can be adjusted based on personal preferences.

29.5 Clinical Evidences

As a therapeutic medicine, Danshen is mostly used in combination with *P. notoginseng* and Borneol. Compound Danshen Tablets and Compound Danshen Driping Pills are two major preparations made with Danshen. There are thousands of clinical related reports or observational studies published on the effects of Danshen and its related preparations for cardiovascular diseases. For Compound Danshen Driping Pills, clinical reports showed that the preparation could effectively relieve the symptom of elder angina pectoris in 136 cases [11], which was better than Compound Danshen Tablets and nitroglycerin that were used as control groups.

Because of the poor water solubility, the structure of tanshinone II_A had been modified as a derivative of sodium sulfuric acid to formulate as an injection, i.e. Sulfotanshinone Sodium Injection. The injection is used for the treatment of coronary disease, angina, and myocardial infarction [14]. It can also be used for premature ventricular contractions.

29.6 Safety Evaluation and Toxicity Data

Few clinical reports on the toxicity or side effects is available that could be directly related to the use of Danshen. Animal studies also did not show noticeable toxicity for various organs through ip or oral administration. One-time dosing of 43 g/kg of Danshen decoction was given to mice via ip, there was no death observed within 48 h. The LD_{50} of one-time ip is 80.5 ± 3.1 g crude drug/kg. The ip LD_{50} of Danshen Injection or Compound Danshen Injection for mice were 136.7 ± 3.8 g/kg and 61.5 ± 5.3 g/kg (calculated as crude drug), respectively. Danshen (2.4 g/kg) or Compound Danshen Injection (3 g/kg) were given via ip consecutively to rabbits for 14 days, and there were no toxic reaction, abnormal blood parameters, liver-kidney function, or body weight change observed [15]. Compound Danshen Extract

(10 g/kg) was ig given to mice for 180 days continuously, which is 971 folds of normal clinical dose, there was no visible pathalogical changes in tested organs. Some pathological effects on liver and blood biochemical parameters were recovered after 30 days of the test [16].

As narrated above, Danshen is definitely a relatively safe herbal medicine often used for the treatment of cardiovascular diseases and health maintaining purposes. But the attention must also be paid when you decide to use this herb personally, without a doctor's advice because it is obvious that Danshen has strong biological activity and cannot be used as regular food. It's strongly suggested to ask your doctor if it's proper for you.

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Chapter 30
Zingiber officinale (Willd.) Rosc. 姜 (Jiang, Common Ginger)

Hui-Min Gao

30.1 Botanical Identity

Jiang, the rhizome of *Zingiber officinale* (Willd.) Rosc., is widely used both as a spice and as a traditional Chinese medicine in the fresh or dried forms [1]. As a medicinal herb, Jiang has long been used in the traditional medicinal practices of all the ginger-growing countries for the treatment of various human ailments including headaches, colds, fever, nausea, and rheumatic disorders [2]. The ginger plant, belonging to a tropical and sub-tropical family—Zingiberaceae family, originated in South-East Asia and then introduced to many parts of the globe. It has been extensively cultivated in the most regions around China for thousands of years and there are different varieties of vegetable forms or for medicinal purposes. *Anqiu*, *Changyi*, *Laiwu* and *Pingdu* in *Shandong* province are famous to produce the vegetable ginger, whereas *Jiangwei* and *Muchuan* in *Sichuan* province as well as *Changshun* and *Xingren* in *Guizhou* province are the main growing areas of medicinal ginger. Regardless whether the plant is of vegetable or medicinal variety, the origin plant has a perennial and tuberous rhizome and the stems are erect, round and 2 or 3 ft. in height (Fig. 30.1). After growing for 5–7 months, the new young rhizomes are dug up manually or by mechanical means and are preserved in sugar syrup or used for crystallized ginger. The older rhizomes (harvested after 8–-10 months) become dried ginger, which is used in baking, in beverages, and in a wide range of other culinary and medicinal applications around the world.

Ginger products can be found in many forms on the market—fresh, dried, pickled, preserved, crystallized, candied, and powdered. Additionally, there are four kinds of traditional herb ginger products with different therapeutic effects such as fresh ginger, dried ginger, prepared ginger and carbonized ginger. Fresh ginger is

H.-M. Gao (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: huimin_gao@126.com

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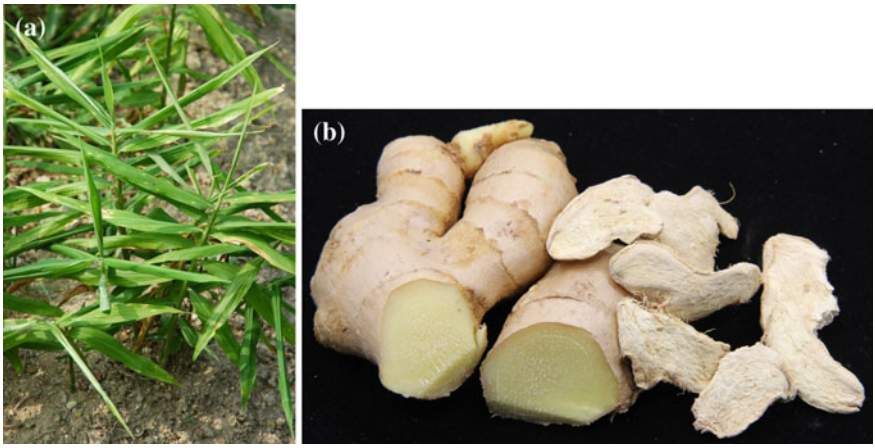
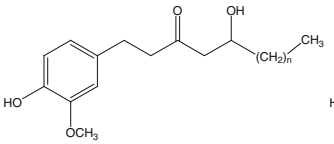


Fig. 30.1 The aerial part (**a**) and crude drugs (fresh and dried slices, **b**) of ginger

usually used as an anti-emetic and dried ginger is preferred for treatment of digestive system diseases as well as for vomiting. The processed product of prepared dried ginger has the effects of anti-dyspepsia and hemostasia, while the carbonized dried ginger is mainly used to treat diarrhea with blood and haemorrhage. Traditionally, fresh ginger is collected in autumn and winter, removed from fibrous roots and soil, washed clean and cut into thick slices before use. The dried ginger is prepared by cutting the fresh rhizome into pieces and drying in the sun or at a lower temperature, and characterized by the flattened slices with fingered branches, 3–7 cm long and 1–2 cm thick. The dried ginger is stewed with hot sand till it becomes inflated and brown externally to obtain prepared dried ginger. The carbonized dried ginger is also prepared from the dried ginger as described under the method for carbonized by stir-baking till the surface becomes black and the inner part brown. In addition, other forms such as ginger juice, ginger skin and etc., are prescribed for the different medicinal purposes in Chinese clinics [1].

30.2 Chemical Constituents

Ginger is reported to contain numerous chemical constituents and these vary depending on the place of origin and whether the rhizomes are fresh or dry. Main chemical constituents in the ginger rhizomes include volatile and non-volatile pungent principles [3]. Among them, the biologically active alkyl phenolics are characterized by the presence in the plants of Zingiberaceae family.



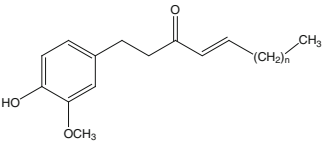
6-gingerol, 1, n=4

4-gingerol, 2, n=2

7-gingerol, 3, n=5

8-gingerol, 4,n=6

10-gingerol, 5, n=8



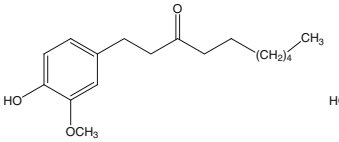
6-shogaol, 6, n=4

4-shogaol, 7, n=2

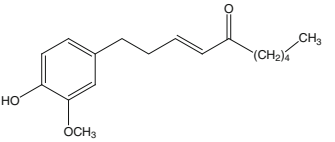
8-shogaol, 8, n=6

10-shogaol, 9, n=8

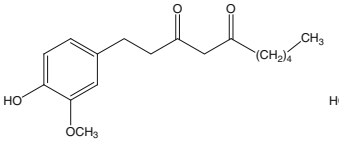
12-shogaol, 10, n=10



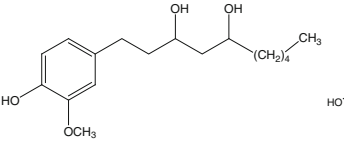
6-paradol,11



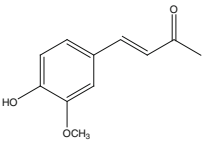
6-isoshogaol, 12



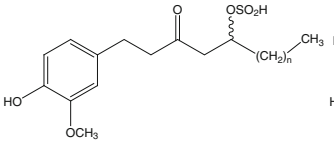
6-gingerdione,13



6-gingerdiol,14

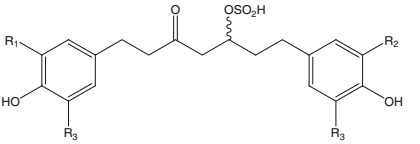


dehydrogingerone, 15



6-gingesulfonic acid, 16

4-gingesulfonic acid, 17



Shogasulfonic acid A, 18, R_1=OCH_3, R_2=OCH_3, R_3=H

Shogasulfonic acid B, 19, R_1=OCH_3, R_2=OH,R_3=H

Shogasulfonic acid C, 20, R_1=OH, R_2=OH, R_3=H

Shogasulfonic acid D, 21, R_1=OCH_3, R_2=OCH_3, R_2=OH

Fig. 30.2 Representative non-volatile pungent compounds isolated from ginger

30.2.1 Volatiles

The yield of volatile oil in ginger varies from 1 to 3 %, which is the highest in the fresh ginger and decreased to some extent in the dried ginger and its processed products. Over 80 components of the oil have been characterized by GC-MS analysis. It contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene, curcumene and farnesene, with lesser amounts of bisabolene

and β-sesquiphellandrene. A smaller percentage of at least 40 different monoterpenoid hydrocarbons are present with 1,8-cineole, linalool, borneol, neral, and geraniol being the most abundant. Many of these volatile oil constituents contribute to the distinct aroma and taste of ginger [3].

30.2.2 Non-volatile Pungent Principles

This species contains biologically active constituents including the non-volatile pungent principles, such as the gingerols, shogaols, paradols and zingerone that produce a "hot" sensation in the mouth. The gingerols (**1**–**5**), a series of chemical homologs, differentiated by the length of their unbranched alkyl chains, were identified as the major active components in the fresh rhizome. In addition, the shogaols (**6**–**10**), another homologous series and the dehydrated form of the gingerols, are the predominant pungent constituents in dried ginger. Paradol (**11**) is similar to gingerol and is formed on hydrogenation of shogoal. 6-gingerol (**1**) and 6-shogaol (**6**) are two representatives of the major bioactive components mentioned above. Other phenolic compounds, such as 6-isoshogaol (**12**), 6-gingerdione (**13**), 6-gingerdiol (**14**) and dehydrogingerone (**15**), only exists in dried ginger, as well as sulfonated gingerol or shogoal derivatives (**16**–**21**) are found to be present in small amounts in the crude material or processed ginger [4]. Because of the presence of the different prescribed forms with various therapeutic effectiveness in Chinese clinical practice, some chemical investigations were comprehensively carried out to display the mechanism of process technology. For example, a steaming process can affect the chemical profile and anticancer potential of ginger [5] (Fig. 30.2).

30.3 Pharmacological Studies

As a medicinal herb, ginger has been historically used as remedy for nausea and vomiting, the recent experimental and clinical studies also verified this beneficial effect, primarily for motion sickness and pregnancy nausea. However, it was not shown to be effective in preventing nausea and vomiting after laparoscopic surgery [6]. In addition, ginger and its major pungent ingredients such as 6-gingerol (**1**), 6-shogaol (**6**) and 6-gingediol (**14**), were also shown to have pronounced antioxidant, anti-inflammatory and immunoregulatory activities as well as chemopreventive and chemotherapeutic effects on a variety of cancer cell lines and on animal models [3]. Aqueous and methanol extracts of ginger were found to have anti-obesity effects in both high-fat and goldthioglucose induced obesity mice.

6-Gingerol, as a specific main ingredient in fresh ginger, has been shown to be the major bioactive component of the blood lipid-lowering effect of ginger methanol extract, in a fructose induced hyperlipidemia and hyperinsulinemia rat model. 8-Gingerol has various pharmacological functions, including anti-platelet

aggregation, spasmolytic activity, modulation of macrophage functions, inhibiting LPS-induced PGE 2 production and LPS-induced COX-2 expression, 5-HT3 receptor blocking activity and immunosuppressive activity [7]. Additionally, 6-gingerol and 6-shogaol have been reported to have antipyretic, analgesic, antitussive and hypotensive effects. Zingerone was found to help reduce body weight and it can prevent fat storage by increasing fat burning in rats [8].

30.4 TCM Applications and Dietary Usage

Ginger is one of the most commonly used spices and flavoring agents in foods and beverages as well as dietary supplement and herbal medicines.

30.4.1 TCM Applications

As a commonly prescribed herb in Chinese medicine, ginger and its processed products could be used as single form or in combination with other herbs for the treatment of various human ailments including headaches, colds, fever, nausea, and rheumatic disorders. More than 50 preparations derived from ginger or its processed products have been authorized by SFDA, such as Jiang tincture, fluid extract and capsule, as well as Jiangzao Quhan capsule, Guiyang capsule, Majiang capsule and Sangjiang Ganmao tablet.

Jiang fluid extract is prepared from single crude material (dried ginger), and widely used as a stomachic and carminative. In addition, it is also used as crude material of Jiang tincture. Jiangzao Quhan capsule is prepared of Ganjiang (rhizome of *Z. officinale*) and Dazao (fruit of *Ziziphus jujuba* Mill.) and it mainly used for the treatment of common cold and pain caused by stomach cold. Guiyang capsule is prepared from Danggui (root of *Angelicae sinensis* (Oliv.) Diels) and Shengjiang (fresh rhizome of *Z. officinale*) as well as limb meat and it is benefit to relieve abdominal pain of postpartum women. Majiang capsule is composed of four herbal components: Mahuang (herb of *Ephedra sinica*), Shengjiang (fresh rhizome of *Z. officinale*), prepared Wuweizi (fruit of *Schisandra chinensis*), prepared Gancao (root and rhizome of *Glycyrrhiza uralensis* Fisch.), and it is used to control the coughing and breathing spell. Sangjiang Ganmao tablet is prepared from six herbal components: Sangye (leaf of *Morus alba* L.), Lianqiao (fruit of *Forsythia suspense* (Thunb.) Vahl), Juhua (flower of *Chrysanthemum morifolium* Ramat), Kuxingren (seed of *Prunus armeniaca* L.), Zisuye (leaf of *Perilla frutescens* (L.) Britt.) and Ganjiang (rhizome of *Z. officinale* Rosc.). It is usually used to treat common cold, cough, headache and sore throat.

A pharmaceutical composition mainly comprised of Ganjiang (rhizome of *Z. officinale* Rosc.), Dazao (fruit of *Z. jujuba* Mill.), Huangqi (root of *Astragalus membranaceus* (Fisch.) Bunge.), Gancao (root and rhizome of *G. uralensis* Fisch.),

Guizhi (twig of *Cinnamomum cassia* Presl.), and green tea. It was effective against Type I allergy. A dietary supplement composition comprising water/alcohol extract of Ganjiang (rhizome of *Z. officinale* Rosc.), Banlangen (root of *Isatis indigotica* Fort.), Sanqi (root and rhizome of *Panax notoginseng* (Burk.) F.H. Chen), Duzhong (bark of *Eucommia ulmoides* Oliv.), Luohanguo (fruit of *Momordica grosvenori* Swingle), Gancao (root and rhizome of *G. uralensis* Fisch.), and Dacong (the whole plant of *Allium fistulosum* L.) was described for ameliorating inflammatory changes in influenza process [2].

30.4.2 Dietary Usage [2, 9]

In addition to the medicinal uses, ginger is typically consumed as dried slices/powder, candy (crystallized ginger) or for flavoring tea and also used as a condiment in various industries of food, beverage, and fragrance. In many countries, especially in China, fresh ginger is used to prepare vegetable and meat dishes as well as many other food preparations [2]. The refreshing pleasant aroma, biting taste and carminative property of ginger, make it an indispensable ingredient of food processing throughout the world. There is no reason for more people not to take advantage of ginger and its health-promoting qualities.

30.4.2.1 Ginger Used as a Condiment in Food and Beverage Industries

Ginger can also be made into candy, or ginger wine which has been made commercially. Ginger powder is usually used as a flavoring for recipes such as gingerbread, cookies, crackers and cakes, ginger ale, and ginger beer.

Candied ginger, or crystallized ginger, is a type of confectionery, which is the rhizome cooked in sugar till soft. Green ginger wine is a ginger-flavored wine produced in the United Kingdom, traditionally sold in a green glass bottle. An acidic beverage was formulated for pregnant women containing carbohydrates, essential vitamins (B_6, C and folic acid) and minerals (ammonium iron citrate, calcium gluconate, calcium lactate, magnesium carbonate) along with ginger juice so as to maintain the good nutritional state of the foetus.

A powder composition for making ginger pudding contains ginger powder (1.6–4 wt%), milk protein (31–62 wt%), wheat protein (7–15 wt%), calcium lactate (1.6–5.5 wt%), carrageenan (0.8–2.4 wt%) and lactic acid bacteria (0.4–1.6 wt%). All the ingredients were mixed with cow milk and heated in a microwave oven. A baby-food composition is comprised of blanched ginger puree (0.1–0.5 %) together with one or more fruits or vegetables at suitable levels.

30.4.2.2 Ginger Used as Household Remedy

Ginger tea is always easily and freshly made at home for cold relief. The fresh ginger is grated and steeped into boiling water for 5–15 min. The honey is often added. Sliced orange, lime or lemon may also be added, depending on preference. Ginger tea can be enjoyed both hot and iced.

Erjiang wine is made by soaking both fresh ginger (15 g) and dry ginger (15 g) in 50 mL of Chinese spirit or yellow wine for more than a week. Sometimes, brown sugar can be added for better taste. Drink 5–10 mL of Erjiang wine one time. The daily dose is 10–20 mL for the treatment of nausea and vomiting.

Ganjiang (rhizome of *Z. officinale*, 30 g) and Dazao (fruit of *Z. jujuba* Mill., 30 g) are boiled in 400 mL of water and then Huajiao (pericarp of *Zanthoxylum bungeanum* Maxim. 9 g) is added to make a Jiangzao Huajiao decoction, which is frequently used to control dysmenorrhea. The decoction is taken three days before catamenia. Twice one day.

30.4.2.3 Ginger Used as Culinary and Dietary Materials

Ginger has a pungent and fresh taste. It is a great spice to use on a daily basis. Ginger is often pickled in vinegar or sherry as a snack or just cooked as an ingredient in many dishes. Fresh ginger can be simply sliced, or dry ginger can be grated while cooking to make the dishes a bit more delicious.

Fresh ginger is put into pork bellies and then boiled to ripeness, and then a little salt can be added to make a stomachic and nutrient diet. Fresh ginger (100 g) is cut into filaments and steeped in 250 mL of vinegar for flavoring fish, shrimp, crab and other seafood as well as goat meat and vegetarian cuisine. Ginger is also finely chopped or ground into a paste to use as a base for chicken and meat dishes alongside onion and garlic, when cooking.

30.5 Clinical Evidences

In four well-controlled, double-blind, randomized clinical studies convincing evidence was provided on the effectiveness of ginger in treating mild-to-moderate nausea and vomiting of pregnancy [10]. Three available studies investigating the antiemetic effect of ginger in preventing postoperative nausea and vomiting and another three trials for nausea induced by each of the following conditions: seasickness, morning sickness and chemotherapy, were critically reviewed by a meta-analysis and these studies collectively favored ginger over placebo, however, the clinical data were insufficient, and further rigorous studies to establish whether ginger is effective for nausea and vomiting are expected [11]. More recent randomized and placebo-controlled trial indicated ginger could not prevent postoperative nausea and vomiting after laparoscopic surgery [12]. In relation to chemotherapy induced nausea

and vomiting, the addition of ginger to the standard antiemetic regimen had no advantage in reducing nausea or vomiting in the acute phase of cisplatin-induced emesis [13].

30.6 Safety Evaluation and Toxicity Issue

Ginger is a safe and effective herbal medicine. The FDA classifies ginger as "Generally Recognized as Safe," and the British Herbal Compendium documents no adverse effects. If consumed in reasonable quantities, ginger has few side effects. When it is consumed in a longer term and at higher dosages, ginger may cause heartburn and gastric reflux, particularly if taken in powdered form. High dose (>6 g) ginger may act as a gastric irritant. Ginger is contradicted in people suffering from gallstones, as it promotes the production of bile.

LD_{50} of roasted ginger decoction administered orally is 170.6 ± 1.1 g/kg, but it is over 250 g/kg with dry ginger. An oral ethanol extract at 2.5 g/kg was not associated with mortality in mice, and the acute oral LD_{50} of ginger oil in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg. A ginger extract at daily doses up to 1000 mg/kg administered to pregnant rats for 10 days during the period of organogenesis caused neither maternal nor developmental toxicity. Ginger powder by a gavage treatment at the dosages of 500, 1000 and 2000 mg/kg body weight for 35 days caused no overt organ abnormality. Only at a very high dose (2000 mg/kg), ginger led to slightly reduced absolute and relative weights of testes (by 14.4 and 11.5 %, respectively) [14].

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Part III
Fruit or Seed Materials

Chapter 31
Alpinia oxyphylla Miquel 益智仁 (Yizhi Ren, Sharpleaf Galangal)

Lihong Wu

31.1 Botanical Identity

In the strict sense, the fruit of the medicinal plant is called Yizhi (means benefit intelligence nut in Chinese), while the seed (without pericarp) is called Yizhi Ren. There are about 230 species of the genus *Alpinia* in the world and 51 species (35 endemic) in China [1]. *Alpinia oxyphylla* Miquel is the only legal source of Yizhi Ren in the genus *Alpinia* recorded in the Pharmacopoeia of the People's Republic of China and all historical records of Chinese herbal works. For the typical botanical and pharmacognostical characteristics, *Alpinia oxyphylla* grows up to the height of 3 m. The leaf blade is lanceolate, growing up to 35 cm. The raceme is terminal growing. The white labellum with red stripes is approximately 2 cm long. The capsule is globose when fresh, and when dry it becomes ellipsoidal and is called Yizhi Ren, with both ends slightly acute and 1.2–2 cm long, 1–1.3 cm in diameter, externally brown or greyish-brown, with 13–20 longitudinal, uneven and prominent lines on the surface, remains of perianth on the apex and fruit stalk at the base (Fig. 31.1).

As a tropical and subtropical medicinal plant, *A. oxyphylla* is mainly distributed and cultivated in Hainan and Guangdong provinces in China. Now some small cultivation areas are also present in Yunnan, Guangxi and Fujian provinces. Qingzhong county of Hainan province is deemed to be one of the ideal GAP cultivation bases.

When the fruit surface turns to light brown in May or June, harvesting involves cutting the fruit cluster, removing the fruit stalk, and drying in the sun or drying equipment. The dried fruit can be stored and marketed as raw material. Generally, for clinical use, the fruit is dry-fried to remove the shells, leaving the kernels and is

L. Wu (✉)
Shanghai R&D Centre for Standardization of Chinese Medicines, Shanghai University of Traditional Chinese Medicine, Shanghai, China
e-mail: wlhlhw@126.com

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Fig. 31.1 Flowering plant (**a**) and crude drug (**b**) of Yizhi Ren

pulverized before dispensing. For reducing the acrid sensory qualities, the kernels are mixed with a proper amount of salt water, laid up until the salt water is mostly absorbed, then fried until they are dry and darker in color. This is known as salt-prepared Yizhi Ren.

31.2 Chemical Constituents

Terpenoids, diarylheptanoids and flavonoids are three major compounds found from the fruit of *Alpinia oxyphylla* [2–5].

31.2.1 Terpenoids

Terpenoids are the main compounds to form the volatile oil of the fruit. Most terpenoids are the sesquiterpenoids, such as nootkatone and valencene which present vasodilation, anti-ulcer and antidiarrheal biological activity. So far more than 50 sesquiterpenoids were isolated from the fruit. Some of them are shown in Fig. 31.2 (compounds 1–10).

31.2.2 Diarylheptanoids

At present, about 4 diarylheptanoids were found (Fig. 31.2, compounds 11–14). Most of them bear anti-cancer and antidiarrheal effects.

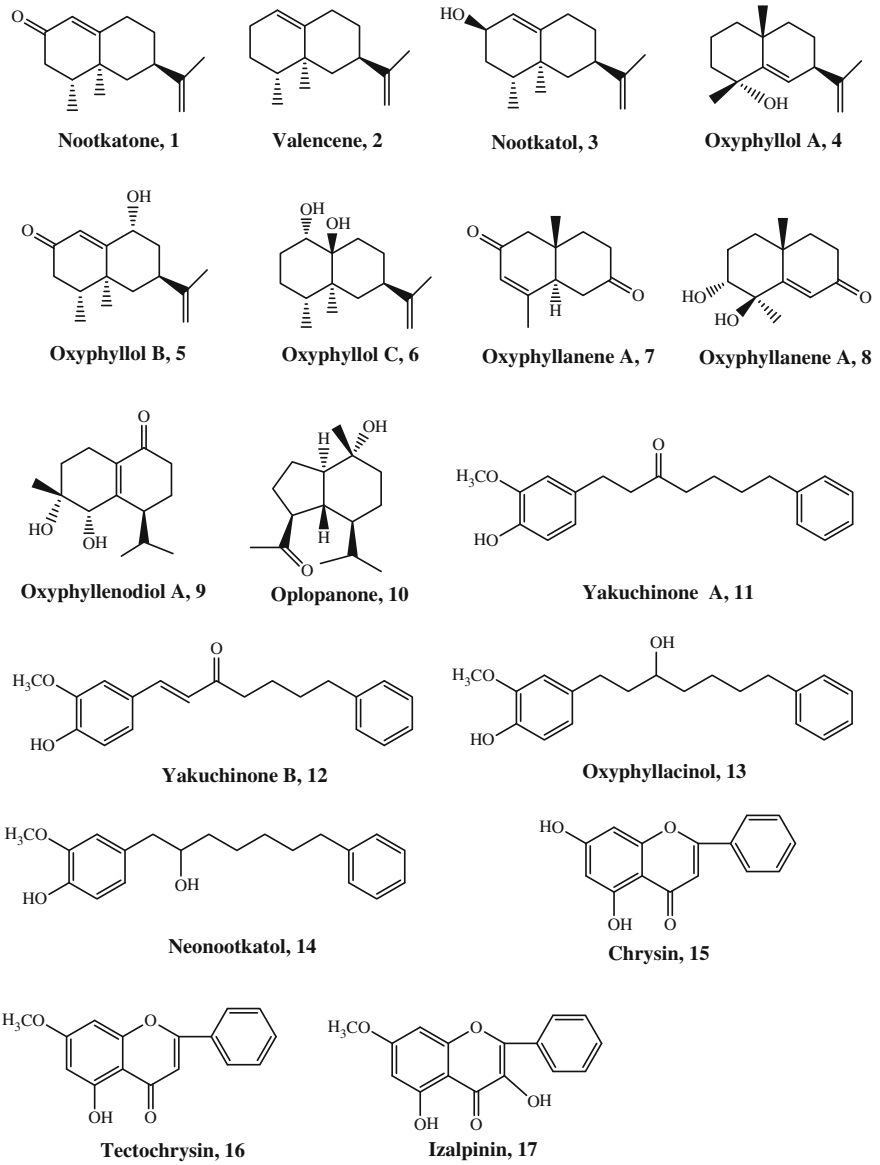

Fig. 31.2 Major compounds from the fruit of *Alpinia oxyphylla*

31.2.3 Flavonoids

Several flavonoids such as chrysin and tectochrysin (Fig. 31.2, compounds 15–17) isolated from the fruit of *A. oxyphylla* showed anti-oxidation activity.

31.3 Pharmacological Studies

Yizhi Ren is widely used as a traditional Chinese medicine to treat dyspepsia, diarrhea, abdominal pain, spermatorrhea, 'kidney' asthenia and dementia. Modern pharmacological studies have revealed that *Alpinia oxyphylla* has antineoplastic, vasodilation, anti-ulcer, calcium-antagonistic and neuroprotective effects. Most sesquiterpenoids, such as nootkatone, indicate having neuroprotective potential which associated with protection on neurons and prevention of dementia [6]. Tectochrysin, nootkatone and yakuchinone A, especially the flavonoid tectochrysin, display the function for curing diarrhea [7].

31.4 TCM Application and Dietary Usage

31.4.1 TCM Applications

The traditional usage of Yizhi Ren includes the following two aspects: (1) warms the Kidney and secures the essence: for such symptoms as frequent urination, enuresis, spermatorrhea, or dribbling of urine from Kidney disease; (2) warms the Spleen, checks diarrhea, and constrains spittle: for such symptoms as diarrhea, cold abdominal pain, excessive salivation caused by Spleen or Stomach cold.

Yizhi Ren is commonly used by compound prescription with other herbs based on TCM theory. Two important compounds are as follows: (1) Suoquan pill is composed of three herbal medicines, salt-prepared Yizhi Ren (fruit of *Alpinia oxyphylla*), Shanyao (rhizome of *Dioscorea opposita*), Wuyao (root of *Lindera aggregate*). This compound could be traced to South Song dynasty (1127–1279 AC) to treat frequent urination and enuresis during the night. (2) Yizhi powder: prepared Chuanwu (root of *Aconitum carmichaelii*), Yizhi Ren (fruit of *Alpinia oxyphylla*), prepared Ganjiang (rhizome of *Zingiber offcinale*), Qingpi (young fruit or unripe fruit peel of *Citrus reticulata*) (4: 2: 0.5: 3, w/w), to cure vomiting and diarrhea, abdominal distention and stomach pain.

31.4.2 Dietary Usage

Yizhi Ren being used as functional food could be traced back to Jin dynasty (265–420 AC) known as Yizhi Zongzi (Rice dumpling). Spice and medicated diet are the two important types of functional foods.

31.4.2.1 Yizhi Ren Gruel

Composition: Yizhi Ren (fruit of *Alpinia oxyphylla*) 5 g, Glutinous rice 50 g.
Preparation: Ground the Yizhi Ren to powder. Put the rice in a marmite with 450 ml water, boil into gruel, then add the powder and add a little salt, keep a moment and then remove from heat.
Function: It is helpful for women suffering from menopausal symptoms. It also can cure stomachache in older persons, frequent and copious urinaton, incontinence of urine.

31.4.2.2 Shexian Flapjack

Composition: Fried Baizhu (rhizome of *Atractylodes macrocephala*) 20–30 g, Yizhi Ren (fruit of *Alpinia oxyphylla*) 20–30 g, Shengjiang (fresh rhizome of *Zingiber officinale*) 50 g, White sugar 50 g, Flour *q.s.*
Preparation: Ground the fried Baizhu and Yizhi Ren into a powder. Clean and crush the Shengjiang to make a juice. Mix the powder, flour and white sugar well, add the juice and water and then roll out into a dough, make into 15–20 small cakes and bake the flapjacks.
Function: It has the function of tonifying the Spleen to treat children's hydrostomia.

31.4.2.3 Yizhi Beef Broth

Composition: Yizhi Ren (fruit of *A. oxyphylla*) 10 g, beef 50 g.
Preparation: Ground the Yizhi Ren into a powder, mince the beef meat; place and mix the meat, the powder, a little condiment and some water in a bowl, then steam well to become meat broth.
Function: It has the functions of invigorating the Stomach, tonifying Spleen, tranquilization, and reinforcing intelligence.

31.4.2.4 Yizhi Ren Flavor

Yizhi Ren is the composition of many flavor compounds. Inexpensive resources that make it sometimes replace with Sharen (fruit of *Amomum villosum*) in some compounds. Yizhi Ren can be seen in Chinese hot pot in Chongqing, Sichuan and other provinces.

31.5 Clinical Evidences

Famous TCM doctors use Yizhi Ren as a compound composition to treat many syndromes. Here is Professor Shen Bao-Fan's "Yizhi Zhi Dai Fang" to cure senile dementia [8]. The compound composition is: Shudihuang (processed root of *Rehmannia glutinosa*), Shanzhuyu (fruit of *Cornus officinalis*), Huangqi (root of *Astragalus membranaceus*), each 13 g, Yizhi Ren (fruit of *Alpinia oxyphylla*), Lujiaojiao (horn of *Cervus elaphus*), each 15 g, Shichangpu (rhizome of *Acorus tatarinowii*), Yuanzi (root of *Polygala tenuifolia*), Yujin (root tuber of *Curcuma wenyujin*), Danggui (root of *Angelica sinensis*), Chuanxiong (rhizome of *Ligusticum chuanxiong*), each 10 g, and Dahuang processed with Chinese wine (root and rhizome of *Rheum palmatum*) 6 g. It has the functions of nourishing Kidney, benefiting vital energy, removing stasis, reduce phlegm. This compound treated many patients who suffered from senile dementia.

31.6 Quality Evaluation and Assurance

Traditional characteristics of good quality Yizhi Ren consist of large, full fruit with an intense aroma. Yizhi Ren is an aromatic traditional materia medica, so testing the content of volatile oil, that not less than 1.0 % (ml/g), is described in the Chinese Pharmacopoeia 2010 edition. Nootkatone, one of the main constituents of volatile oil, is approved by the FDA for food use and was given GRAS status as a flavor ingredient [9]. It also presented inhibited gastric ulcer formation in rats, so nootkatone is proposed to be an active constituent with a minimum content of 0.15 % in some literature [10].

31.7 Safety Evaluation and Toxicity Issue

There was no report on the toxicity and side effect on Yizhi Ren and its compounds. Many Bencao literatures said that the drug properties and characteristics are a pungent taste, warm, and non-toxic. Though they all gave some advice of contraindication: do not use it with the ill symptoms narrated above due to Heat.

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Chapter 32
Amomum villosum 砂仁
(Sharen, Amomum Fruit)

Li-hua Gu

32.1 Botanical Identity

According to Pharmacopoeia of the People's Republic of China (2010 Edition), Sharen has been identified as the dry ripe fruits of *Amomum villosum* Lour., *A. villosum* Lour. var. *xanthioides* T.L. Wu et Senjen or *A. longiligulare* T.L. Wu. The three species belong to the genus *Amomum* of the Ginger Family, which includes more than 150 species, widely distributed in tropical regions of Asia and Oceania. 24 of these species can be found in China which are mainly produced in the southwestern and southeastern regions. Important medicinal plants in this genus include *A. villosum* Lour, *A. villosum* Lour. var. *xanthioides* T.L. Wu et Senjen, *A. longiligulare* T.L. Wu, *A. kravanh* Pierre ex Gagnep., and *A. taso-ko* Crevostet Lem.

A. villosum is mainly produced in Guangdong and Guangxi provinces of China, and Guangdong is the genuine area; *A. villosum* Lour. var. *xanthioides* is mainly produced in Vietnam, Myanmar, Thailand, and Indonesia. In Vietnam, the quality of the product is much better. *A. longiligulare* is mainly produced in China, such as Guangdong, Hainan, and Tsankiang. Both of the latter two kinds of Sharen have hardly been demanded in the market. *A. villosum* becomes the mainstream product in the Chinese medicinal market [1]. Sharen is not only commonly used in the clinic of Chinese medicine, but can also be used as food, flavor, health care, diet, tea, and as veterinary drugs.

As the typical botanical character, *A. villosum* grows at a height between 1.5 and 3 m. Rhizomes is procumbent above ground. It is clothed with brown, scale-like sheaths. Leaves that are sessile or sub sessile have a leaf sheath that is netlike, and contains depressed squares, are 3–5 mm ligule semi orbicular, a leaf blade is lanceolate. Spicae are ellipsoid with 4–8 cm peduncle; Ovary is covered by white

L. Gu (✉)
Shanghai University of Traditional Chinese Medicine, Shanghai, China
e-mail: gulihua1228@163.com

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Fig. 32.1 The plant (**a**) and crude drug (**b**) of Sharen

pubescent and capsule is ellipsoid, purple when it is in mature and become brown after drying. The seeds are many angled with strongly aromatic smell. The flowering period is from May to June and the fruit period from August to September [2].

Sharen is collected during the summer and autumn when the fruits are ripe, and dried in the sun or cryodrying. It is the better when it has a uniform fruit where the seed granule is close to a brown color and has an oily, aromatic, and strong pungent taste due to its traditional characteristics.

The traditional processing method is to eliminate foreign matter and mash it before use. In Chinese medicine, some medicinal materials need to be processed in a special way for clinical usage. For example: salt-prepared Sharen [3]. In this processing method, Sharen is mixed with salt water and layed horizontally to facilitate absorption. It is then fried with moderate heat until it is dry. This method of preparation reduces its acrid warmth to benefit for *Qi*-descending and calming the fetus. It can guide other herbs downward, warm the Kidney, and inhibit urination. Thus it can be used for morning sickness, a restless fetus, frequent urination, and urinary incontinences.

Another variation is the ginger-prepared Sharen. To produce ginger-prepared Sharen, it needs to be first fried and then mixed with ginger juice, which proceeds to heating in a gentle manner until the ginger juice is completely absorbed.

32.2 Chemical Constituents

The main active component of Sharen is volatile oil, approximately 1.7–3 % [4]. The major components in volatile oils include bornyl acetate (1), camphor (2), borneol (3), limonene and camphene (4) There are more than 60 different volatile oil components identified in *A. villosum* by GC-MS method [5] (Fig. 32.1).

The proportions of volatile oils in fruits of *A. villosum*, *A. longiligulare*, and *A. villosum* var. *xanthioides* are different [3, 6]. The major components in volatile oil of *A. villosum* are bornyl acetate, camphene, camphor, borneol, limonene and α-pinene (5), with bornyl acetate content of 59.60 %. It is believed that bornyl

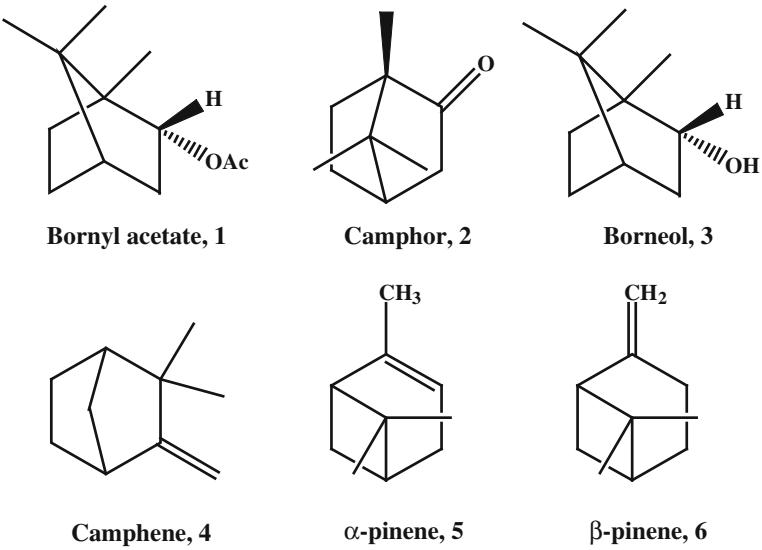

Fig. 32.2 Main constituents in volatile oils of Sharen

acetate is the effective component, which plays an important role in promoting the flow of *Qi* to kill pain [7]. It also possesses significant anti-inflammatory, an analgesic effect, and eliminates phlegm. The major components in volatile oil of *A. longiligulare* include α-pinene, β-pinene (6), 1, 8-cineole, p-cymene, limonene, camphene, bornyl acetate and camphor. The volatile oil of *A. villosum* Lour. var. *xanthioides* consists of camphor, nerolidol, bornyl acetate, borneol, limonene and α-pinene (Fig. 32.2).

Moreover, some flavonoids (7–9) and water-soluble monoterpene glycosides (10–11) were isolated from *A. villosum* [8, 9] (Fig. 32.3).

32.3 Pharmacological Studies

A study on pharmacological activity of Sharen, reveals that it has analgesia and anti-diarrhea activity, promoting the gastric dynamic effect, anti-microbial and anti-inflammation antioxidant [10–13]. Because of these pharmacological and biological activities, Sharen is used in treatment of digestive system and gynecological diseases. It is used for gastroduodenal ulcer, enteritis, hepatosis, abdominal pain in children, chronic diarrhea, irritable bowel syndrome, and gastrointestinal symptom caused by chemotherapy.

The active component of volatile oil has the effects of protecting gastric mucosa and anti-gastric ulcer, and improving gastrointestinal function, analgesia and anti-diarrhea [14]. For example, it can be used in obstetrical and gynecological diseases,

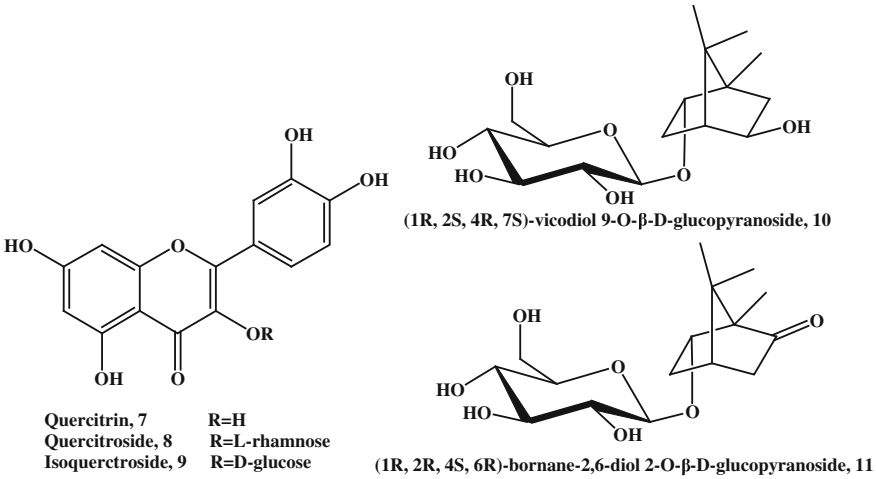

Fig. 32.3 Main flavonoids and typical monoterpene glycosides isolated from Sharen

which include the treatment of threatened abortion and pernicious vomiting. It can be applied in renal diseases such as chronic renal failure, glomerulonephritis and urolithiasis; and tumors, such as chronic myeloid leukemia, malignant lymphoma.

32.4 TCM Applications and Dietary Usage

32.4.1 TCM Applications

In clinical traditional Chinese Medicine, Sharen is widely utilized in the form of decoction, Chinese patent medicine and herbal cuisine, especially in the treatment of gastrointestinal disease.

In clinical application, it can be used in following four ways: (1) It can be used for treatment of dyspepsia combined with Muxiang (root of *Aucklandia lappa*). This combination can strengthen the effects of analgesia and invigorating stomach. For acute indigestion, the better formulation consist of Sharen, Muxiang (root of *Aucklandia lappa*), plus Zhishi (immature fruit of *Citrus aurantium*) and Baizhu (rhizome of *Atractylodes macrocephala*). If indigestion is caused by weak *Qi* or deficiency of spleen and stomach in result from abdominal stuffiness, it is necessary to improve the spleen and stomach by accompanying medicine to restore vital energy, such as Xiangsha Liujunzi Decoction and XiangshaYangwei Decoction. (2) 'The application can also be used for diarrhea due by cold and dampness. As for acute enteritis, a combination of Cangzhu (rhizome of *Atractylodes lancea*) is recommended, while for chronic dysentery with abdominal pain and inappetence, the addition of Muxiang (root of *Aucklandia lappa*) to prescriptions for dysentery

works well to enhance the effects of analgesia and anti-diarrhea. (3) It can be applied in the stomach for illnesses caused by deficiency-Cold, assisting Lizhong Decoction or Wuzhuyu Decoction to reinforce analgesia. (4) It is able to cure morning sickness from pregnancy (malign obstruction) and threatened abortion related to deficiency-Cold syndrome of the spleen and stomach. Sharen is effective for regulating the stomach, arresting vomiting and miscarriage prevention, as Xiangsha Liujunzi Decoction.

32.4.2 Dietary Usages

Sharen has a strong aroma, and is a fantastic food. In folk, ripe fruit is grinded into powder, which can be used for food seasoning; the powder has the effects of eliminating the smell of mutton, deodorization, flavoring and aroma enhancement. The herbal cuisines are suitable for people who are in appetent or abdominal distension and anorexia. Besides that, Sharen can be made into candy, wine, vinegar or comfiture, which are all quite popular foods [15].

32.4.2.1 Sharen Porridge

When Sharen (fruit of *Amomum villosum*) is combined with different food materials, it becomes herbal porridge for eliminating dampness and warms the stomach. One example is to put 5 g of Sharen into a pot with appropriate amount of water, soak for 5–10 min, boil, and then take the decoction and add 100 g of rice and make porridge. After it is cooked, add a small amount of sugar and let it boil for a while. The porridge can be used for diarrhea caused by deficiency-cold, epigastric, and abdominal stuffiness. Another example is: with 20 g of Sharen, 10 g of fresh ginger, 15 g of fresh bamboo shavings and 70–100 g of rice. First decoct the three traditional Chinese medicines, take 50 ml of the condensed decoction, then add 500 ml of water and cook the rice until it gets moderately sticky. The function of this porridge is to warm the stomach and cause anti-abortion, and used for improving vomiting occurring in early pregnant stage.

32.4.2.2 Sharen Dishes

Sharen can be cooked with meat, pork belly, fish, etc. which prepares a herbal diet to improve people's appetite. One example is to cook 5 g of Sharen (fruit of *Amomum villosum*), with 50 g of Yiyiren (seed of *Coix lacryma-jobi* L. *var. mayuen*.), one duck, moderate flavorings, some mushroom and pakchoi. The preparation is to put duck pieces, powder of Sharen and Yiyiren into a pot, add appropriate water and boil, then add scallion, ginger, Chinese prickly ash and cooking wine to flavour. Simmer on low heat, add salt, monosodium glutamate,

mushroom and pakchoi after the duck is completely cooked, and boil a little while longer. This dish can be used for weakness and poor appetite. Another example is Sharen pork belly. It needs 25 g of Sharen, 1000 g of pork belly, 15 g of ground pepper, moderate capsicol and monosodium glutamate. Put the pork belly into a pot full of water, add pieces of fresh ginger and cook them until the pork belly is done. Take it out and cut it into slices. Mix Sharen powder with ground pepper, then add the mixture and capsicol, monosodium glutamate into prepared pork belly slices and mix evenly. It is used for the treatment of diarrhea, abdominal distension and lack of appetite.

32.4.2.3 Sharen Wine

Sharen combined with other herbs can be prepared as wine, which is great for abnormal menstruations, such as menstruation delay, small quantity, dark color and with clot, pain in lower abdomen and breast, as well as depression. One example is Sharen Foshou Shanzha wine. The preparation is to put 30 g of Sharen, 30 g of Foshou (fruit of *Citrus medica var. sarcodactylis*), 30 g of Shanzha (fruit of *Crataegus pinnatifida*) into 500 g of rice wine, and steep for 7 days.

32.5 Clinical Evidences

In clinical, Xiangsha Liujunzi Decoction is used for treatment of gastrointestinal diseases, such as chronic gastritis, ulcerative colitis, diabetic gastroparesis, functional dyspepsia. Furthermore, this formulation is also effective in treatment of nausea and vomiting during chemotherapy, and in treatment of ascites due to cirrhosis. In clinical practice, the use of the original formulation is limited. In most cases, it is modified in formulation according to the individual indications [16].

Dai et al. [17] reported modified Xiangsha Liujunzi Decoction was used for the treatment of chronic atrophic gastritis in 136 cases. 42 patients were fully recovered, 53 got tangible effects, 35 were effective, and only 6 cases were of no effect; the total effective rate was 95.58 %.

In a clinical investigation, Xiangsha Yangwei pill was used for the treatment of peptic ulcer, 94 patients who were in the control group received Famotidine granule, and 106 patients who were in the treatment group took Xiangsha Yangwei pill. In the treatment group, 96 cases were fully recovered, 7 cases were effective, and only 3 cases had no effect, with overall effective rate of 97.1 % [18].

Xiangsha Zhizhu pill is mainly used in weakness of spleen and stagnation of *Qi*, inappetence and loose stool. In clinical, it is applied for chronic gastroenteritis, dyspepsia, as well as gastroptosis and gastrointestinal neurosis.

Chen [19] combined Xiangsha Zhizhu pill with Baohe pill is to treat pediatric patients with functional dyspepsia. Patients in observation group received Xiangsha Zhizhu pill and Baohe pill; patients in control group received Baohe pill. After half

of a month of treatment, total effective rates of observation group and control group were 84 and 72 % respectively. After a one-month treatment, total effective rates of observation group and control group were 92 and 76 % respectively, both without adverse reaction. The result indicated that the combination of Xiangsha Zhizhu pill and Baohe pill is significantly effective on functional dyspepsia treatment of pediatric patients.

32.6 Safety Evaluation and Toxicity Issue

There was little clinical report on the toxicity and side effect directly related with Sharen and its preparations. Tests on animals did not show clear toxicity for various organs through ip and oral administration.

The doses of 25 g/kg of Sharen decoction were given consecutively to mice for 3 days. There were no toxic reaction and death observed. 10 of the rats (weight of 160–285 g) were given 1.62 g/kg of Sharen extract by intragastric administration once daily for 30 days. The weights of the rats were measured before and after intragastric administration injection. On completing the administration, blood samples were tested for SGPT and NPN, and pathological examinations were carried out. The weight of the rats had no obvious changes. Hepatic function and renal functions were within normal range, and there was no abnormity in pathological examination.

A long-term toxicity study of volatile oil of Sharen (fruit of *Amomum longiligularg*) was conducted on Sprague-Dawley rats for 3 months. There was no toxicity reaction when the dose was 1900 mg/kg. At the same time it was found that pathological changes occurred in the spleen and lung when the dose was 3800 mg/kg [20].

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Chapter 33
Arctium lappa L. 牛蒡子 (Niubangzi, Great Burdock)

Yang Zhao and Xin Zhou

33.1 Botanical Identity

Niubangzi is the dried and mature fruits of *Arctium lappa* L., which belongs to family compositae [1]. All the roots, leaves, and fruits of *Arctium lappa* L. can be used as medicines, however the fruits are generally used clinically.

Infructescences are harvesed when the fruits are mature, which are then picked off from the inflorescence when they are totally dried. The physical characteristics of Niubangzi are typically a little flat, micro-bending with length between 5 and 7 mm, and width between 2 and 3 mm. The surface of the fruit seems to be a color which is a mixture of grey and beige with spots and longitudinal ridges. One or two of the ridges in the middle are relatively apparent. The skin of the fruit is hard and is abundant with oils.

Arctium lappa grows mainly in the wild, and is found mainly in northeast China, north China, and southwest China. Northeast China is said to have the best quality of Niubangzi [2]. They can be found growing on the side of the road, in wastelands, meadows, and on the edges of the woods. Niubangzi has strong resistance and adaptability to rugged environments, and therefore is able to grow in mountainous areas, flat grounds, however, wet warm and flat environments are preferable for its cultivation.

When necessary, Niubangzi is often fried to increase their inner contents of arctigenin (Fig. 33.1).

Y. Zhao · X. Zhou (✉)
Key Laboratory for Information System of Mountainous Areas and Protection of Ecological Environment, Guizhou Normal University, Guiyang 550001, China
e-mail: alice9800@sina.com

Y. Zhao · X. Zhou
The Research Center for Quality Control of Natural Medicine, Guizhou Normal University, Guiyang 550001, China

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Fig. 33.1 The flowering plant (**a**) and crude drug (**b**) of Niubangzi

33.2 Chemical Constituents

Liganans are the major class of bioactive compounds found in Niubangzi with anti-diabetic [3], anti-influenza virus [4], anti-cancer [5] activities. Arctigenin (1), matairesinol (2), and arctiin (3) (shown in Fig. 33.2) are representative components isolated from Niubangzi [6, 7] and usually used for quality evaluation of the crude drug and related pharmaceutical products.

33.3 Pharmacological Studies

Modern pharmacological studies have confirmed that arctigenin, one of the major bioactive component in Niubangzi, exhibits antioxidant, antitumor and anti-inflammatory activities as a phenylpropanoid dibenzylbutyrolactone lignan [8–10]. Lappaol F and diarctigenin were reported to strongly inhibit NO production in LPS-stimulated RAW264.7 cells with IC_{50} values of 9.5 and 9.6 μM, respectively [11]. Arctiin has shown the ability to induce cell growth inhibition through the down-regulation of cyclin D1 expression [12]. Diarctigenin could down-regulate zymosan-induced transcription of inflammatory genes through suppression of DNA binding ability of nuclear factor-κB in macrophages [13]. Total lignans, or extract from Niubangzi, were found to have anti-diabetic, anti-cancer, anti-influenza virus, anthelmintic, and anti-inflammatory activities [3–5, 14].

33.4 TCM Applications

Niubangzi is a common herb in China which has been used clinically to treat inflammation, such as the affection of anemopyretic cold, swelling of throat, cough, measles and syphilis and so on.

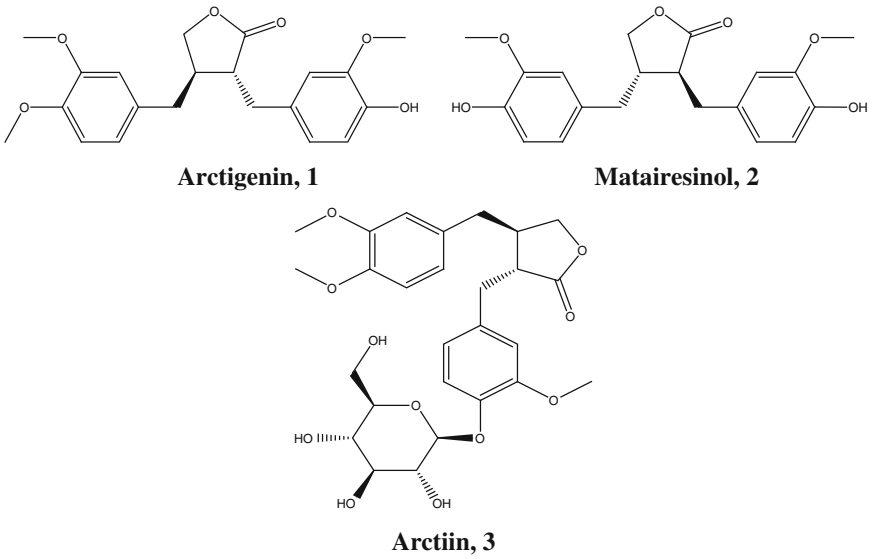

Fig. 33.2 Representative liganan compounds isolated from Niubangzi

Common Niubangzi preparations used clinically include the following forms: (1) Compound Niubangzi Lozenge: mainly composed of Niubangzi, Jinyinhua (flower of *Lonicera japonica*), Mudanpi (root bark of *Paeonia suffruticosa*) and Jiegeng (root of *Platycodon grandiflorum*). This is used for the treatment of acute pharyngitis; (2) Compound Xiling Jiedu Tablet: composed mainly of Jinyinhua (flower of *Lonicera japonica*), Lianqiao (fruit of *Forsythia suspense*), Jingjiesui (flower spikes of *Schizonepeta tenuifolia*), Niubangzi, Gancao (root of *Glycyrrhiza uralensis*) and Bingpian (synthetic borneol). Many manufacturers make this product based on the same formula in China. It is usually used to treat headache, cough and pharyngitis; (3) Compound Bishu Spray: composed of Xinyi (flower bud of *Magnolia biondii*), Baizhi (root of *Angelica dahurica*) and Niubangzi. This is effective in anaphylactic rhinitis and acute and chronic rhinitis; (4) Preparations made from active components including arctigenin and arctiin are also in the market used as chemical drugs.

33.5 Clinical Evidences

As one of the famous heat-clearing and detoxicating herb, Niubangzi is usually used in combination with Jinyinhua (flower of *Lonicera japonica*), and Xinyi (flower bud of *Magnolia biondii*). Niubangzi functions to disperse wind-heat symptoms, detoxify, bring rashes to surface, and relieve sore-throat. Compound Niubangzi Lozenge, Compound Xiling Jiedu Tablet and Compound Bishu Spray

are famous preparations made with Niubangzi. There are a plenty of clinical related reports or observational studies published on the effects of Niubangzi and its related preparations. Compound Niubangzi Lozenge was reported to have therapeutic effect on acute pharyngitis and inflammation in mice cause by dimethylbenzene [15]. Arctigenin compound exerted an inhibitory effect on influenza virus A, and its in vivo antivirus action may be related to the induction of in vivo interferon [16].

33.6 Safety Evaluation and Toxicity Data

Niubangzi Extract is of lower toxicity, but arctiin led to tonic convulsion in frogs, mice, and rabbits which resulted in paralysis. After being processed, the toxicity of Niubangzi is reduced [17].

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Chapter 34
Canarium album (Lour.) Raeusch. 青果 (Qingguo, Chinese Olive)

Chunnian He

34.1 Botanical Identity

Canarium album (Lour.) Raeusch., called Qingguo in Chinese and known as the Chinese olive tree (normally called Ganlan in China), is an evergreen tree in the Burseraceae family that grows to 30 m tall in the southeast area of China. Qingguo is mainly produced in the provinces of Guangdong and Fujian, located in China, and has been introduced to other Asian tropical and semi-tropical regions. It is a hardy species, cited as growing in various conditions, including saline or alkaline soils and rocky hillsides. The Chinese olive tree is extensively cultivated in China, as it produces an edible drupe fruit sold fresh in markets and are consumed in ways that are considered typical in Canada. It is considered a digestive aid and used to regain sobriety. It is dried as a traditional anti-bacterial, anti-viral, and anti-inflammatory medicinal agent. Its fragrant, sticky sap is also harvested for incense [1].

C. album fruit is a drupe, similar to the Mediterranean olive (*Olea europaea* L.) and other drupes of stoned fruits, such as apricots or cherries, and with the same anatomy. Its main parts are the epicarp or epidermis, the mesocarp or flesh and the endocarp or pit, which consists of a fusiform woody shell enclosing three kernels. Like its Mediterranean counterpart, the olive, the *C. album* fruit flesh has the organoleptic characteristics of strong bitter and astringent tastes. The natural bitterness and astringency of the fruit can be eliminated, or at least reduced, by processing it to make it acceptable as food or as an appetizer [2].

The fruit has special medical value and health effects such as quenching thirst, stimulating the appetite and helping digest, detoxicating, and curing throat disease and halitosis. The famous Three Ridge Olive, also called Sanleng olive, was the

C. He (✉)
Institute of Medicinal Plant Development, Chinese Academy of Medical Science, Beijing, China
e-mail: cnhe@implad.ac.cn

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Fig. 34.1 The fruiting plant (**a**) and crude drug (**b**) of Qingguo

treasure for hospitality gift in the Spring Festival in Chaozhou area of Guangdong province. The excellent cultivation varieties are showed 5–10 times or more value than the common varieties, and often in short supply.

Chinese olive has a rich cultivar resource. Since it reproduces from seed, which makes its variance is large and brings about many local cultivars after natural selection and manual cultivation for long time. These cultivar's Chinese olive have a different utility pattern, some suitable as fresh fruit, some for processing, some only as rootstock for propagation.

The date of fruit harvest varies depending on the purpose of use; fresh eating, processing, or medicinal use. Harvest starts from August, for fresh fruit and continues into October–December until the first or second frost. The later the fruit is picked, the stronger the flavor is, and the better the fruit is judged. However, the outcome is that the yield decreases markedly in the next year, for shoots bearing fruits can't germinate in the autumn. The fruiting plant and crude drug of Qingguo are shown in Fig. 34.1

34.2 Chemical Constituents

Among the secondary metabolites isolated from *C. album* (Lour.) Raeusch. are essential oil, terpenes (triterpenes, sesquiterpenes), coumarins, flavonoids, tannins, and phenolic acids.

34.2.1 Phenols [3–6]

Polyphenols are one of the most important effective compositions in Qingguo. The bitterness of the Qingguo and many pharmacological effects are related to polyphenols. Flavonoids, tannins, and phenolic acids are the main phenolic

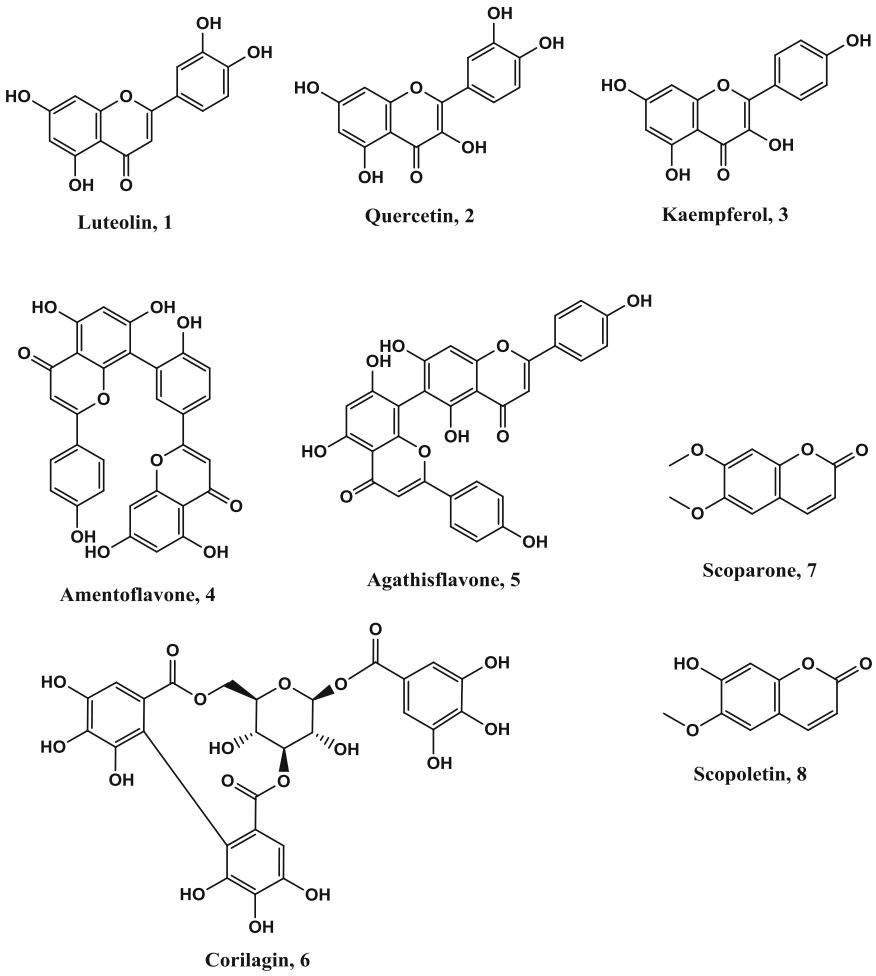

Fig. 34.2 Representative phenolic compounds isolated from Qingguo

compounds in Chinese olive. Representative compositions have been proven to be luteolin (**1**), luteolin-7-*O*-*ß*-D-glucoside, quercetin (**2**), quercetin-3-*O*-*ß*-D-glucoside, kaempferol (**3**), kaempferol-3-glucoside, amentoflavone (**4**), agathisflavone (**5**), sinapic acid, corilagin (**6**), gallic acid, ellagic acid, brevifolin carboxylic acid, ethyl gallate, and methyl gallate, etc. Representative phenolic compounds isolated from Qingguo are shown in Fig. 34.2.

34.2.2 Terpenes

As one of the major classes of bioactive compounds found in Qingguo, terpenes; including triterpene and sesquiterpenes, are mainly contained in the Qingguo fruit. α-Amyrin, β-amyrin, 3-epi-α-amyrin, 3-epi-β-amyrin, urs-12-ene-3α,16β-diol, olean-12-ene-3α,16β diol, and oeanlic acid are representative components of triterpenes and possess heptoprotective function. α-Cubenene, α-copaene, β-cubebene, (*E*)-β-caryophyllene, α-humelene, germacrene D, and spathulenol are representative components of sesquiterpenes [7, 8].

34.2.3 Coumarins

Three coumarins scoparone (**7**), scopoletin (**8**), and (*E*)-3, 3′-dihydroxy-4, 4′-dimethoxystilbene were isolated from Qingguo [1].

34.2.4 Essential Oil

Qingguo contains volatile oil, which causes its unique aroma. Monoterpenes, sesquiterpenes, long chain fatty hydrocarbons, and aromatic components are the main chemical constituents of essential oil derived from Qingguo. Among these compounds, the high content compounds are caryophilene (24.78 %), (±)-2-methylene-6, 6-dimethy, 1-bicyclo [3.1.1]-heptane (13.51 %), *p*-menth-1-en-8-ol (7.15 %), and so on. Research has shown that species or Qingguo from different origins have different volatile compositions [9].

34.3 Pharmacological Studies

Qingguo has been used in China to treat bacterial and viral infections, inflammation, poisoning and for detoxification. In Chinese folk medicine, the dried fruits of *C. album* have been used for treatment of angina, dysentery, snake bites, cough-hematemesis, enteritis, diarrhoea, and toxicosis from swellfish and alcohol. Modern pharmacological studies have indicated that the extract and pure compounds derived from Qingguo showed a variety of pharmacological activities, such as antioxidant, antibacterial, antifungal, antitumor, anti-inflammatory, hepatoprotective, analgesic, and anti-diabetic.

The ethyl acetate extract of *C. album* fruits was found to exhibit an inhibitory effect on six-helix bundle formation of the human immune deficiency virus (HIV) glycoprotein transmembrane subunit gp41 [10]. Polyphenols from *C. album*

possess a strong ability to revert hydroxyl radicals (OH) and nitrite (NO-2). In a certain scope, the effect grew stronger as mass concentration increased [11]. The extract of *C. album* had good inhibitory activity on tested bacteria and yeasts, but it did not have inhibitory activity on fungus. The acetic ester fraction had good inhibitory activity on *Staphylococcus aureus*, *Escheriehia coli* and *B. subtilis* [12]. Polyphenol from Fructus Canarii could obviously inhibit the proliferation of Hela cells in a time- and dose-dependent manner. Polyphenol could induce apoptosis by stimulating caspase-3 [13].

34.4 TCM Applications and Dietary Usage

34.4.1 TCM Applications

Qingguo, as one of the commonly used drugs of TCM, is widely used in the folk medicine of Southern China. Furthermore, ethnic minorities such as Dai, Mongol, Uighurs nationalities use to a different extent it in different extent. TCM regards that Qingguo can remove heat from the lung, relieve sore throats, promote production and detoxification of body fluid. It is also used to treat a swollen and sore throat, excessive thirst, hematemesis due to cough, lacillary dysentery, epilepsy, puffer poisoning, and alcoholism, etc. [14]. Qingguo can be used as on its own or in combination with other herbs based on TCM theory.

Common Qingguo preparations used clinically include the following forms: tea agent, big and small honey pill, mixture, granules, tablets, and pills, etc. As the main ingredients contained in prescription drugs, representative drugs are Zangqingguo Granules, Zangqingguo Throat Tablets, Qingguo Pills, Qingguo Zhisou Pills, and Zhisou Qingguo Oral Liquid, etc. [7].

34.4.2 Dietary Usages

The raw fruits are sold on markets as dietary or health maintaining material, which are believed to help indigestion and combat drunkenness. To date, Qingguo has been processed into types of preserved fruits, beverages, jams, oil, fruit wine, candied fruit, juices, pickles, and olive sugars, etc. However, preserved fruits are the most common product. The seeds are also edible and are eaten in China. Modern research has shown that the kernels have a high percentage of fat (52.8 %) and proteins (29.5 %). Kernel oil revealed that oleic acid (30.5 %) and linoleic acid (41.8 %) are the major unsaturated fatty acids, while palmitic acid (18.0 %), stearic acid (7.83 %) and arachidic acid (0.39 %) are the main saturated ones. Potassium, calcium and magnesium are the predominant mineral elements present in the

kernels. Sodium, iron, manganese, and zinc are also detected in appreciable amounts. The kernel proteins are rich in arginine, glutamic and aspartic acids (3.19, 5.02 and 2.47 %, respectively) while the limiting amino acids are methionine and lysine [15].

34.5 Clinical Evidences

The dried fruits have been a traditional medicine material and have a long history in China. The fresh fruits are widely used in food industry, which has caused people to realize that Qingguo has a good curative effect to human body. Modern clinical studies have shown that whether it is used on its own, or in combination with other herbs, the exact curative effects are found. For example, the mixed liquor of Qingguo in combination with radix isatidis has an obvious effect in preventing the upper respiratory tract infection [16].

Ganlan Jiangzhi Capsule composed of *C. album*, Medicated leaven, *Crataegus pinnatifida*, *Curcuma aeruginosa*, *Bupleurum chinense*, *Alisma plantago-aquatica*, *Rheum officinale* was observed the therapeutic effectiveness in treating hyperlipmia. 56 cases of hyperlipmia were randomly chosen as the treated group (treated by Ganlan Jiangzhi Capsule) and 38 cases as the controlled group treated by Xuezhikang Capsule (A commonly used traditional Chinese medicine for the treatment of hyperlipidemia). Two groups had effective rates of 91.07 and 89.47 %, respectively. No significant difference was found between the two groups ($P > 0.05$). The levels of cholesterol and triglyceride in the treated group were lower than that of the controlled group after the treatment, the difference had significance ($P < 0.05$) [17].

Based on 40 cases of patients' clinic trials, Qingguo tablet composed of the *C. album*, *Lonicera japonica*, *Scutellaria baicalensis*, *Menispermum dauricum*, *Ophiopogon japonicus*, *Scrophularia ningpoensis*, *Paeonia lactiflora*, *Platycodon grandiflorus*, has good effect on acute pharyngitis, and the dry throat, sore throat, pharynx mucosa hyperemia swelling, and other symptoms were visibly improved [18].

34.6 Safety Evaluation and Toxicity Data

Except for being commonly used traditional Chinese medicine (TCM), Qingguo also used as fruits with higher safety.

Qingganlan Liyan Lozenge (Give priority to with green olives, supplemented by *Ophiopogon japonicus*, *Mentha haplocalyx*, *Rehmannia glutinosa*, *Panax quinquefolius*, etc.) were fed to rats for 4 weeks with the dosage of 8.0 g/kg, the result showed that the lozenge didn't show any toxicity [19].

The acute toxicity reaction of total flavonoids from Qinguo in mice was observed in the successive 7 days. All mice in both experimental and control groups

survived. The weight of mice in the two groups increased by 28.0 and 25.0 % ($P > 0.05$), respectively, and no acute toxicity was observed in both groups. The maximal tolerant dose of total flavonoids from Qingguo by ig in mice was 11.46 g/kg, which was about 115 times that of the adult clinical daily dose. Total flavonoids from Qingguo have little acute toxicity [20].

According to TCM theory, the patients with problem or disorder in spleen and stomach, cold, and constipation need to be careful to use Qingguo.

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Chapter 35
Cassia Obtusifolia L. 决明子 (Juemingzi, Semen Cassiae)

Yulan Wang

35.1 Botanical Identity

Semen Cassiae, called Juemingzi in Chinese, is the seeds of the *Cassia obtusifolia* L. plant, an annual semi-shrubby herb about 0.5–2 m tall. The color of Semen Cassiae is light brown. Their shape is rhombic or slightly flat, with linear concave ramp on each side. The seeds of the same genus plant *C. tora* L. are also a legal source of Semen Cassiae. The color of the seeds of *C. tora* L. is gray-green and the shape is normally rhombic.

Semen Cassiae is known clinically for its antiseptic, diuretic, antidiarrheal, antioxidant, and heptaprotection effects [1]. It is processed into dry seeds as a crude drug for clinical usage or as a dietary supplement. Cultured plants have become an important source of Semen Cassiae-derived commercial products in the market. Figure 35.1 shows the flowering plant (a) and dry seeds (b) of *C. obtusifolia* L.

35.2 Chemical Constituents

35.2.1 Anthraquinone

A diversity of anthraquinones have been identified from Semen Cassiae. The majority of them are emodin-type anthraquinones, which have a stable cyclic nucleus. In total, eight positions of the nucleus can be substituted. The substitutions lead to the generation of a large number of structurally different derivatives, which are defined by the type, number, and location of the substitution group(s). Commonly, anthraquinone

Y. Wang (✉)
Dalian Institute for Drug Control, Dalian, China
e-mail: lisaylwang@aliyun.com

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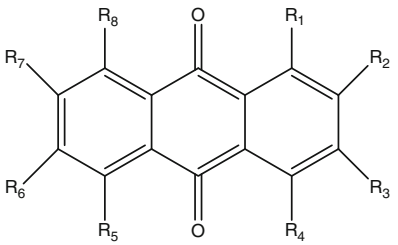
Fig. 35.1 Flowering plant (**a**) and dry seeds (**b**) of *Cassia obtusifolia* L.

glycosides have sugar groups, such as glucose, gentiobiose, murine, rhamnose, and sucrose, at the C-1, C-2, and C-8 position. *C.obtusifolia* L. and *C.tora* L. are different in the composition of anthraquinonesin terms of type and content. More than 40 anthraquinones have been isolated from Semen Cassiae [2]. Representative compounds and typical structures are shown in Fig. 35.2. This type of compound is mostly like to be found from *Rheum*, *Polygonum*, and *Aloe* besides *Cassia*, and so has been used as marker or control compounds for quantitative and qualitative analysis of herbal products containing these herbs.

Fig. 35.2 Representative compounds and typical structures of anthraquinones isolated from Semen Cassiae



Chrysophanol: R_1, R_8=OH; R_3=CH_3

Obtusin: R_2,R_8=OH;R_1,R_6,R_7 =OCH_3; R_3=CH_3

Physcion: R_4, R_5=OH; R_2=CH_3, R_7=OCH_3

Physcion-8-O-β-glucoside: R_1=OH;R_8=Glu, R_3=CH_3, R_6=OCH_3

35.2.2 Naphthopyrone

Naphthopyrone is another type of major component in Semen Cassiae [3–7]. Many naphthopyrones exist in the form of glycosides, of which the sugar groups can be glucopyranose and gentiobiosyl formed into a single chain or two chains. Normally the length of a sugar chain is less than four monosaccharides.

35.2.3 Other Compounds

Other bioactive compounds such as proteins, amino acids, and organic acids are present in Semen Cassiae [8, 9]. The proteins are effective in reducing the level of blood lipid. The total content of free amino acids in Semen Cassiae is around 9.584–15.995 μmol/g [10]. Diverse organic acids are identified from Semen Cassiae, including (Z,Z)-9,12-octadecadienoic acid, oleic acid, *n*-hexadecanoic acid, chrysophanol, octadecanoic acid and (E)-9-octadecenoic acid [11].

35.3 Pharmacological Studies

Semen Cassiae is used clinically to treat many diseases and disorders [1]. Previous studies have reported that anthraquinones are anti-viral, anti-inflammatory, anti-tumor, inhibit platelet aggregation, regulate microcirculation, and reduce lipids in blood. The extract of Semen Cassiae is used to treat dizziness and headache and to profit the eyes by anchoring and nourishing the liver. In addition, Semen Cassiaeis found to have neuroprotective effects in brain diseases. For example, the extract of Semen Cassiae demonstrated neuroprotective effects against neurotoxicities in Parkinson's disease (PD) models [12].

35.4 TCM Applications and Dietary Usage

35.4.1 TCM Applications

Semen Cassiae is considered in TCM as an herb to treat inflammation, fever, and congestion. It is a diuretic, therefore it is often used in clinical medicine for tuning kidney functions. Semen Cassiae is also one of the important herbs that can treat chronic constipation. Particularly, it is used in Ophthalmology for treating glaucoma, cataract and conjunctivitis. In addition, Semen Cassia is also able to relieve or prevent hyperlipidemia, hypertension, and atherosclerosis, which are common diseases suffered by many people in the world.

35.4.2 Dietary Usages

Semen Cassiae is a valuable dietary botanical material because of its bioactive functions and high safety. It has been processed into different style products, such as roasted tea. Semen Cassiae is rich in anthraquinones. This property renders Semen Cassiae an attractive material for treating many disorders such as hyperlipidemia and inflammation. For example, Sunburn Radix, Semen Cassiae with honey, was found to be especially suitable for summer deficiency caused by intestinal dryness [13]. Alisma, Semen Cassiae and green tea, were used together to reduce body weight [14].

35.5 Clinical Evidences

Semen Cassia is often used clinically in combination with other herbs to treat high blood pressure, hyperviscosity, constipation, Meniere's disease, chronic atrophic gastritis, viral keratitis, and fatty liver. Its clinical use shows satisfactory results [15]. Semen Cassia appears particularly useful for the treatment of constipation, which is a disease suffered by many senile people. For example, in a clinical trial, 196 cases of senile constipation patients were randomly divided into the control group and the Cassia treatment group. The evaluation showed that the total effective rate was 93.8 % for the Cassia treatment group, significantly better than the control group [16].

35.6 Safety Evaluation and Toxicity Data

In general, Semen Cassiae is a highly safe material if used at low dosage for a short-term period. However, it can become toxic when the dosage is improperly high [17]. When SD rats were fed with food containing different contents of Semen Cassiae (1, 2, 4, 8, 16, and 32 %), all the rats receiving 32 % Semen Cassiae died after 8 days. The weight of rats and water consumed decreased proportionally to the contents of Semen Cassiae in the food. When the content of Semen Cassiae was higher than 8 %, it caused apparent reduction in the number of sperms and the number of red blood cells in bone marrow. In addition, anthraquinones may have carcinogenic effects. Hydroxyanthraquinones have an obvious structure-activity relationship with reproductive toxicity. For example, when the 1, 3-positions or side chain are substituted with a hydroxyl group, an anthraquinone (e.g. emodin) has reproductive toxicity. These results indicate that Semen Cassiae should not be used for a long-term period or without doctor's advices [18].

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Chapter 36
Chaenomeles speciosa 木瓜 (Mugua, Flowering Quince)

Caifang Wang

36.1 Botanical Identity

Mugua, belonging to the family *Rosaceae*, is a thorny deciduous or semi-evergreen shrub native to eastern Asia. As a traditional crude drug in TCM, Mugua is the dried nearly ripe fruit of *Chaenomeles speciosa* (Sweet) Nakai, called flowering quince. *C. speciosa* is taller than another commonly cultivated species like *C. japonica*, usually growing to about 2 m or more. The flowers are usually red, but may be white or pink, and the fruit is a fragrant but hard pome that resembles a quince.

As a crude drug, Mugua is collected in summer and autumn when the fruit turns greenish-yellow. It is boiled in water until the exocarp becomes off-white in colour, halved longitudinally, and dried in the sun.

The quality Mugua, named to be Zhoupi Mugua, is the mature fruits of the *C. speciosa* (Sweet) Nakai. Another two species used as Mugua, called Guangpi Mugua and Mugua Haitang, are the mature fruits of the *C.* sinensis (Thouin) Koehen and *C. cathayensis* (Hemsl) C. K. Schneid. Additionally, Tibet Mugua (*C. thiretica* Yu) and Japan Mugua (*C. japonica* (Thunb) Lindl) are also used as substitutes of Mugua in China [1]. The fruiting trees and slices as crude drug of Mugua (*C. speciosa*) are illustrated in Fig. 36.1.

Additionally, Fanmugua (*Carica papaya* L.), also called Mugua in folk, belongs to the *Caricaceae* family, was known as a famous fruit.

C. Wang (✉)
Capital Medical University, Beijing, China
e-mail: cfwang1040@126.com

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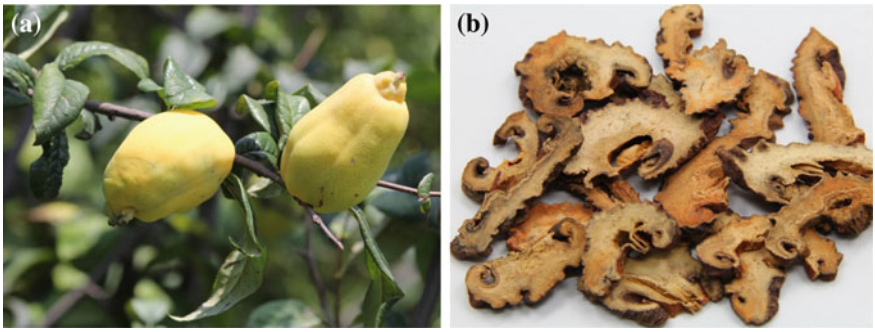
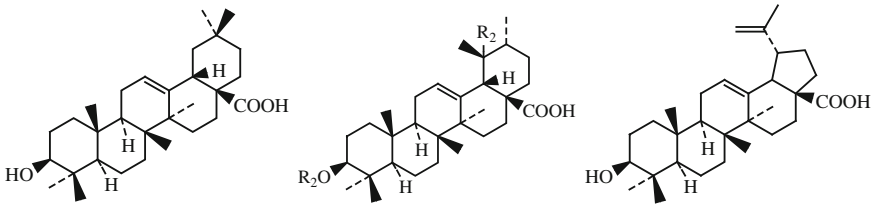


Fig. 36.1 Fruiting trees (**a**) and slices as crude drug (**b**) of Mugua (*C. speciosa*)

36.2 Chemical Constituents and Quality Evaluation

There are a lot of active constituents isolated from Zhoupi Mugua. The structural types of these compounds include triterpenoids, flavonoids, organic acids, amino acids, and so on. Some triterpenoids like oleanic acid (**1**), ursolic acid (**2**), acetyl ursolic acid (**3**), pomolic acid (**4**), and betulinic acid (**5**) [2–4] (Fig. 36.2) were isolated from this species. Some flavonoids including quercetin (**6**), quercetin-3-O-galactoside (**7**), quercetin-3-O-rhamnoside (**8**) [5, 6] (Fig. 36.3) and a lot of organic acids [7–10] including common fatty acids, caffeic acid, chlorogenic acid, malic acid, citric acid, benzoic acid, succinic acid, and aconitic acid were also reported from this plant. The content of total organic acids is up to 6.01 % and the content of citric acid up to 20.74 % of all. Amino acids are abundant in fresh materials and the contents of seven essential amino acids are up to 41.0 % of all [11]. Additionally, there are also sterols, saccarides, various vitamins, and active proteases.

Some analytical methods are used for the quality control of Mugua. The content of total organic acids in Mugua is required to be 2.09–3.47 % by direct potentiometric



Oleanic acid, **1**

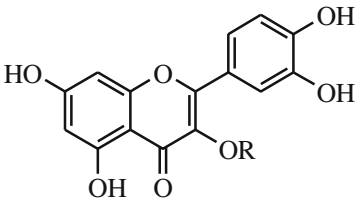
Ursolic acid, **2**, R_1=R_2=H;

Acetyl ursolic acid, **3**, R_1=Acetyl, R_2=H;

Pomolic acid, **4**, R_1=H, R_2=OH

Betulinic acid, **5**

Fig. 36.2 Typical trieterpenoids from Mugua (*C. speciosa*)



Quercetin, **6**, R=H;

Quecetin-3-O-galactoside, **7,** R=Gal

Quecetin-3-O-rhamnoside, **8**, R=Rha

Fig. 36.3 Typical flavonoids from Mugua (*C. speciosa*)

titration [12]. High performance liquid chromatography (HPLC) is used to analyze the contents of chlorogenic acid and caffeic acid in Mugua [13]. Twenty-six trace elements in Mugua were analyzed by ICP-MS [14], among them K, Na, Ca, and Mg were abundant.

36.3 Pharmacological Studies

36.3.1 Anticancer Activity

Crystalline materials from Mugua showed potent inhibitory effect on mice Ehrlich's ascites carcinoma [15]. (−)-Potassium malate along with fumaric acid displayed inhibitory effect on the mice Ehrlich's ascites carcinoma [16].

36.3.2 Hepatoprotective Activity

The extract from Mugua showed hepatoprotective effect on acute liver damage by CCl_4 in rats [17], which can alleviate necrosis of liver cells and hepatic steatasis, prevent swelling of liver cells, promote repair of liver cells and lower the effect of Alanine aminotransferase (ALT). Oleanic acid in Mugua had a potent protective effect on acute liver damage in rats [18].

36.3.3 Antiinflammatory and Antibacterial Activity

Mugua has a potent curative effect on rheumatoid arthritis (RA) [19]. Oleanic acid, pomolic acid, and sterols can resist hemolytic streptococci. And phenols of Mugua can inhibit some kinds of shigella dysenteriae [20].

36.3.4 Other Pharmacological Activity

Polysaccarides from Mugua showed pharmacological activities such as anti-coagulation, prevention of infection, anti-cancer, anti-inflammation, anti-virus, and anti-aging, which are ideal immunopotentiator. Mugua proteases can decompose proteins and be used as adjuvant therapy on enterogastritis, dyspepsia, and cerebral thrombosis. Water-soluble vitamins from Mugua like vitamin C can help repair body tissues, clear up toxic materials harmful to body tissues and enhance disease resistance. Glycosides of *C. speciossa* (CCS) [21] showed anti-inflammatory and demulcent effect, and can influence immunology function so that CCS can allieviate pathological symptoms such as secondary paw swelling, arthralgia, and polyarticular arthritis, etc.

36.4 TCM Applications and Dietary Usage

36.4.1 TCM Applications

Baishao Mugua Soup composed of Baishao (Radix paeoniae alba, 30–60 g), Mugua (Chaenomeles speciosa, 12–25 g), Jixieteng (Millettia dielsiana, 12–30 g), Weilingxian (Clematis chinensis, 15–30 g), Gancao, (Glycyrrhiza uralensis, 12 g) is used to cure hyperosteogeny [22] and osteoarthrosis [23] with the significant effect. Gecan Mugua Soup containing Mugua (20 g) and other ingredients, i.e. Gegen (Lobed Kudzuvine Root, 25 g), Cansha (Bombyx mori L, 12 g), Yiyiren (Coix lacryma-jobi, 15 g), Haifengteng (Kadsura Pepper Stem, 15 g), Guizhi (Cinnamomum cassia Presl (10 g), Duhuo (Radix Angelicae Biseratae, 10 g), Tubiezi (Eupolyphaga seu Steleophaga, 10 g), Danggui (Angelica sinensis, 10 g), Qinjiao (Gentiana macrophylla, 10 g), Niuxi (Achyranthes bidentata, 9 g), and Sanqi powder (Panax Notoginseng powder, 6 g) (taking after mixing it with water)) was used to treat 58 patients with arthrolithiasis in a clinical trial, the total effective percentage is up to 94.8 % [24]. Mugua is beneficial for patients with cerebral infarction through increasing the activity of SOD in red blood cells [25].

36.4.2 Dietary Usage

Mugua is widely used as food and the material in health products alone or mixed with others. Fanmugua (Carica papaya L., from *Caricaceae*) is a famous fruit with a good reputation and the nickname “Pawpaws” and “King of hundreds of fruits”, and an ingredient in juice, tea, soup, porridge, in prescription diets and Mugua (Flowering quince, from *Rosaceae*) can, also be used in diets or some desserts. These products can reduce tiredness, nourish skin and maintain beauty, etc. [26, 27].

36.5 Clinical Evidence

Mugua was used clinically to cure lower limb swelling, muscular atrophy and so on. The chymotrypsin from the Mugua juice was injected into intervertebral disc cartilage for pain relief by American doctor. The papayotin of Mugua was also used to reduce tumor tissues clinically [28].

36.6 Safety Evaluation and Toxicity Issue

It has been reported that a woman got contact dermatitis, caused by Mugua (from *Rosaceae*) and then healed by antianaphylactic treatment [29]. A study on reproductive toxicology indicated that glycosides of *C. speciossa* (CCS) showed no embryo toxicity and no teratogenicity on mice in dosage 83.1–1330.0 mg/kg [30].

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Chapter 37
Citrus medica L. var. *sarcodactylis* Swingle 佛手 (Foshou, Finger Citron)

Qi-wei Zhang

37.1 Botanical Identity

Citrus medica L. var. *sarcodactylis* Swingle is cultivated and sometimes naturalized in Guangxi, southwest of Guizhou, Hainan, Sichuan, east of Xizang, and Yunnan in China.

Citrus medica var. *sarcodactylis* grows into a shrub or small tree. Its branches, leaves, and flowers are purplish when young. Branches grow with about 4 cm spines. Leaves are usually simple or in rare cases unifoliolate. The petiole is short, not winged and the leaf blade is elliptic to ovate-elliptic. The leaf margin is serrate, its apex may be rounded, obtuse, or in rare cases mucronate. The inflorescences are axillary, and usually contain about 12-flowers. Plants flowers can be solitary. Flowers have 5 petals, which are 1.5–2 cm in length. The fruit is pale yellow, elliptic, with separated segments surrounded by the pericarp. The fruit's surface is coarse and the pericarp can be white to pale yellow. The centre of the pericarp is soft, thick, and usually contains no seeds. Removing the centre of the pericarp is difficult. The sarcocarp contains 10–15 segments. It is nearly pellucid to pale milky yellow, acidic to slightly sweet, and fragrant. When seeds are present in the sarcocarp they are small in size and the seed coat is smooth. The flowering period is from April to May, and the fruit period from October to November [1] (Fig. 37.1).

Foshou is the dried fruit of *Citrus medica* L. var. *sarcodactylis* Swingle (the Rue Family). The drug is collected in autumn when the fruit turns yellow. The fruit is cut longitudinally into slices, dried in the sun or at a low temperature (lower than 60 °C) [2].

Q. Zhang (✉)
China Academy of Chinese Medical Sciences, Institute of Chinese Materia Medica, No. 16 Nanxiaojei, Dongzhimennei, Dongcheng District, Beijing 100700, China
e-mail: zhangqw1955@163.com

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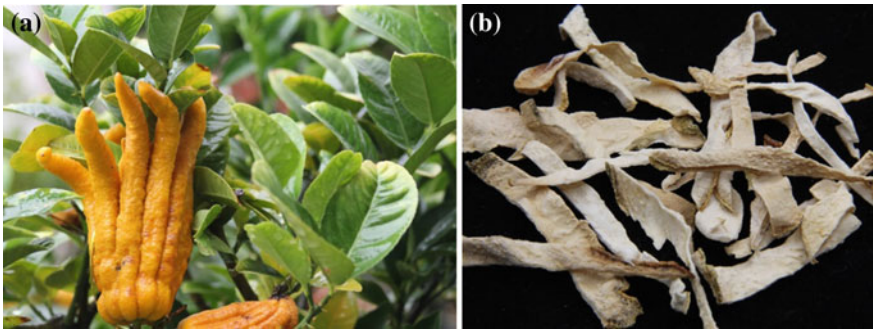


Fig. 37.1 The fruiting plant (**a**) and sliced crude drug (**b**) of Foshou

37.2 Chemical Constituents

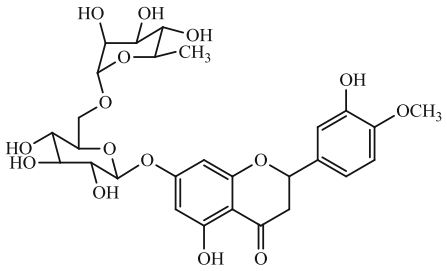
Four major classes of compounds found in the fruit of *Citrus medica* L. var. *sarcodactylis* Swingle include: Volatile oil, flavnoids, coumarines and phenolic acids.

37.2.1 Volatile Oil

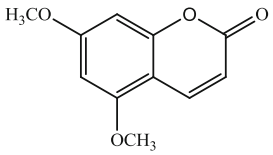
Essential oil contents and chemical compounds vary in plants grown in different areas. The oil concentrations are generally from 0.125 to 0.325 %, and there are anywhere from 30 to 50 chemical compounds contained within the oil. The main components of the oils are the same and include D-limonene (its relative contents from 37.96 to 57.10 %), gamma-terpinene (15.89–33.71 %), alpha-pinene (0.70–3.40 %), and beta-pinene (1.38–2.88 %) [3].

37.2.2 Flavonoids

Flavonoids are bioactive compounds. It was reported that diosmetin, 3,5,8-trihydroxy-3′,4′-bimethoxyflavone, 3,5,8-trihydroxy-7,4′-bimethoxyflavone, 3,5,6-trihydroxy-7,4′-bimethoxyflavone, 3,5,6-trihydroxy-3′,4′,7-trimethoxyflavone, citflavanone, diosmin, and hesperidin (**1**) were separated and identified from Foshou.



Hesperidin, 1



5,7-dimethoxycoumarin, 2

Fig. 37.2 Representative flavonoid and coumarin in Foshou

37.2.3 Coumarins

The compounds isolated from Foshou include: 5,7-dimethoxycoumarin (limettin) (**2**), 6,7-bimethoxycoumarin (scoparone), 7-hydroxy-6-methoxycoumarin (scopoletin), aviprin, 7-hydroxycoumarin (umbelliferone), 7-hydroxy-5-methoxycoumarin, 7-methoxy-5-prenyloxy-coumarin, byak-angelicin [4], 5-hydroxy-7-methoxy-8-prenyloxycoumarin (sibiricol), bergapten, and 6-hydroxy-7-methoxycoumarin (7-methylesculetin) [5] (Fig. 37.2).

37.2.4 Phenolic Acids

The phenolic acids found in Foshou are ferulic acid, vanillic acid, protocatechuic acid, and p-coumaric acid.

37.2.5 Others

Compounds limonin, obacunone, 5-methoxyfurfural, and polysaccharides, are included here, as they do not belong in any of the above classes.

37.3 Pharmacological Studies

Foshou alcohol extract has been shown to releive cough, have anti-asthma effects, and eliminate phlegm [6, 7]. The alcohol extract significantly enhanced rabbit ileum smooth muscle contraction, and aided in mice intestinal propulsion [8]. Foshou essential oils inhibited *Bacillus subtilis, Escherichia coli, Staphylococcus aureus* and *Saccharomyces sereviciae* [9], and inhibited B16 melanoma cell line and MDA-MB-435 cancer cell growth in vitro [10, 11].

37.4 TCM Applications and Dietary Usage

37.4.1 TCM Applications

In Traditional Chinese Medicine (TCM), Foshou is used to regulate the *Qi* flow of the Liver and Stomach, and pain relief. It is used to treat stagnation of *Qi* of the Liver and Stomach marked by distending pain in the chest and hypochondriac regions, stuffiness feeling in the stomach, poor appitite, and vomiting [2].

Foshou is seldom used as alone in treating patients. More often, Foshou is used in combination with other herbs based on TCM theory.

Stagnation of *Qi* of the Liver is marked by distending pain in the chest and stomach regions. Foshou is commonly used to treat this condition in combination with Yujin (root tuber of *Curcuma wenyujin*), Baishao (root of *Paeonia lactiflora*), and/or Xiangfu (rhizome of *Cyperus rotundus*).

Qi stagnation of the stomach is marked by stuffiness feeling in the stomach, poor appitite and vomiting. Foshou is used to treat this condition in combination with Doukou (fruit of *Amomum kravanh*), Banxia (tuber of *Pinellia ternate*), and Muxiang (root of *Aucklandia lappa*) to strengthen the action.

For treating damp phlegm accumulation marked by panting, cough, phlegm, and chest tightness, Foshou is commonly used with Banxia (tuber of *Pinellia ternate*), and Fuling (sclerotium of *Poria cocos*) to eliminate dampness and phlegm.

37.4.2 Dietary Usage

Foshou is not only used as an herbal medicine, but is processed into candied fruit and used to make some functional beverages, foods, and dishes, such as Foshou Dazao (fruit of *Ziziphus jujuba*) porridge. These foods are used to treat poor appetite and indigestion.

37.5 Safety Evaluation and Toxicity Data

The acute toxicity test using 1 mL of emulsion/100 gbw (equivalent to 2000 mg/kg of FC fruits) per os daily for 7 days was shown to be totally nontoxic. Finger citron fruits were safe for use [12].

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Chapter 38
Citrus reticulata Blanco and Cultivars 橘皮 (Jupi, Mandarin Orange Peel)

Qi-wei Zhang

38.1 Botanical Identity

Citrus reticulata is extensively cultivated in the vast regions south of the Qin Ling Mountains in China, especially in the provinces of Guangdong, Sichuan and Fujian.

Citrus reticulata Blanco of the Rue Family are small citrus trees. The trees contain numerous branches with few spines. The leaves are mono-foliolate and the leaf blade can be lanceolate, elliptic, or broadly ovate. The basal portion of the leaf is usually narrow, the midvein of the leaf furcates near the apex and the leaf margin is crenate or in rare instances, entire. The leaf apex is marginated, or a different colour than the other parts of the leaf. The trees flowers can be solitary or there can have up to 3 flowers in a fascicle. The calyx is irregular in shape and contains 3–5-lobes. Petals are usually 1.5 cm or smaller, and stamens are 20–25 cm in length. The style is long, slender and the stigma is clavate. The fruit is oblate to subglobose. The pericarp can be pale yellow, orange, red, or carmine its texture can be smooth or coarse and it can be very thin to thick. The pericarp can be easily removed. The sarcocarp can have 7–14 segments or more in rare circumstances. The sarcocarp is can be sweet, sour, and sometimes bitter. The sarcocarp usually has seeds from a few to many seeds. Rarely is the sarcocarp seedless. Pulp vesicles are usually plump and short, and rarely are they slender and long. Seeds are usually ovoid, with a round base. The apex is narrow and acute, there are usually multiple embryos. The cotyledons can be dark or pale green, or milky white and the chalazaeare purple. Flowering periods are from April to May, fruiting periods from October to December [1] (Fig. 38.1).

Jupi (orange peel) is the pericarp of the ripe fruit of *Citrus reticulata* Blanco or its cultivars (Rue Family). In Chinese medicine it is also called Chenpi (陈皮).

Q. Zhang (✉)
China Academy of Chinese Medical Sciences, Institute of Chinese Materia Medica, Beijing 100700, People's Republic of China
e-mail: zhangqw1955@163.com

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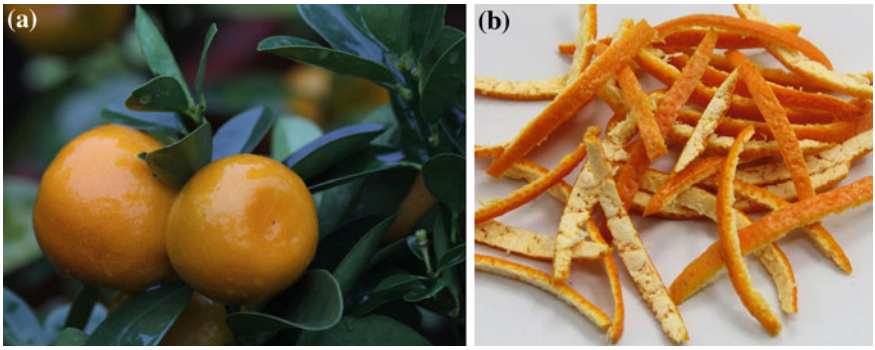

Fig. 38.1 The fruiting plant (**a**) and crude drug (**b**) of Jupi

Here Chen in Chinese means old, so the longer the dried mandarin orange peel is stored for, the better the quality of the drug according to Chinese medicine.

38.2 Chemical Constituents

Essential oils and flavonnoids are two major classes of bioactive compounds found in the fruit peel of *Citrus reticulata* Blanco.

38.2.1 Essential Oils

As a major bioactive portion, essential oil contents and chemical compounds are different due to the different cultivars, growing areas, and storage times. The concentration of oil is generally from 1.21 to 3.65 %, and there have been anywhere from fourty to eighty chemical compounds identified from the oils. D-limonene is the predominant chemical compound found in the oils. Its proportion varies from 48.78 to 82.20 %. Other highly represented chemical compounds are γ-terpinen (5.32–20.20 %), linalool (0.61–5.77 %), β-myrcene (0.59–4.37 %), α-pinene (0.46–2.27%), β-pinene (0.09–2.18 %), and 2-(methylamino)-benzoic acid methyl ester (not detected–7.22 %). The other compounds are present in the concentrations less than 1 % or even 0.1 % [2].

38.2.2 Flavonnoids

38.2.2.1 Polymethoxylated Flavonoids (PMFs)

It was reported that the PMFs in Chenpi included natsudaidai, desmethylnobiletin, 3, 5, 6, 7, 8, 3′, 4′-heptamethoxyflavone, tangeretin (**1**), 5, 6, 7, 8, 4′-pentamethoxyflavone,

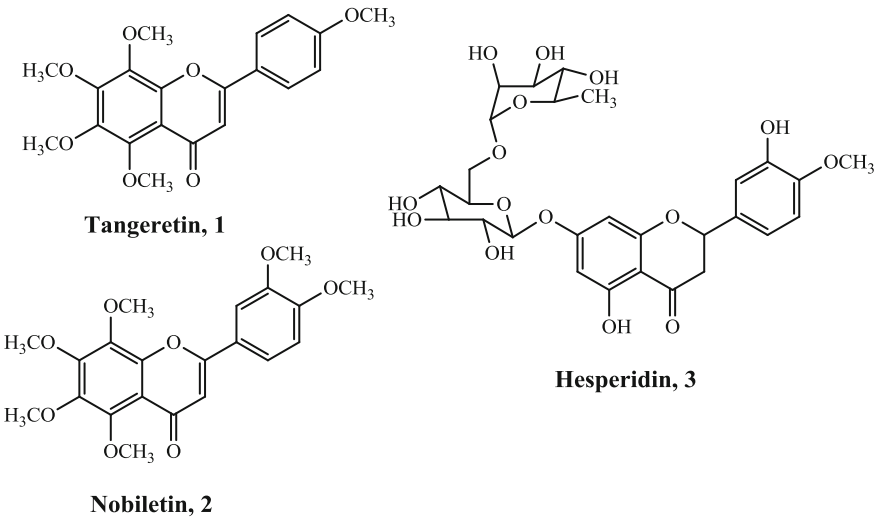

Fig. 38.2 Representative compounds in Chenpi

5-hydroxy-6, 7, 8, 3′, 4′-pentamethoxyflavone, 3, 5, 6, 7, 3′, 4′-hexamethoxyflavone, nobiletin (**2**), and 5-hydroxy-6, 7, 8, 3′, 4′-pentamethoxyflavone.

Recently on the basis of the ESI-MS (n) characteristics of PMF standards, 32 polymethoxylated flavonoids (PMFs) including 24 flavones and 8 flavanones or chalcones were screened and identified from the complex extract of the peels of 'Shatangju' mandarin (*Citrus reticulata* Blanco) by high-performance liquid chromatography coupled to electrospray tandem mass spectrometry. Among them, there were 10 hydroxylated polymethoxyflavonoids (OH-PMFs), and the rest were all permethoxylated PMFs [3].

38.2.2.2 Other Flavonoids

These compounds in Chenpi included hesperidin (**3**), neohesperidin, naringenin, and hesperetin.

The chemical structures of representative compounds are shown in Fig. 38.2.

38.3 Pharmacological Studies

Pharmacological studies in early years have shown that Chenpi had bioactive properties including inhibition of the gastrointestinal tract smooth muscle contraction, inhibition of experimental gastric ulcer and gastric acid secretion, protection of experimental liver injury, and positive choleretic effects. Its alcohol extracts have shown anti-bronchoconstriction effects in guinea pigs in vitro.

The alcohol extracts were shown to relieve cough and resolve sputum in guinea pigs exposed to histamine. Chenpi decoction also has shown to have stimulatory effects on heart muscle in vitro and in vivo, dilation of coronary arteries, increase of coronary artery blood flow, and rapid elevation of blood pressure in rabbits and dogs when administered intravenously. Chenpi has significant anti-allergic and anti-bacteria effects [4]. In recent years, studies have revealed that Chenpi possesses anti-oxidation and anti-tumor effects [5–7].

38.4 TCM Applications and Dietary Usage

38.4.1 TCM Applications

In traditional Chinese medicine, the action of Chenpi is to regulate the flow of Qi, invigorate spleen function, eliminate damp, and resolve phlegm. It is used to treat distention and fullness in the chest and epigastrium with anorexia, vomiting and diarrhea, and cough with copious phlegm [8].

Chenpi is commonly used in combination with other herbs based on TCM theory. Jupi Zhuru decoction is from ***Jinkui Yaolue***, an ancient famous classical Chinese medical works (about 210 AD). It is composed of Jupi (fruit peel of *Citrus reticulata*), Zhuru (stem intermediate of *Bambusa tuldoides*), Dazao (fruit of *Ziziphus jujuba*), Shengjiang (fresh rhizome of *Zingiber officinale*), Gancao (root and rhizome of *Glycyrrhiza uralensis*), Renshen (root and rhizome of *Panax ginseng*). It is used to calm the adverse-rising energy, tonify Qi and clear Heat. It is also used in treatment of hiccups or retching.

It is seldom used as a single form. It was reported that Chenpi powder was used alone to treat functional dyspepsia and positive effects were observed.

38.4.2 Dietary Usages

Chenpi is commonly used in herbal medicine. It is used in food and beverage production to produce items such as Chenpi moon cake, Chenpi flapjack, Chenpi jam, Chenpi tea and Chenpi wine.

38.4.2.1 Chenpi Tea

Steep Chenpi(10 g) with boiling water. Drink 2 to 3 times a day for sore throat.

38.4.2.2 Chenpi Used in Medicated Foods

Chenpi is used to cook some functional dishes to address poor appetite and indigestion. Common recipes include: Chenpi porridge, Chenpi duck, and Chenpi pigeon.

38.5 Safety Evaluation and Toxicity Data

There are no reports on adverse reactions of administration of Chenpi. One report suggest subacute oral toxicity when used in combination with carotenoids extracted from citrus peel (*Citrus reticulata* Blanco).

In this study, no statistically significant, dose-related effects on food consumption, food efficiency, body weight gain, clinical signs, or ophthalmoscopic parameters was observed in any treatment group. Urinalysis, hematological, blood coagulation and serum biochemical examination as well as necropsy or histopathology showed that no observed adverse effects were found with doses of at least 2000 mg/kg body weight/day [9].

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Chapter 39
Coix lacryma-jobi L. var. *ma-yuen* (Roman.) Stapf 薏苡仁 (Yiyiren, Jobstears)

Fei Yu, Yazhuo Li, Jun Zhang and Changxiao Liu

39.1 Botanical Identity

Coix lacryma-jobi var. *ma-yuen* is an annual or perennial herb in the family of Cramineae. Its seed has now become one of the most popular Chinese herbal medicines. Although frequently used as a dietary supplement there is still controversy in terms of its classification in China and globally. It is considered to be 7–10 different species overall. 4 species included in "The Picture Index of Senior China Plant" are *Coix lacryma-jobi* L., *Coix puellarum* Balansa, *Coix agrestis* L., *Coix aguatica* Roxb, as well as 9 varieties. *Coix lacryma-jobi* L. var. *ma-yuen* is the main and legal source recorded in The Pharmacopeia of People's Republic of China and other historical records of Chinese herbal medicine. As a typical botanical trait the plant can grow to a height between 100 and 200 cm. Leaves are alternatively arranged depending on their position on the stem. Flower petals are white, yellow or red. The medicinal part is mainly the seeds with the length of 4–8 mm and the wide of 3–6 mm. They are glossy, ovalor eggshaped with a milky white outer surface and a slightly sweet taste [1, 2].

Traditionally wild Coix seeds were harvested, but now cultivation has become the main source of supply. As an increasing amount of Coix seed derivative commercial

F. Yu · J. Zhang
Tianjin Key Laboratory on Technologies Enabling Development of Clinical Therapeutics and Diagnostics, School of Pharmacy, Tianjin Medical University, Tianjin 300070, China

Y. Li · C. Liu (✉)
State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, Tianjin Institute of Pharmaceutical Research, 308 An-Shan West Road, Tianjin 300193, China
e-mail: liuchangxiao@vip.163.com

Y. Li
e-mail: liyz8@tjipr.com

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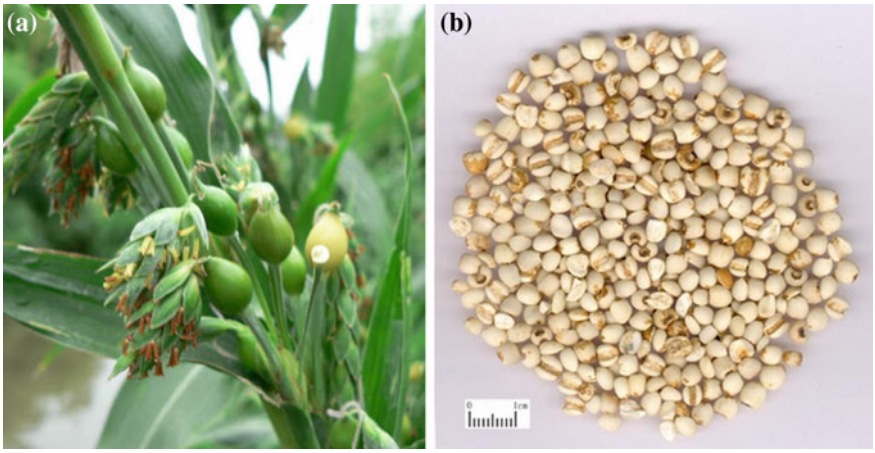


Fig. 39.1 The coix plant (**a**) and coix seeds (**b**) [4]

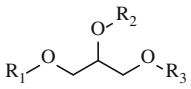
products are on the market, there has been shortage of wild seeds. Generally, the seeds are harvested in autumn from September to October in the second year of growth. Then the Coix plants ripen and are sundried for 3–4 days. After threshing and either being sundried for 2–3 days or stir-baked until the outer shell looks yellowish the dried and cleaned seeds are usually used as raw material [1, 3]. Coix seeds are mainly produced in Fujian, Jiangsu, Hebei and Liaoning provinces in China, as well as in the Southeast Asia and islands of Pacific Ocean (Fig. 39.1).

39.2 Chemical Constituents

Coix seeds contain a large number of nutrients, for instance, proteins, superior amino acids and carbohydrates. Additionally several major classes of bioactive ingredients were identified in Coix seeds with many beneficial functions to human health, particularly coixenolide, triglyceride, fatty acid, and triterpenes [5].

39.2.1 Nutritional Ingredients

As a nourishing grain, Coix seeds contain 14 % protein, 5 % fat, 65 % carbohydrates, 3 % crude fiber, 0.07 % calcium, 0.242 % phosphorus, and 0.001 % iron. The levels of all nutrients in Coix seeds are higher than those in rice. It also contains mineral substances and essential amino acids, for example, leucine, arginine, lysine and tyrosine. Due to high content of unsaturated fatty acid and extremely low levels of heavy metal and toxic residues in Coix seeds, it has become a typical “Green Food”.



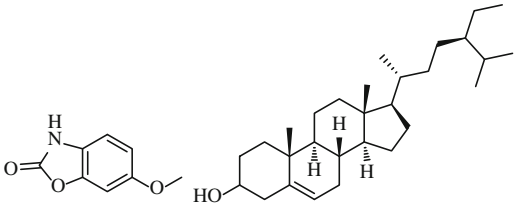
Hexadecanoic acid (C16), 1, R_1= R_2=R_3 =$CO(CH_2)_{14}CH_3$

Octadecoic acid (C18), 2, R_1= R_2=R_3=$CO(CH_2)_{16}CH_3$

Octacenic acid (C18-1), 3, R_1= R_2=R_3 =$CO\text{-}(CH_2)_7CH{=}CH(CH)_7CH_3$

Octadedienoic acid (C18-2), 4, R_1= R_2=R_3=$CO\text{-}(CH_2)_7\text{-}CH{=}CH\text{-}CH_2CH{=}CH(CH_2)_4CH_3$

Triglyceride



CoixoI, 5 **β-sitosterol, 6**

Fig. 39.2 Representative ingredients isolated from Coix seed

39.2.2 Bioactive Ingredients [6, 7]

Up until now, more than 41 chemical ingredients have been isolated and identified in Coix seeds, including coixenolide, triglyceride, fatty acid, lactams, coixol, saccharides, sterols and triterpenes. Coix seeds mainly contain abundant amounts of coixenolide, coixan and total triterpenes. Their contents on average are 44.60, 59.03 and 22.83 mg/g respectively. As two major bioactive ingredients identified in Coix seeds, fatty acid and coixenolide were reported to present significant anti-tumor activity. In Coix seed oil the content of triglyceride is up to 87 %, and unsaturated fatty acid residues in all triglyceride fatty acid residues are over 84 %, mainly including oleic acid (31.42 %) and linoleic acid (47.38 %). Three active polysaccharides were also obtained and they are able to regulate blood glucose levels. After purification, polysaccharide A consists of rhamnose, arabinose, xylose, mannose and galactose (1:1:1:11:10); polysaccharide B consists of rhamnose, arabinose, xylose, mannose, galactose and glucose (3:18:13:3:10:5); polysaccharide C is glucan (Fig. 39.2).

39.3 Pharmacological Studies

As a tasty food, Coix seeds were commonly seen on dinner tables. Most importantly it is widely used as a traditional Chinese medicine over thousands of years in treatment of diseases such as cancer, metastasis, hypertension, arthritis, asthma, and immunological disorders [8, 9]. According to the ethnopharmacological theory, Coix seeds stimulate functions of spleen, stomach and lung, remit fever (which helps in the drainage of pus), and induce diuresis. They have long been used in China to treat warts, chapped skin, rheumatism, and neuralgia [3]. Recent study showed that Coix seeds presented antiproliferative, antitumor and various immunomodulatory activities, for instance, anti-complementary, anti-inflammatory and anti-allergic effects. In addition modern research found that Coix seed oil could prevent or reduce the contracture action of striated muscle and stimulate action on uterus. The fatty oil is also able to reduce serum calcium and blood glucose levels. Coix seed oil also exerts beneficial effects on cancer with multiple mechanisms as seen in clinical trials. It presented activities of blood lipid-reducing and antioxidant effects, and could be used as a supplementary in healthcare food products and drugs for prevention of chronic diseases (particularly arthrosclerosis and coronary artery disease) [4, 10, 11]. While the active component of Coix seed, coixenolide, promotes cellular immunity and humoral immunity; coixan A, B, and C significantly reduce the blood glucose level [12, 13]. Moreover, the consumption of Coix seed extracts can increase the activities of cytotoxic T cells and natural killer (NK) cells. The methanol extract of Coix seeds inhibits production of NO and $O_2^{-\cdot}$ by activating macrophages [14].

39.4 TCM Applications and Dietary Usage

39.4.1 TCM Applications

Coix seed is one of the most common herbs traditionally used in herbal medicines and healthcare products. In terms of classification of traditional Chinese medicine (TCM), the herb is sweet and tasteless in flavour, slightly cold in nature. Tasteless is for removing dampness, sweet is for tonifying spleen, slight coldness is for clearing heat. Coix seed is neutral, neither oily nor drastic [15]. The herb exerts therapeutic healthcare actions in the following aspects: inducing diuresis, excreting dampness, strengthening spleen, arresting diarrhea, clearing heat and pus, antitumor and enhancing immunologic function. Coix seeds could be used alone or in combination with other herbs based on TCM theory [3, 14]. The amount of Coix seeds needed to be taken depends on its usage. Generally, the daily dosage recommendation is 9–30 g, while dosage in clinical use is 12–30 g with the highest dosage being up to 30–60 g. Coix seeds are either mixed with water for a decoction or grounded into powder to make pills; it also can be mixed with wine or rice porridge [16].

Clinically, Coix seeds are used in the following preparations: (1) Coix seed extract and its powder are convenient for administration, which can be made from either only Coix seeds or mixed with other herbs. The significant advantage of this form is ease of use and absorption; (2) Kanglaite injection (KLT), a lipid emulsion for intravenous and intra-arterial injection containing 10 % oil (a triglyceride containing four fatty acids) extracted from the Coix seeds. The injection was approved by SFDA for manufacturing and marketing in 1997, and it has been successfully applied in the treatment of a variety of malignant tumor such as carcinomas of lung, liver, stomach, esophagus, colon, pancreas, kidney, ovaries, malignant lymphoma, leukemia for more than 200,000 cases with no obvious toxicity or side effects [17].

39.4.2 Dietary Usages

As a nourishing food and one of the most valuable dietary botanical materials, it was the tribute for imperial palace known as "Yiyi Pearl" in ancient China. Adlay was also called "the Gramineae of Life and Health" in Europe. The grain is prepared by roasting and may be eaten dry, used as porridge, or processed into flour [18]. Coix seeds have always been considered very precious for nourishment, healthcare, bath and skin moisturizer in Japan. Historically, Coix seeds have been widely used for its beneficial components, especially its high protein content and superior amino acid composition. These products are Coix seed tea, Coix seed health care wine, Coix seed yoghurt, Coix seed porridge, Coix seed pastry, Coix seed powder, and Coix seed extract. Some of the following dietary forms can be easily made at home, others are more difficult and some have been industrialized for sale [8].

39.4.2.1 Coix Seed Teas

Herbal tea made of Coix seeds mixed with other herbs is the most common way to use Coix seeds. Here are several examples: Coix seed Tea composed of fried Coix seeds (10 g), hawthorn (5 g) and fresh lotus leaf (5 g); Coix seed jasmine Tea composed of Coix seeds (10 g) and jasmine tea (3 g), etc. To make the herbal tea hot water is used to freshly brew all raw materials. Softened water or natural spring water with less mineral and alkaline is recommended in order to reduce the loss of nutrients.

39.4.2.2 Coix Seed Health Care Wine

Coix seed either on its own or combined with other herbs are used to prepare herbal wine for health care. Different from the conventional method of wine making, the

nutrition and health-care Coix seed wine is produced by direct fermentation with Coix seeds as raw materials followed by distillation. Components with high boiling point (coixenolide and specific triterpenoids) in Coix seeds are distilled into the wine.

Another example is the half solid state fermentation process which was used for making fermented glutinous wine from Coix seed. Taking the Coix seeds and the glutinous rice as the starting stock, the sweet wine tune and the white sugar as the supplementary materials, the best fermentation process for fermented glutinous wine was when Coix seeds were fermented for 48 h at 33 °C, liquor tune recruitment 1 %. The ratio of Coix seed to the glutinous rice was 1.4:1; the mixture was cooked for 60 min, boiled for 25 min, and then steamed for 30 min. The ratio of material to water was 1:2.5; the final sweetness was 12 %. The fermented glutinous wine from Coix seeds under these conditions described presented white color, rich in pure liquor, rice wine unique fragrance, mellow liquor body, suitable crisp, sour and sweet [19]. Coix seed can also be used to make herbal wines in combination with many other herbs depending on the specific needs of functions. Daily intake amount will vary depending on the content of Coix seed, other herbs, and alcohol.

39.4.2.3 Coix Seed Used in Medicated Foods

In general, Coix seed is used to make porridge with lily, yam, red beans, rice, and sticky rice. A typical way is to boil 30 g of Coix seed with other herbs, such as 30 g of Shanyao (rhizome of *Dioscorea opposita*), 15 g of Lianzi (seed of *Nelumbo nucifera*), 50 g of millet, and 10 Dazao (fruit of *Ziziphus jujuba*). This rice porridge was recommended to be taken twice daily for prevention of cancer, weak spleen and stomach, or related diseases. Epidemiologists have long suspected that the low cancer rate in Southeast China might be related to Coix seeds because it is a dietary staple in the region.

Mutton, carp, spareribs, Chinese cabbage, peanuts, corn, and most of cereals can be boiled with Coix seed. Nutrients and the health-maintaining effect of Coix seeds can be utilized simultaneously. The taste of foods that contain Coix seeds can be adjusted according to personal preferences.

In addition, extracted juice of Coix seed and fresh milk were mixed together and fermented into yogurt. It was rich in nutrients with a good taste. It also exerted many healthcare functions such as anticancer, blood sugar reduction, pain relief, enhancement of body immunity system, cosmetic functions and so on.

39.5 Clinical Evidences

Pharmacological studies and clinical investigations suggest that Coix seed oil has certain anti-hepatoma effects. It exerts anti-hepatoma activity by inhibiting hepatoma cells proliferation via inducing apoptosis and reducing nutritive supplies for

growing tumors. This is done through inhibiting angiopoiesis in tumor tissue, as well as by increasing immunologic function against tumors. In the treatment of primary liver carcinoma, either single Coix seed oil or Coix seed oil in combination with other medicines can be used. When combined with chemotherapeutic drugs, it can reduce the occurrence of immune degeneration and bone marrow inhibition. Therefore, it has great potential for further development [20].

In clinical practice, Coix seed has been used in patients with verruca vulgaris and verruca planae juveniles, which have been considered to be induced by viral infection. However, Kanglaite (KLT) injection is mainly made of Coix seed oil, which was extracted from Coix seeds through supercritical CO_2 extraction. KLT injection has been successfully applied in the treatment of a variety of malignant tumors, such as carcinomas of the lung, liver, stomach, esophagus, colon, pancreas, kidney, ovaries, malignant lymphoma, and leukemiain over 200,000 cases in China and Russia. When combined with chemotherapy, radiotherapy and surgery, it could improve the response rate, regulate the energy of advanced patients, and improve life quality and prolong survival time. A Phase II clinical trial has been approved by FDA to evaluate its efficacy in treating non-small- cell lung cancer in 2003. For the first time, drug derived from a traditional Chinese herbal remedy entered into clinical trials in the United States [8, 17].

39.6 Safety Evaluation and Toxicity Data

Clinical studies on the toxicity or side effects that could be directly related to the use of Coix seeds remain limited. Currently, pre-clinical studies have not shown toxicity for various organs through intravenous drip or oral administration. The maximal oral dose of Coix seed oil in mice was 40 ml/kg or 32.8 g/kg, there was no irritation in rectum and normal or damaged skin of rabbits was observed. It is considered safe for both routine oral administration and external use of Coix seeds. It was reported that LD_{50} (per oral administration) was higher than 20 g/kg. Ames test, micronucleus test of bone marrow cells in mice and shape abnormality test in mice were negative and less toxic [17, 21]. There were no adverse actions when people took decocted Coix seeds at the normal dose (no more than 30 g). As reported, gastrointestinal reactions and bone marrow suppression in the experimental group receiving Kanglaite Injection combined with chemotherapy were significantly lower than that in the control group with chemotherapy alone ($P < 0.05$). Kanglaite Injection enhanced efficacy and reduced the side effects of chemotherapy, and improved quality of life of gastric cancer patients [22]. In conclusion, in clinical practice the adverse reaction of KLT (Coix seed oil) is mild, merely manifesting as liver enzyme transient elevation, hypersensitive skin rash, etc., with most side effects naturally disappeared in 3–5 days after administration. As discussed above, the safety of this herb is satisfying. Coix seed is considered as a safe herbal medicine to be used in the treatment of cancer, dampness, tonifying spleen and healthcare.

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Chapter 40
Cornus officinalis Sieb. et Zucc. 山茱萸 (Shanzhuyu, Medicinal Dogwood)

Jin Yang

40.1 Botanical Identity

Shanzhuyu, belonging to the family of Cornaceae, is the dried sarcocarp of *Cornus officinalis* Sieb. et Zucc. and one of the most popular herbal medicines in TCM clinical application. It can be used in dietary supplements and cosmetics. As a small to medium deciduous tree or shrub, *C. officinalis* grows to a height of 3–7 m. Simple and opposite leaves are ovate-elliptic sharp. Umbel of flowers is yellow and axillary. The elliptic fruit when maturated is red to dark red in colour [1].

C. officinalis grows naturally in the shadowed and moist mountainous areas. Funiu mountain in Henan province, Tianmu mountain in Zhejiang province, and Qinling mountain in Shanxi province are the main producing area. The largest production base of *C. officinalis*, which has acquired GAP authentication, has been established in Xixia County, Henan province [2]. The cultivar is the main source of supply for the commercial products on the market now. The fruit is harvested between late fall to early winter when its skin has turned red. The harvested fruit is baked or warmed gently in boiling water, and the stone is removed [3]. The dried, cleaned and cored sarcocarp can be stored and marketed as the raw material of Shanzhuyu.

Shanzhuyu forms irregular flake, with 1–1.5 cm long and 0.5–1 cm broad. The shrunken and glossy surface is purple-red to purple-black in colour, with a persistent calyx mark on the top and fruiting pedicels at the base [1]. Historically, other processing methods can be used in clinics for various specific medicinal purposes. Alcoholic Shanzhuyu is the most common among these processing products. Flowering plant (a), ripen fruit-bearing tree (b), and crude drug of *C. officinalis* are shown in Fig. 40.1.

J. Yang (✉)
Beifang University of Nationalities, Yinchuan, Ningxia, China
e-mail: youngkin@126.com

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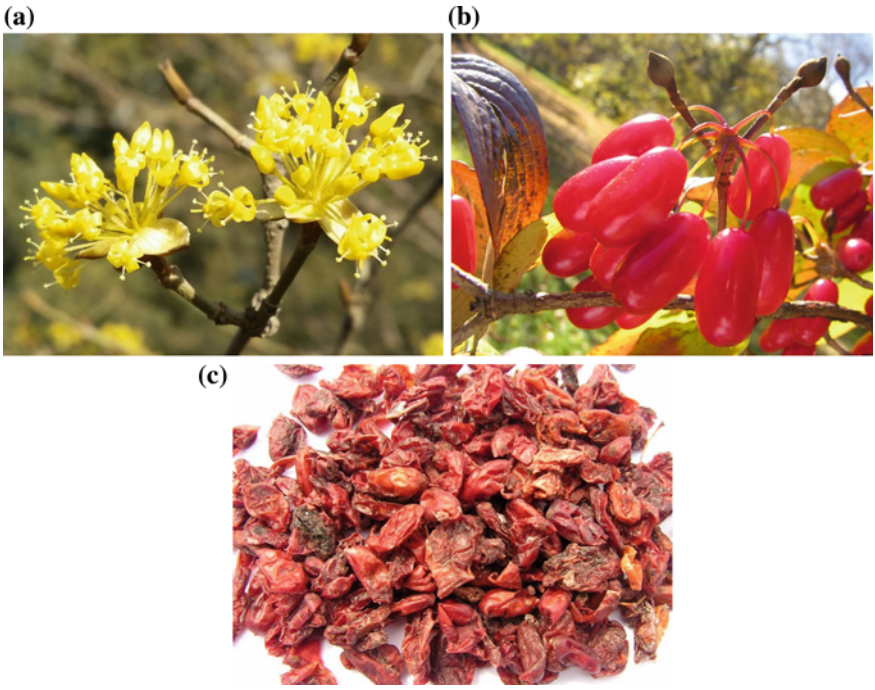

Fig. 40.1 Flowering plant (**a**), ripen fruits-bearing (**b**), and crude drug (**c**) of *C. officinalis*

40.2 Chemical Constituents

Iridoid glycosides, organic acids, tannins, and polysaccharides are the major bioactive constituents found from the fruit of *C. officinalis* (see Fig. 40.2).

40.2.1 Iridoid Glycosides

Pharmacological investigations point to iridoid glycosides as a major, if not the most important, contributor to the hypoglycemic activity of this plant [4–6]. About 10 iridoid glycosides had been isolated from Shanzhuyu [7]. Among these compounds, loganin (**1**) serves as the primary marker compound to control the quality of crude drug Shanzhuyu in the Pharmacoepia of People's Republic of China. Recent studies suggest that the iridoid glycosides have bioactive mechanisms that accommodate immunity [8], and protection of nerve cells [9]. Morroniside (**2**) would play a substantial role in the bioactivity of the latter.

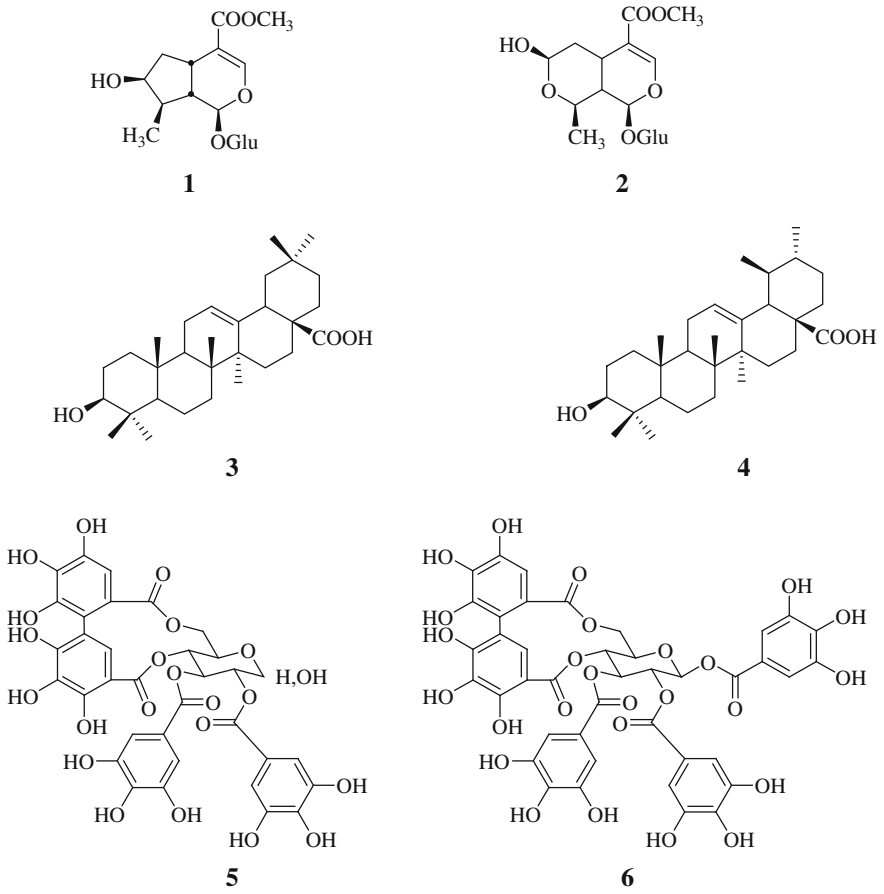

Fig. 40.2 Representative iridoid glycosides, triterpenoids, and tannins isolated from Shanzhuyu

40.2.2 Organic Acids

For a long time, organic acids, mainly triterpenoids, including oleanolic acid (**3**) and ursolic acid (**4**), have been regarded as the essential component of the bioactivities of Shanzhuyu, and recent works have provided additional support for the bioactivities of organic acids, i.e., antimicrobial [10], anti-inflammation [11], lowering blood-glucose [12], and heptoprotective activities [13].

40.2.3 Tannins

Tannins can be found in the sarcocarp and the stone of Shanzhuyu. So far, more than 20 hydrolysable tannins are isolated from this plant. A research trial considered that 1,2,3,6-tetra-O-galloyl-β-D-glucopyranose, 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose, tellimagrandin I (**5**), and II (**6**) would be related to the effect of heptoprotection [11].

40.2.4 Polysaccharides

The sugar content in the fresh Shanzhuyu is about 4.5–10 %. As a bioactive constituent of this herbal medicine, polysaccharides were found at the turn of the century. These complex macromolecular chemicals rapidly became a area of interest in an attempt to understand the bioactive mechanisms of Shanzhuyu, for example, anti-oxidation and anti-aging [14], accommodation of immunity [15], etc.

40.3 Pharmacological Studies [2, 11]

In China, Shanzhuyu has a long history of being used as an herbal medicine to nourish liver and kidney. Modern pharmacological investigations suggested that the Shanzhuyu possesses some bioactive abilities, such as anti-inflammation and germ, accommodation of immunity, lowering blood-glucose, heptoprotection, anti-cancer, anti-shock, and anti-oxygenation etc. Iridoid glycosides display a significant hypoglycemic effect on type 2 diabetic cardiopathy and can delay the occurrence of nephropathy. The polysaccharides and iridoid glycosides showed increased specific and nonspecific immune enhancing activity and improved the defense system. Organic acids and tannins exhibited antimicrobial effect.

40.4 TCM-Applications and Dietary Usage

40.4.1 TCM Application

As described previously, Shanzhuyu is one of the most common traditional Chinese medicines and health-care products. According to the theory of TCM, Shanzhuyu can nourish the liver and kidneys, and has an astringent effect. In general, it is commonly used in combination with other herbs to treat spontaneous perspiration, night sweating, spermatorrhea, and frequent urination because of deficiency of Yin [16]. For example, Liuwei Dihuang Pill, composed of *Cornus officinalis* and other

five herbal components (*Rehmannia glutinosa, Dioscorea opposita, Poria cocos Wolf, Paeonia suffruticosa, Alisma plantago-aquatica*), is the most famous formula in TCM and produced by hundreds of medicinal manufacturers according to the same formulae in China. It can be used to treat neurasthenia, hyperthyroidism, and diabetes mellitus with hyperactivity of fire due to *Yin* deficiency. Many people in China consider it as a health care product for long-term use, and use it for the treatment of subhealth, to enhance immunity, and for anti-aging, etc. During the past few decades, people who want this herbal medicine have had more choices because of the availability of modern forms, such as tablet, capsule, granule, besides Liuwei Dihuang Pill, can be easily obtained in the market.

In addition, Shanzhuyu extract/instant powder can be mixed with other herbal extracts/instant powders for convenient clinical administration.

40.4.2 Dietary Usages

Historically, Shanzhuyu was used as a food plant in China, Japan and Korea. In Zhejiang province, Shanzhuyu is named as Zaopi, which means Shanzhuyu likes the skin of jujube. In some ways, this name also means Shanzhuyu can be used as dietary materials. There are many ways to use this food plant, including Shanzhuyu wine, Shanzhuyu tea, Shanzhuyu gruel, and so on.

40.4.2.1 Shanzhuyu Wines

Actually, there are commercial fermented wines and soaps made from Shanzhuyu available on the market. At home, 60 g of Shanzhuyu can be soaked in 500 ml rice wine for 7 days to prepare an herbal wine for puerperal spontaneous sweating. The recommended dose is 50 ml daily. Combining with other herbs, Shanzhuyu can be soaked in Chinese spirit to make medicinal wine depending on the specific effect. Although medicinal wine can be prepared easily at home, we strongly suggest that you consult your doctor before taking it.

40.4.2.2 Shanzhuyu Teas

Shanzhuyu, mixed with other herbs, can be decocted to prepare Shanzhuyu tea for spontaneous perspiration, night sweating, spermatorrhea, and frequent urination because of deficiency of *Yin*. Some examples are: Shanzhyu tea composed of Shanzhuyu (5 g) and jasmine tea (3 g); Shanzhuyu (9 g), Fangfeng (*Saposhnikovia divaricata*, 9 g), and Huangqi (*Astragalus membranaceus*, 9 g); Shanzhuyu (9 g), Wuweizi (*Schisandra chinensis*, 9 g) and Yizhiren (*Alpinia oxyphylla*, 9 g), etc. You can add sugar to the Shanzhuyu tea if you don't like the sour taste.

40.4.2.3 Shanzhuyu Gruel

Shanzhuyu can be made into gruel with rice or sticky rice. A usual way to make this is to boil Shanzhuyu (18 g), Gouqizi (*Lycium barbarum*, 18 g) and sticky rice (100 g) in flares, and then simmer gently for 30 min. This gruel would benefit the eyesight.

40.5 Clinical Evidences

According to TCM theory, Shanzhuyu is usually used in combination with other herbs for specific clinical effects depending on which herbs are combined. Liuwei Dihuang Pill and its derivatives, including Zhibai Dihuang Pill, Mingmu Dihuang Pill, Qiju Dihuang Pill and so on, are the major preparations made from Shanzhuyu. These traditional compound preparations are considered as health products in the long-term use of the drug and are used for maintaining mental acuity, cardiovascular health, and sexual function, as well as avoiding common problems of middle age (e.g., effects of menopause, benign prostatic hypertrophy, and elevated blood pressure and cholesterol levels) [17]. Furthermore, there are many clinical reports or observation investigations published on the effects of these complex preparations for diabetes mellitus and its syndromes [18, 19].

40.6 Safety Evaluation and Toxicity Data [20]

With hundreds to thousands of years of human consumption, there is little record of serious deleterious effects when Shanzhuyu is taken as recommended. The acute toxicity experiment showed that the LD_{50} of one time ip was 55.35 g crude drug/kg. No visible pathological changes were detected in mice when cumulative dose was 5 times of LD_{50} in the cumulative toxicity testing. The 10 g/kg of Shanzhuyu decoction was given to mice via ip in once time, there was no influence on bone marrow micronucleus and no sperm malformation observed. This extract has no teratogenic effect to mice.

Consequently, Shanzhuyu can be considered as a safe herbal medicine and food plant. Shanzhuyu itself or combined with other edible herb can be easily made into many dietary forms at home. Those individuals that are Yang excessive should pay special attention to their consumption of Shanzhuyu, as it has been deemed unsuitable for them by the TCM theory. Hence, it is strongly suggested to ask your doctor if you want to take it.

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Chapter 41
Crataegus pinnatifida Bge. 山楂 (Shanzha, Hawthorn Fruit)

Caifang Wang

41.1 Botanical Identity

Shanzha, known as the Hawthorn fruit in English, is one of the common traditional Chinese medicines, which was first recorded in *Tang Materia Medica.*

Shanzha is the dried ripe fruit of *Crataegus pinnatifida* Bge. var *major* N.E.Br., or *C. pinnatifida* Bge. belonging to the family *Rosaceae*. Additionally, the fruits of 8 other *Crataegus* species including *C. cuneata* Sieb. Et Zucc., *C. scabrifolia*, *C. hupehensis*, *C. kansuensis* Sarg., *C. sanguinea*, *C. matiouiczii* Scgneid, *C. wilsonii* Sarg., and *C. Altaca* (Loud.) Lange, were used as conventional varieties of Hawthorn in many places of China [1, 2]. It is reported that *C. pinnatifida* Bge var major N.E.Br. or *C. pinnatifida* Bge., are widely distributed in the northern temperate regions of the world, primarily in East Asia, Europe and North America [3]. *C. pinnatifida* Bge. is a deciduous tree with a height of 6 m, and a covering of coarse ravidous bark. Furthermore, thorns found on the tree were approximately 1–2 cm, and sometimes no thorns existed. The twigs were cylindrical and the leaves were broad ovate with the length of 5–10 cm and the width of 4–7.5 cm. The fruits were red and long kidney-shaped. Compared with above species, the fruits of *C. pinnatifida* Bge. var *major* N.E.Br. were bigger and had more white spots on peel. The fruits of other species had some differences with them [4, 5].

The fruits were collected in autumn when ripe, cut into slices, and dried. These dried fruit slices were commonly used as snacks like “Tang Hu Lu”, “Guo Dan Pi” or “Shan Zha Gao” with a sweet and sour taste. These fruit had the effects of stimulating digestion and invigorating the stomach, promoting Qi (gas) circulation and resolving blood stasis to improve blood circulation, lipid management etc.

C. Wang (✉)
Capital Medical University, Beijing, China
e-mail: cfwang1040@126.com

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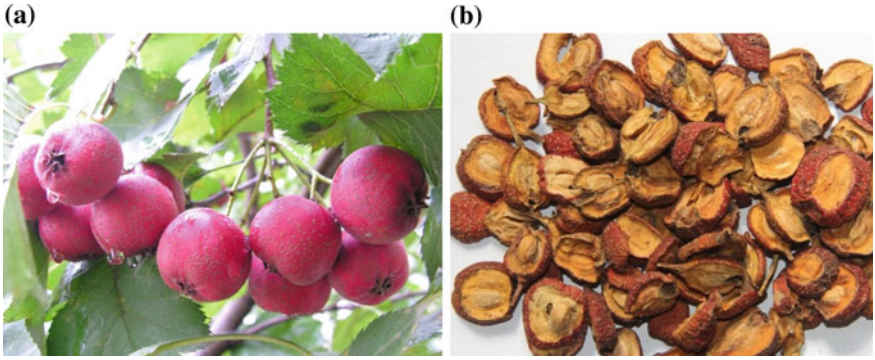

Fig. 41.1 Ripe fruits on the tree (**a**) and slices as crude drug (**b**) of *Crataegus pinnatifida* Bge. var *major* N.E.Br

The preparation of Shanzha has been used traditionally as a peptic agent in oriental medicine and more recently as a local soft drink material for the diet. An image of both the ripe fruit and dried slices of fruit can be seen in Fig. 41.1.

41.2 Chemical Constituents

So far over 150 chemical constituents, including flavonoids, organic acids, triterpenes, amino acids, organic amines and so on, have been isolated from the sarcocarp, kernels (seeds), leaves, and roots of *C. pinnatifida* [6]. In addition, the phytochemical studies on these materials also revealed many active phenylpropanoids in the seeds [7], monoterpenes, sesquiterpene, lignans, sesquilignan, hexane and their glycosides in the leaves [3, 8–10] of *C. pinnatifida.*

Before the 1950s, studies on Shanzha focused mainly on vitamins, tannins, and triterpenoids. Afterwards, flavonoids progressed very fast and those flavonoids from Shanzha showed obvious pharmacological activities on cardiovascular systems. Since then, many flavonoids were separated from these materials, including apigenin (**1**), kaempferol (**2**), luteolin (**3**), quercetin (**4**), rutin (**5**), and dihydroflavonoid (**6**) etc. and their derivatives [6]. Some flavonoids ketohexosefuranoside, like pinnatifinoside A-D, have also been isolated from the leaves of *Crataegus pinnatifida* Bge. var. *major* N.E.Br [11].

As is known to all, quercetin and its glycoside rutin have potent activities on cardiovascular systems such as hypolipidemic effect, lowering blood pressure, reducing capillary fragility, coronary dilating, and increasing coronary blood flow.

Another important type that exists in Shanzha is triterpenoid. Triterpenoidal compounds isolated from Shanzha include ursolic acid (**7**), corosolic acid (**8**), oleanolic acid (**9**), maslinic acid (crataegolic acid, **10**) etc. [12]. Several of these

ingredients have shown strong activities of strengthening cardiac function, increasing coronary blood flow, and improving blood circulation etc.

Furthermore, there are large quantities of organic acids such as oxalic acid, malic acid, citric acid, chlorogenic acid, tartaric acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and succinic acid isolated from Shanzha. These organic acids are the main active ingredients on aiding digestion and conducting stagnation.

41.3 Pharmacological Studies

41.3.1 Improve Digestion

Shanzha was traditionally used as food to improve digestion and increase appetite. It is reported that organic acids of Shanzha can improve lipodieresis and promote gastrointestinal movement [13]. Moreover, maslinic acid is said to enhance the activity of proteolytic enzymes so that these components can improve digestion.

41.3.2 Hypolipidemic and Preventive Effects on Atherosclerosis

Shanzha has shown hypolipidemic and preventive effects on atherosclerosis (AS). A study done on rats reported that Shanzha ethanolic extract showed significant hypocholesterolaemic effect in terms of reducing the plasma total cholesterol and LDL-cholesterol in the rats fed a hypercholesterolaemic diet [14]. Both hyperoside and ursolic acids are the main ingredients of Shanzha which significantly decreased the plasma total cholesterol and LDL-cholesterol in the mice and increased the high-density lipoprotein (HDL) [15]. AS is a major pathogenic part of cardiovascular disease as well as a leading cause of mortality and morbidity, which results from lipid metabolism, inflammatory responses and endothelial dysfunction etc. Pharmacological study showed that Shanzha extract not only decreases the levels of blood lipids and inflammatory responses in atherosclerotic rats, but also regulates the endothelial function of rats. In combination, these effects may account for its beneficial effects in the prevention and reduction of the development of atherosclerosis [16]. Maslinic acid has shown protective effect on cardiac myocytes with ischemia in vitro [17]. It also demonstrated that total flavonoids of Shanzha have the protective effects on cardiac myocytes, and it can inhibit myocardial necrosis and enzyme release [18].

41.3.3 Hepatoprotective Function

The administration of Shanzha extract could exert good hepatoprotective function in terms of reducing overall lipid contents in the liver of rats [14]. It is reported that maslinic acid (MA) can decrease lipid synthesis as well as the accumulation in cells. It can prevent lipid accumulation in human liver normal L02 cells by suppressing the SCAP mRNA expression and protein levels induced by free fatty acid (FFA) [19].

41.3.4 Antitumor Activity

Polyphenol extract from Shanzha inhibited TPA-induced tumor transformation by blocking the AP-1 and NF-κB signals and tumor promotion by decreasing inflammation and oxidative stress [20]. Maslinic acid can enhance the anti-tumor activities of TNFα and inhibit pancreatic tumor growth and invasion by activating caspase-dependent apoptopic pathway and by suppressing NF-κB activation and its downstream genes expression [21].

41.3.5 Antioxidant Activity

Polyphenols [22] including procyanidins [23] from Shanzha showed potent anti-oxidant activity and can be used as a natural antioxidant to deal with diseases caused by oxidative damage.

41.3.6 Anti-aging Activity

Chronic intake of *Crataegus* extract could prevent aging-related endothelial dysfunction by reducing the prostanoid-mediated contractile responses, which is most likely caused by improving the increased oxidative stress and the overexpression of COX-1 and COX-2 [24].

41.3.7 Hair Growth Activity

C. pinnatifida extract showed the hair growth activity on C57BL/6 Mouse Model [25].

41.4 TCM Applications and Dietary Usage

Shanzha alone or in prescriptions were clinically or routinely used to heal patients with hyperlipidemia and dyspepsia. Shanzha Jiangzhi decoction is composed of Yinchen (*Artemisia scoparia*) 30 g, Shanzha (*Crataegus pinnatifida*) 20 g, Fuling (*Poria cocos* Wolf) 20 g, Zexie (Alisma plantago-aquatica) 10 g, Juemingzi (Catsia tora Linn) 20 g, Juhua (*Dendranthema morifolium*) 10 g, Danshen (Salvia miltiorrhiza) 20 g, Danggui (*Angelica sinensis*) 20 g, Chuanxiong (*Ligusticum chuanxiong*) 10 g, Gouqi (*Lycium chinense*) 10 g, Dahuang (*Rheum palmatum* L.) 20 g, and Heshouwu (*Polygonum multiflorum* Thunb.) 20 g. Combination with auricular acupressure, this can further improve clinical symptoms, lipids metabolism, liver function, and radiographic parameters of patients with non-alcoholic fatty liver disease [26]. Shanzha Xiaozhi capsule could clinically resist on atherosclerosis and reduce major adverse cardiovascular event [27, 28]. Compound Shanzha Oral Liquid was used to treat 90 child patients with apositia displaying remarkable results of 27.8 % and a favorable turn of 53.3 % [29]. Shanzha syrup was orally administrated to 212 baby patients with diarrhea with the full healing effect [30]. Also some important clinical parameters of patients with heart failure were improved by Shanzha extract, which showed the effect of enhancing coronary flow, lowering peripheral vascular resistance, anti-arrhythmia, and reducing the myocardial oxygen consumption [31].

41.5 Quality Evaluation and Assurance

According to structural characterization of chemical constituents, the quality evaluation of Shanzha was accomplished by analyzing its chemical constituents qualitatively and quantitatively. Phenolic compounds were quantified by RP-HPLC/DAD [32], HPLC/MS [33, 34], and LC/MS/MS [35] technologies. Trierpenoids such as oleanolic acid and ursolic acid were also quantified by LC/MS [36]. Determination of six organic acids were accomplished by high performance liquid chromatography based solid phase dispersion [37]. The Xin Ke Shu preparations including Shanzha were analyzed qualitatively and quantitatively by LC-ESI-MS method [38].

41.6 Safety Evaluation and Toxicity Issue

In general terms, Hawthorn is used safely with regards to medicine and food characteristics; however usage should be continually monitored. It was reported that one woman who ate more than ten hawthorns every day for an extended period of time suffered from severe stomach stone. This was likely caused by mixing tannic acids with food residue etc., resulting in the formation of agglomerate clot [39].

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Chapter 42
Dimocarpus longan Lour. 龙眼肉 (Longyanrou, Longan)

Yang Yi and Ming-wei Zhang

42.1 Botanical Identity

Longan (*Dimocarpus longan* Lour.) is a large evergreen tropical fruit tree in the genus *Dimocarpus* of *Sapindaceae* family that originated in northern Burma and northeast and southern China [1], and now is cultivated and occasionally naturalized in semitropical areas throughout Southeast Asia with more than 400 species [2]. The longan tree typically grows 10–12 m with a diameter of up to 1 m. Its branches are commonly pilosulose and scattered with glaucous lenticels; large leaves are paripinnately compound with 3–6 pairs of leaflets which are 6–15 cm long and 2.5–5 cm wide; inflorescence is a many-flowered cluster and borne terminally or axillary. Longan fruits are yellowish-brown to -gray, flattened spherical, and around 1.2–2.5 cm in diameter (Fig. 42.1a).

Longan fruit is non-climacteric and will not continue to ripen once removed from the tree. Consequently, the fruit must be harvested when its skin become yellow-brown and its flesh reaches optimal eating quality. It has a thin, leathery and indehiscent pericarp surrounding a succulent edible aril with a relatively large dark or brown seed (so given a Chinese name of Longyan because it resembles a dragon eye), and is prized on world markets with strong demand for its desirable flavor and semi-translucent to white aril [3, 4]. Longan aril is named as 'Longyanrou (龙眼肉)' in China and is included as a traditional Chinese medicine in Pharmacopeia of People's Republic of China [1]. Medicinal Longyanrou is prepared through processes including drying mature fruit, removing pericarp and seed, and then drying

Y. Yi
College of Food Science and Engineering, Wuhan Polytechnic University, Wuhan 430023, China

M. Zhang (✉)
Sericultural and Agri-Food Research Institute, Guangdong Academy of Agricultural Sciences, Guangzhou 510610, China
e-mail: mwzhh@vip.tom.com

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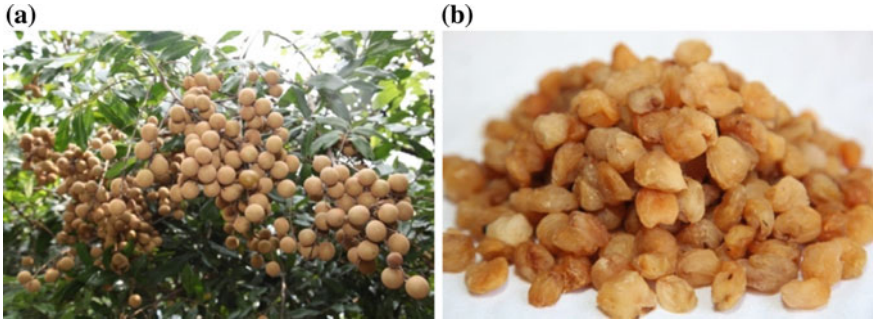

Fig. 42.1 The fruiting plant (**a**) and crude drug (**b**) of *Dimocarpus longan* Lour

aril to moisture content less than 15.0 %. Moreover, the ratios (g/g) of total ash and water-soluble extractum to Longyanrou are less than 4.0 and 70.0 %, respectively. Longyanrou is lengthways fractured to irregular slices about 1.5 cm long, 2–4 cm wide and 0.1 cm thick. The slices are yellow-brown to brown, semi-translucent and plicated surface [1], as seen in Fig. 42.1b.

42.2 Chemical Constituents

Polysaccharides and phenolic acids are two major classes of bioactive compounds found in the aril of *Dimocarpus longan* Lour.

42.2.1 Polysaccharides

Water-soluble polysaccharides are major bioactive macromolecules of Longyanrou. The polysaccharide contents of different longan genotypes mostly range from 0.44 to 2.64 % (mass ratio of polysaccharide to dried aril containing 15 % moisture), and the average content is about 1.09 % [5]. Longyanrou polysaccharides are mainly composed of (1 → 6)-α-D-Glcp, (1 → 4)-β-D-Manp and (1 → 5)-α-L-Araf, and are partly bound with proteins. Their molecular weights are in the range of 14.59–5282 kDa [6].

42.2.2 Phenolics

Phenolics in Longyanrou exist in free form and bound form, and are identified to be mainly composed of epicatechin (1), vanillic acid (2), gallic acid (3), 4-methyl-catechol (4), p-cumaric acid (5), etc. (shown in Fig. 42.2). The contents of free and

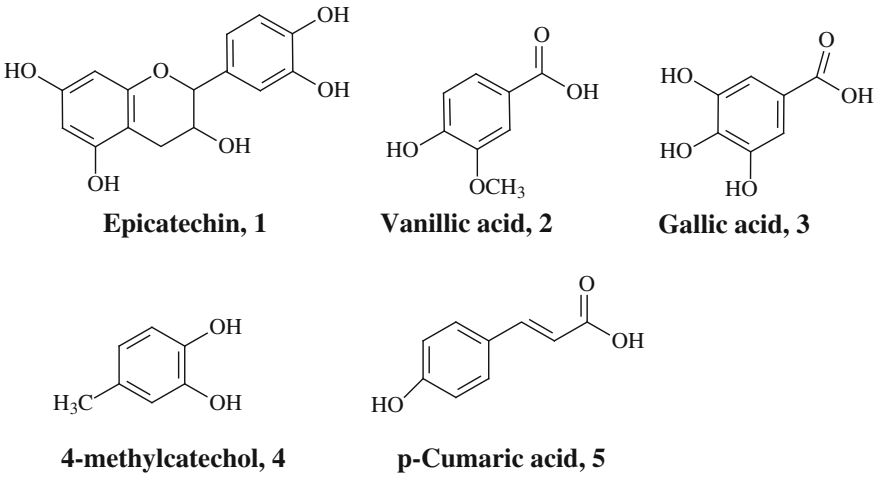

Fig. 42.2 Representative phenolic acids isolated from Longyanrou

bound phenolics in Longyanrou (cv. Chuliang, one of major cultivars in China), which are expressed as the mass ratio of gallic acid equivalents to dry weight, are respectively 3.01 and 0.06 mg/g. There is no significant difference in phenolic content between dried and fresh longan aril, indicating that the drying process does not decrease the content of total phenolics. In fact, the composition of phenolics has been significantly changed after drying. Especially, the content of epicatechin decreases markedly due to the oxidization catalyzed by polyphenol oxidase, which is in agreement with the change of Longyanrou from white to brown [7, 8].

42.3 Pharmacological Studies

Modern pharmacological studies have confirmed that Longyanrou possesses bioactivities including anti-oxidant, anti-tumor, immunomodulatory, anti-anxiolytic, memory-enhancing and anti-bacterial effects. The main bioactive components contributing to its beneficial effects are classed as water- and alcohol-soluble extracts. Water-soluble polysaccharides from Longyanrou have been indicated to have radical scavenging, immunomodulatory and anti-tumor activities in vivo and in vitro [9], in which the immunomodulatory effects are greatly related to their molecular structures [6]. The alcohol-soluble extract of Longyanrou, containing significant amounts of phenolic compounds, exhibits great anti-oxidant and anti-cancer functions [4]. Both the water- and alcohol-soluble extracts can enhance learning and memory, and their effects are mediated, in part, by brain derived neurotrophic factor expression, immature neuronal survival and anti-oxidant activity [10, 11].

42.4 TCM Applications and Dietary Usage

42.4.1 TCM Applications

Longyanrou has been widely used in TCM applications for promoting blood metabolism, soothing nerves, relieving insomnia and preventing amnesia. It is one of the few fruits which can be used in herbal medicines and health-maintaining products. Usually, Longyanrou is applied in TCM preparations in combination with other herbs such as Dangshen (root of *Codonopsis pilosula*), Yuanzhi (root of *Polygala tenuifolia*), Baizhu (rhizome of *Atractylodes macrocephala*), Fuling (sclerotium of *Poria cocos*), Danggui (root of *Angelica sinensis*) and Zhigancao (processed root of *Glycyrrhiza uralensis*) [1].

The TCM products of Longyanrou included in Pharmacopoeia of People's Republic of China are all compound honeyed pills, which are respectively named as Guipi Wan, Ankun Zanyu Wan and Shenrong Baotai Wan according to their functions. There are hundreds of manufacturers producing these products using the same formula legally in China without patent protection. (1) Guipi Wan is composed of eleven herbs and has been used in Chinese folk medicine for more than 450 years for the functions of replenishing Qi, invigorating the spleen, nourishing the blood and tranquilizing the mind. It can be clinically applied for symptoms such as heart-spleen deficiency, palpitation, insomnia, dizziness/headache, tiredness/weakness, inappetence and metrorrhagia/metrostaxis [1]. In recent years, pharmacological studies have further expanded the clinical application of Guipi Wan. The product can be also used to cure leucopenia, thrombocytopenic purpura, climacteric syndrome, idiopathic edema and hypothyroidism. (2) Ankun Zanyu Wan is composed of sixty-three medicinal herbs and possesses the functions of replenishing Qi, nourishing blood and invigorating liver and kidney. The product has been mainly used for the treatment of menoxenia, leukorrheal diseases and metrorrhagia/metrostaxis. Specially, administerment to pregnant woman should be strictly according to medical instruction. In addition, clinical studies have confirmed new applications in neurasthenia syndrome, hypertension, coronary disease, prostatic hyperplasia, etc. (3) Shenrong Baotai Wan containing twenty-three medicinal herbs can nourish the liver and kidneys, replenish blood and prevent miscarriages. The product is mainly used for the treatment of clinical symptoms such as liver-kidney deficiency, waist-knee pain and threatened abortion [1]. (4) Longyanrou extract and instant powder, which may incorporate the extracts from other herbs into a application, are convenient forms with significant advantages as they can be easily used and absorbed.

42.4.2 Dietary Usage

Longyanrou served as both food and medicine has attracted great attentions in dietary usage because of its health-protection function. It is commonly eaten

directly or habitually added in soup, tea and wine [12]. The dietary forms of Longyanrou described below are easily made at home.

42.4.2.1 Longyanrou Teas

Herbal tea is one of the most common ways to use Longyanrou. Some examples are: Longranrou-Xiyangshen Tea composed of Longyanrou and Xiyangshen (root of *Panax quinquefolium*) at the mass ratio of 1:1; Longyanrou-Hetaoren Tea composed of Longyanrou (30 g), Hetaoren (seed of *Juglans regia*, 10 g), Xiyangshen (3 g), Gancao (root of *Glycyrrhiza uralensis*, 5 g) and water (500 g); Longyanrou-Juemingzi Tea composed of Longyanrou, Juemingzi (seed of *Cassia obtusifolia*), Shanzha (fruit of *Crataegus pinnatifida*), Wuweizi (fruit of *Schisandra chinensis*), Danshen (root of *Salvia miltiorrhiza*) and Heshouwu (root tuber of *Polygonum multiflorum*), et al. To avoid the decomposition of phenolic compounds induced by minerals and alkalinity, softened and neutral water is recommended to make the herbal tea.

42.4.2.2 Longyanrou Wine

Longyanrou can be used as a fermentation substrate to produce wine, or, soaked in Chinese spirit with or without other herbs. One simple example is Longyanrou (100 g) soaked for more than two weeks in 400 mL Chinese spirit to prepare wine with a recommended dosage of 10–20 mL per day. A health-protection Longyanrou wine is prepared by soaking Longyanrou (40 g), Gouqizi (fruit of *Lycium barbarum*, 10 g), Danggui (5 g) and Juhua (flower of *Chrysanthemum morifolium*, 3 g) in 1500 mL Chinese spirit. Jiannanshen wine is prepared by soaking several herbs, mainly including Longyanrou, Hongjingtian (root of *Rhodiola crenulata*), Dongchongxiacao (*Cordyceps sinensis*), Gouqi (fruit of *Lycium barbarum*), Renshen (*Panax ginseng*) and Honghua (flower of *Carthamus tinctorius*) in Chinese spirit, and is beneficial for enhancing immune function at the recommended dose. Daily intake of Longyanrou wine should synthetically resemble the contents of Longyanrou, other herbs and alcohol.

42.5 Clinical Evidences

As a kind of fruit product, Longyanrou is used widely in field of Chinese medicine. At present, clinical reports and observational studies related to the effects of Longyanrou and its preparations are rarely published. One of them indicated that Guipi Wan could effectively improve the symptom of ventricular premature beat in 46 cases and chronic fatigue syndrome in 120 cases. In addition, Shenrong Baotai Wan combined with dydrogesterone successfully cured subchorionic hematoma within two weeks in 30 cases [13].

The therapeutic and functional effects of Longyanrou are beneficial for clinical recovery. The recommended dosage of Longyanrou by the China Pharmacopoeia Committee ranges from 9 to 15 g daily. *Puerpere* would have some adverse symptoms, such as the decrease of breast milk secretion and the inhibition of uterus recovery, after up-taking an over-dose of Longyanrou or its extracts. It was partly related to the inhibition of Longyanrou ethanol extract on the secretion of prolactin [14].

42.6 Safety Evaluation and Toxicity Data

Up to now, there is no evidence from clinic research and animal test indicating the toxicity and side effects of Longyanrou. According to the daily dosage of 90 g Longyanrou for a person with 60 kg body weight, the basal feed containing 45 g/kg Longyanrou or 38 g/kg water-soluble Longyanrou extract was used to breed mice for 35 days. No adverse symptoms were observed; in contrast, immunity enhancement was confirmed (as seen in Fig. 42.3) [15]. After water-soluble Longyanrou polysaccharides were per orally given to cyclophosphamide-immunosuppressed mice in the dose range of 50–200 mg/kg for 15 days consecutively,

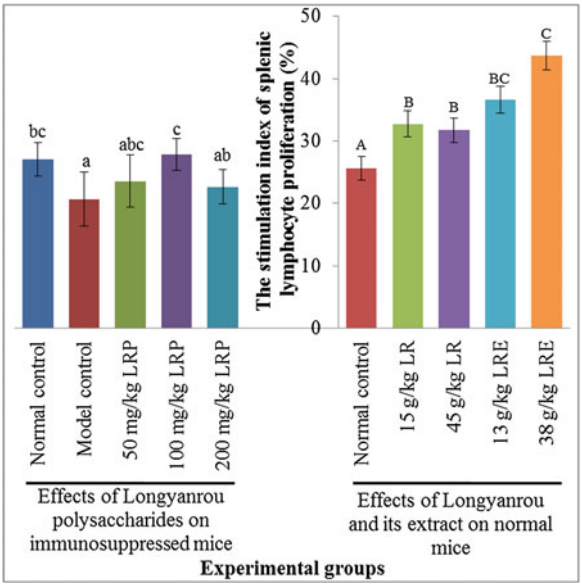

Fig. 42.3 Effects of longyanrou (LR), its aqueous extract (LRE) and polysaccharides (LRP) on the proliferation of splenic lymphocyte in mice [15, 16]. LR and LRE were respectively incorporated in basal feed with different doses to breed normal mice for 35 days. LRP was perorally administrated to cyclophosphamide-immunosuppressed mice with various doses for 15 days. Data presented were means ± standard deviation (n = 10). The significant differences among the groups were evaluated with ANOVA followed by the S-N-K test. Columns with different letters are significantly different ($P < 0.05$)

some visible improvements in appetite, sleep, activity and depilation were obtained, and the immunological parameters related to immune organ and blood were also recovered [16].

The LD_{50} values of Longyanrou and its products are still unavailable. But as presented above, Longyanrou as a functional fruit product is definitely a relatively safe herbal medicine for enhancing immunity, promoting blood metabolism, soothing nerves, relieving insomnia and preventing amnesia. In view of the multiple and strong biological activities of Longyanrou, there is a recommended dose range of 9–15 g daily for a health-maintaining purpose. *Puerpere* should use this herb according to doctor's advice.

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Chapter 43
Euryale ferox 芡实
(Qianshi, Gordon Euryale Seed)

Caifang Wang

43.1 Botanical Identity

Qianshi, referred to as Gordon Euryale Seed in English, is the dried kernel of a ripe seed of *Euryale ferox* Salisb. This seed is in the Nymphaeaceae family, which is an aquatic tonic used as dual purpose of medicine and food. It was originally recorded in *Shennong's Herbal Classic* for the top grade, which was alternatively named as Jitou (chicken head) and recorded in all versions of *Chinese Pharmacopoeia* [1, 2].

The seeds are round with the diameter of 6 mm, one end of which is white while the other is brown. The skin of the seed is smooth with patterns and its texture is hard and crisp. The root of Qianshi is fibrous with a length of 90–120 cm. The part of the petiole under the water is very slim resembling a string, while the part above the surface is brawny with a big round leaf [3]. The ripe fruit is collected in late autumn and early winter, peeled, and the seed is taken out, washed, removed from its hard shell testa, and dried in the sun. With the efficacy of solid kidney essence, invigorating the spleen, eliminating dampness and antidiarrheal effect, Qianshi is mainly used for the treatment of nocturnal emission, spermatorrhea, enuresis, urinary frequency, gonorrhea, and leucorrhea, etc. It is one of the popular traditional Chinese materia medica and precious natural tonic, and so called *Ginseng and Longan in Water* for its value [4].

E. ferox Salisb. is the only species of the genus *Euryale* and differentiated as South *E. ferox* and North *E. ferox*. South *E. ferox* (Nan Qian) is alternatively named as Su *Euryale ferox* (Su Qian), which is originally cultivated in the suburban district of Suzhou and now distributed in the areas of Hunan, Guangdong, southern Anhui, and southern Jiangsu province. North *E. ferox* (Bei Qian), alternatively named as thorn *E. ferox* (Ci Qian), originates from wild materials or cultivar, which is mainly distributed in Shandong, northern Anhui and northern Jiangsu province. Bei Qian is

C. Wang (✉)
Capital Medical University, Beijing, China
e-mail: cfwang1040@126.com

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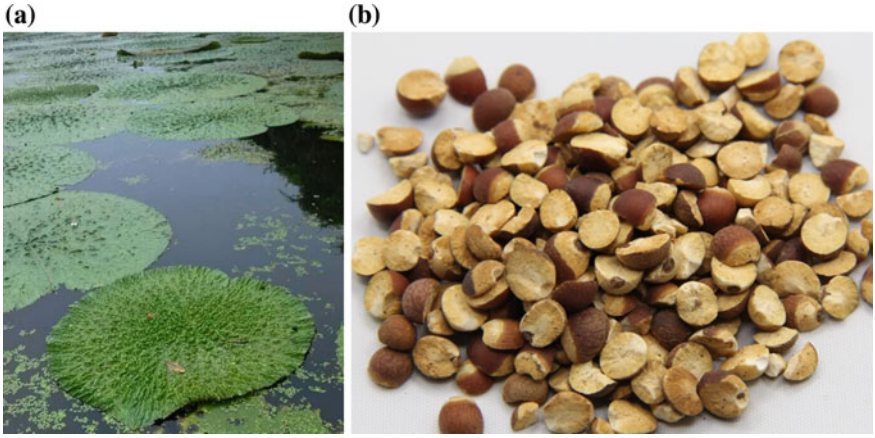


Fig. 43.1 Growing plant (**a**) and dry seeds as crude drug of *Euryale ferox* Salisb (**b**)

inferior compared to Nan Qian in the aspect of quality. Generally Bei Qian is mainly used as medicine while Nan Qian is primarily used as food [2]. The typical morphological traits and dry seed as crude drug are shown in Fig. 43.1.

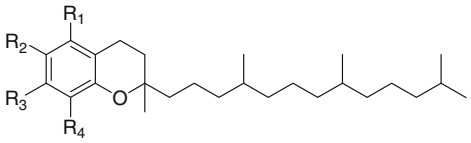
43.2 Chemical Constituents

For a long time, Qian Shi has been monitored for its notable efficacy and miscellaneous health care functions. For revealing the essence of its effects, various ingredients are analyzed with multiple analytical techniques. According to its functional characteristics, the chemical constituents of Qianshi are classified as nutritional ingredients and functional ingredients.

43.2.1 Nutritional Ingredients [2]

The nutritional ingredients of Qianshi include starch, proteins, lipid, amino acids, minerals, and Vitamins. The proteins are rich and easy to digest and absorb so that it is suitable for both children and older adults. Furthermore, it includes nearly 20 amino acids, among which there are six essential amino acids including leucine, isoleucine, lysine, threonine, valine, phenylalanine and two other essential amino acids histidine and arginine needed specifically for young children. There are many vitamins found in Qianshi that are vital for the human body, including Vitamin C and E (Fig. 43.2) along with plenty of β-carotene. The minerals Na, Mg, Ca, Se, P,

Fig. 43.2 Representative compounds isolated from *Euryale ferox* Salisb

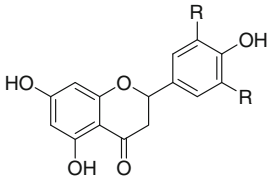


Vitamin E

(α-Tocopherol, **1**, R_1=R_3=R_3=CH_3, R_2=OH

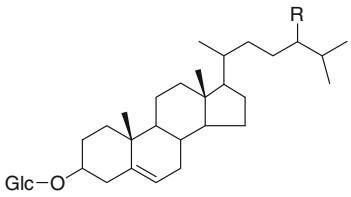
β -Tocopherol, **2**, R_1=R_2=CH_3, R_3=OH, R_4=H

γ -Tocopherol, **3**, R_1=H, R_2=OH, R_3=R_4=CH_3)



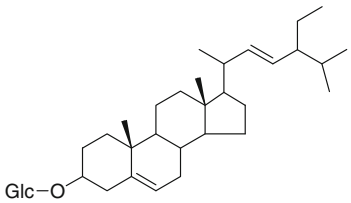
5, 7, 4'-Trihydroxy-dihydroflavone, **4**, R=H**;**

5, 7, 3',4', 5'-Pentahydroxy-dihydroflavone, **5**, R=OH**;**

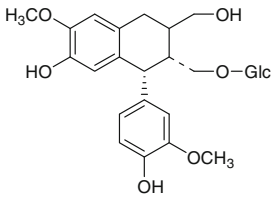


24-Methylcholest-5-enyl-3 -O-β-pyranoside, **6**, R=methyl**;**

24-Ethylcholest-5-enyl-3 -O-β-pyranoside, **7**, R=ethyl



24-Ethylcholest-5, 22E-dienyl-3 -O-β-pyranoside, **8**



Isolariciresinol-9-O- β -D-glucopyranoside, **9**

Zn, Fe, Mn, Co, and Sn are also rich in Qianshi. More importantly, it shows high contents of Fe and Se in Qianshi, while element Fe is called to be blood hormone and Se to be anticarcinogenic agent.

43.2.2 Functional Ingredients

The functional ingredients isolated include antioxidant compounds like Vitamin E (α- tocopherol, **1**; β-tocopherol, **2**; and γ-tocopherol, **3**) and dihydroflavonoids (5, 7, 4′-trihydroxy-dihydroflavone, **4**; 5, 7, 3′, 4′, 5′-pentahydroxy-dihydroflavone, **5**), steroid glycosides like compounds (**6**, **7**, **8**) which were supposed to be active ingredients, lignan like isolariciresinol-9-O-β-D-glucopyranoside (**9**), cyclopeptides, unsaturated fatty acids like linolic acid which had many activities such as anticancer, prevention of atherosclerosis and anti-inflammation and so on, cerebrosides, polyphenols, sesquiterpene lactone lignans [2, 5–8], and polysaccharide [9], etc. It reported flavonoids of *Euryale ferox* had free radical DPPH scavenging effect [10].

43.3 Pharmacological Studies

Pharmacological research indicated that Qianshi showed potent antioxidants such as Vitamin E (α-tocopherol) as well as polysaccharides, which abundantly existed in Qian Shi so that the Qianshi extract could be used as a natural antioxidant [8–12].

There is a report that the EtOH extract of Qianshi showed a preventative effect on acute gastric mucosal lesion [13] as well as an improvement on the aging brain of a mouse induced by D-galactose [14]. The extract can also obviously reduce the size of cardiovascular embolism in mice, thus improving the damaged symptoms of regional myocardial anemia.

Furthermore, Qianshi can play an important role in hypoglycemic symptom [15, 16].

43.4 TCM Applications and Dietary Usage

There are abundant elements such as calcium and iron in Qianshi and thus it shows a good prospect on developing dietary supplement rich in calcium and iron. Also abundant selenium, which is the component to compose glutathione peroxidase, participate in the synthesis of coenzyme Q and coenzyme A, prevent the formation of peroxides and resist on some chemical carcinogen [17].

There are plenty of starches and vitamins in Qianshi which could provide energy and nutrition for the human body. Qianshi is used in all kinds of congee to eat and

has tranquilizing and tonic effects. For example, Qianshi congee (composition 1: Qianshi 150 g, glutinous rice 150 g, castor sugar 10 g); Lianzi Qianshi congee (composition: Rice 300 g, semen Nelumbinis 50 g, Qianshi 15 g) [18]; Immortal Porridge (composition 2: yam 30 g, Qianshi 15 g, Japonica rice 60 g, leek seed 10 g) [19].

Generally, Qian shi is used clinically in compound traditional Chinese medicine to treat sterilitas virilis of men, e.g. Huangjing Zanyu Capsule [20] which is composed of Huangjing (Rhizoma polygonati), Shudihuang (Prepared rehmannia root), Gouqi (Lycium chinensis), Qianshi, Lianzi (Semen nelumbinis), Shanyao (Chinese yam), Dangshen (*Salvia miltiorrhiza*), Fuling (Poria cocos), Yiyiren (Semen coicis), Danggui (Umbelliferae angelica); yellowish leukorrhea of women, e.g. Jiawei Yihuang Decoction [21] which is primarily composed of Shanyao (Chinese yam, 15 g), Qianshi (15 g), Tufuling (Rhizoma Smilacis Glabrae, 15 g), Jinyinhua (Flos Lonicerae, 15 g), Yiyiren (Semen coicis, 20 g), Cheqianzi (Semen Plantaginis, 10 g), Yinxingrou (Ginkgo meat, 10 g), Hongteng (Sargentgloryvine Stem, 12 g), Huangbai (Amur Corktree Bark, 6 g) and changed according to the different symptoms; or to treat nephritis proteinuria [22, 23], diabetes [24] and dyspepsia [25].

43.5 Quality Evaluation and Assurance

Qianshi could be identified and observed for its internal structure by modern methods such as powder X-ray diffraction Fourier mapping [26] and Fourier transfer infrared spectroscopy [27]. The different groups of Qianshi can also be identified and distinguished by analyzing their extracts with ultraviolet spectral line group (UASLG) [28] and fingerprint technology [29] and so on.

The volatile constituents from the seeds of Qianshi were analyzed by GC-MS method [30] and the minerals can be determined with atom absorption spectrometry [31, 32].

43.6 Safety Evaluation and Toxicity Issue

To our knowledge, there has been no report of the toxicity or safety issues of Qianshi. It is a safe nutritional food material and unique traditional herbal medicine with therapeutic effects.

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Chapter 44
Gardenia jasminoides Ellis 栀子 (Zhizi, Capejasmine)

Jianhui Liu and Fei Yin

44.1 Botanical Identity [1]

Gardenia jasminoides Ellis (common *gardenia*, *capejasmine* or *cape Jessamine*) is an evergreen flowering plant of the family *Rubiaceae*. It grows on mountaintops or on road sides as an ornamental plant and distributes widely in the tropical and subtropical regions of the world. The dried ripe fruits of this plant have been recorded as Zhizi (Chinese herbal name) in Chinese Pharmacopoeia and included in traditional Chinese medicine (TCM) formulations [2].

Gardenia jasminoides (Fig. 44.1) originates from Asia. In Vietnam, Southern China, Taiwan, Japan and India it can be found growing wild. It is widely used in gardens because of its shiny green leaves and heavily fragrant white summer flowers, in warm temperate and subtropical climates, and as a houseplant in temperate regions. In China *Gardenia jasminoides* has been in cultivation for at least a thousand years, and was introduced to English gardens in the mid-eighteenth century.

Gardenia jasminoides has grayish bark and dark green shiny leaves with prominent veins. Depending of the variety, it grows 2–6 feet in height and about 6 feet in width, with glossy and dark-green foliage with a leaf length of 2–4 inches and half as wide. The waxy, white and very fragrant flowers bloom in spring and summer, which can be either single or double and up to 4 inches in diameter depending on the cultivar. Followed by the flowers is small oval fruit.

J. Liu (✉) · F. Yin
College of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, China
e-mail: jhliu@cqut.edu.cn

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Fig. 44.1 Flowering plant (**a**) and crude drug (**b**) of Zhizi

44.2 Chemical Constituents

Several classes of compounds such as iridoids, iridoid glycosides, flavonoids, monoterpenes, triterpenoids and other compounds are found in *Gardenia jasminoides*. Iridoid glycosides, organic acid esters, saffron glycosides and flavonoids are the major bioactive compounds found in the fruit of *Gardenia jasminoides* [3].

44.2.1 Iridoid Glycosides

The major class of bioactive compounds from *Gardenia jasminoides* is Iridoids [4]. Geniposide (1), gardenoside (2), shanzhizide (3), jasminoidin (4), geniposidic acid (5), genipin (6), gardoside (7), and 10-acetyl geniposide (8) are representative components. Among them, geniposide and gardenside are the standard compounds used for evaluation of quality of crude drug Zhizi and related pharmaceutical or natural health product preparations containing Zhizi (Fig. 44.2).

44.2.2 Organic Acid Esters

Another kind of major bioactive compounds found in *Gardenia jasminoides* are organic acids and their esters. Other organic acids have been isolated from Zhizi, such as chlorogenic acid (7), quinic acid (8) and ursolic acid (9) (Fig. 44.3).

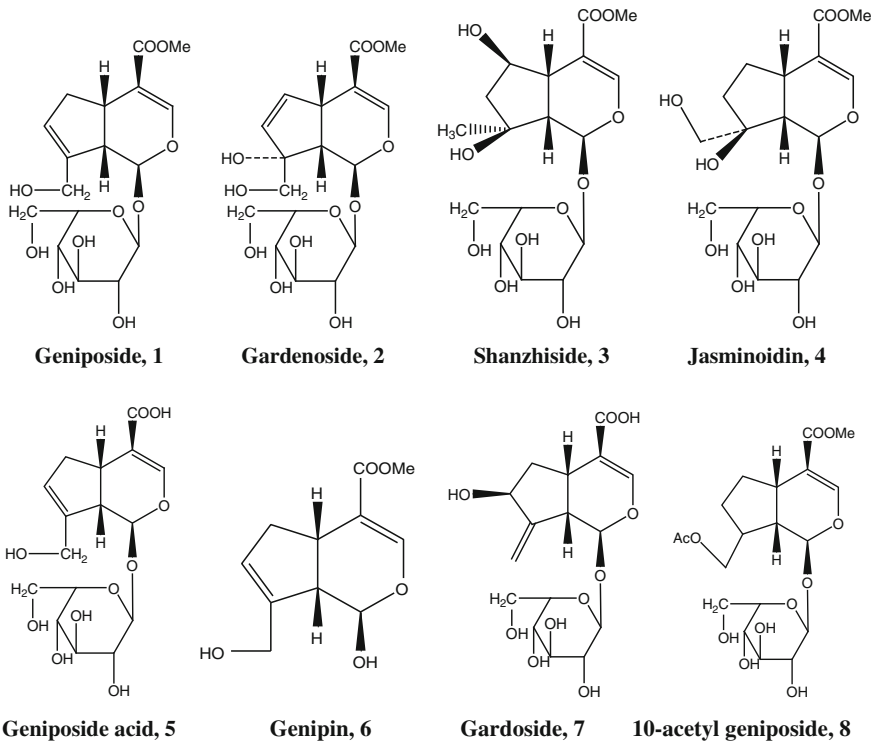


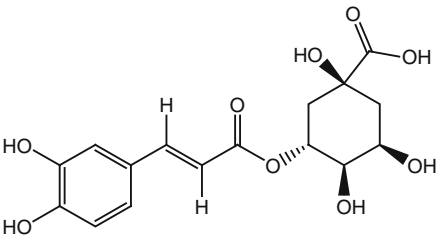
Fig. 44.2 Representative iridoid compounds isolated from Zhizi

44.2.3 Saffron Glycosides

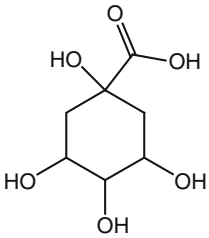
The two representative compounds of saffron glycosides found in *Gardenia jasminoides* are crocin (10) and crocetin (11) (Fig. 44.4).

44.2.4 Flavonoids

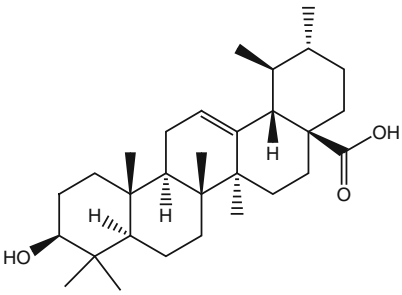
Flavonoids are another kind of bioactive components found in *Gardenia jasminoides*. Quercetin (12), rutin (13), umuhengerin (14), nicotiflorin (15), and 5,7-dihydroxyflavone (16) are among these flavanoids (Fig. 44.5).



Chlorgenic acid, 7



Quinic acid, 8



Ursolic acid, 9

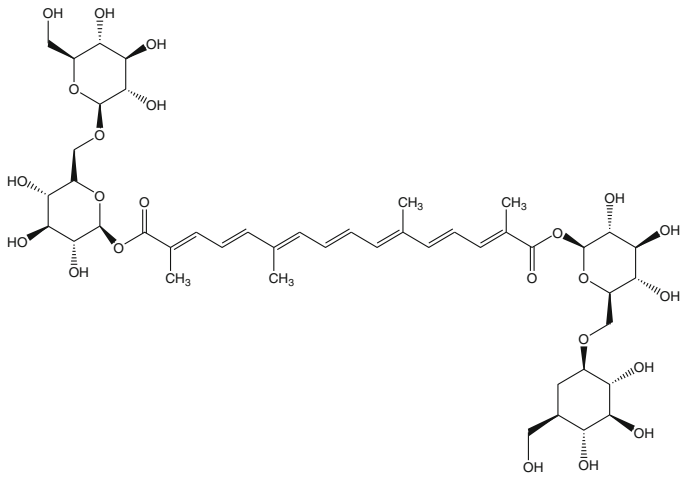
Fig. 44.3 Representative organic acids isolated from Zhizi

44.3 Pharmacological Studies

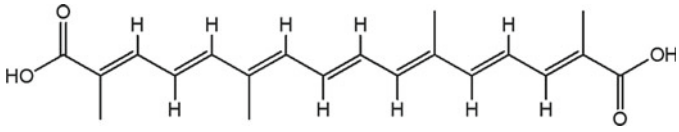
Gardenia jasminoides has been used for its diuretic, cholagogue, anti-inflammatory, neuroprotective, and aiti-pyretic effects.

44.3.1 Antioxidative Effect of Gardenia jasminoides

Glycoprotein separated from *Gardenia jasminoides* Ellis fruit (GJE glycoprotein) has been used to heal hepatic and inflammatory diseases in folk medicine. GJE glycoprotein showed a single band on the 15 % sodium dodecyl sulfate polyacrylamide gel and the molecular weight is 27 kDa. The main components of GJE glycoprotein are carbohydrate (57.65 %) and protein (42.35 %). In cell-free systems GJE glycoprotein has scavenging activities for DPPH, lipid peroxyl, superoxide anion and hydroxyl radicalsin a dose-dependent manner. GJE glycoprotein is probably a natural antioxidant and one of the modulators of apoptotic signal pathways in NIH/3T3 cells for it was reported that GJE glycoprotein has dose-dependent blocking activities against G/GO- or HX/XO-induced cytotoxicity and apoptosis in NIH/3T3 cells [5].



Crocin, 10

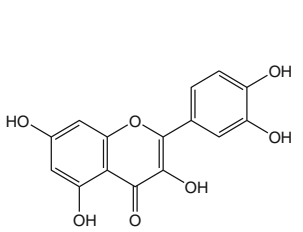


Crocetin, 11

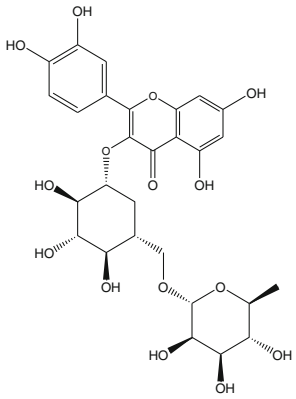
Fig. 44.4 Representative saffron glycosides isolated from Zhizi

Crocin isolated from the fruits of *Gardenia* (*Gardenia jasminoides* Ellis) and the stigmas of saffron (Crocus sativuslinne) is a water soluble carotenoid. The anti-oxidative activity of purified croin with purity of >99.6 % is comparable to that of BHA at a concentration of 20 ppm. The thiocyanate method was superior to the thiobabituric acid method for evaluating the antioxidant property of crocin [6].

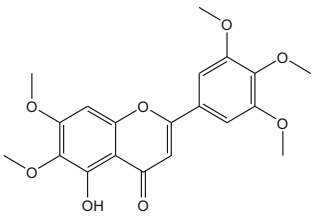
Genipin is another component isolated from *Gardenia jasminoides* Ellis. It markedly reduced the increases in serum aminotransferase activities and lipid peroxidation on d-galactosamine (GalN) and lipopolysaccharide (LPS)-induced mice according to another research. Besides it offered marked hepatoprotection against damage induced by GalN/LPS related with its antioxidative, anti-apoptotic activities, and inhibition of NF-kappaB nuclear translocation and nuclear p-c-Jun expression [7].



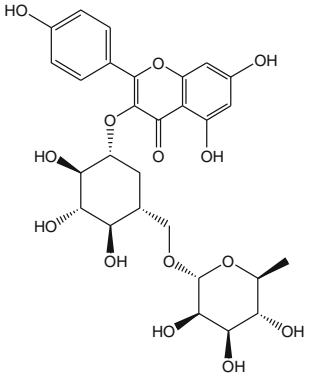
Quercetin, 12



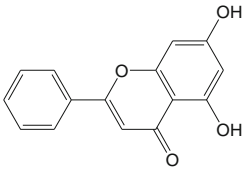
Rutin, 13



Umuhengerin, 14



Nicotiflorin, 15



5,7-dihydroxyflavone, 16

Fig. 44.5 Representative flavonoids isolated from Zhizi

44.3.2 Anti-inflammatory Effects of G. jasminoides

Inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha) enhance binding of low-density lipoprotein to the endothelium and upregulate the expression of endothelial leukocyte adhesion molecules during atherogenesis. It was reported that pretreatment with ethanol extract of *Gardenia jasminoides* (EGJ) inhibited TNF-alpha-induced expression of vascular cell adhesion molecule-1 (VCAM-1) and endothelial cell-selectin (E-selectin) expression on vascular inflammation in primary cultured human umbilical vein endothelial cells (HUVEC). In a functional study, EGJ dose-dependently attenuated adhesion of HL-60 monocytes to endothelial monolayers. A further analysis indicated that EGJ attenuated TNF-alpha-induced nuclear p65 nuclear factor-kappa B (NF-kappaB) translocation, suggesting that EGJ primarily affects the TNF-alpha-induced NF-kappaB signaling pathway [8].

In one animal study, *Gardenia jasminoides* significantly lowered serum IL-1β and TNF-alphalevels in rats with rheumatoid arthritis, showing an inbititory effect in the development of the disease [9].

Besides, the severity of pancreatitis and pancreatitis-associated lung injury on cerulein-induced acute pancreatitis (AP) in mice was decreased significantly by *Gardenia jasminoides*. It was showed that treatment with *Gardenia jasminoides* attenuated the severity of AP compared with saline-treated mice. The similar reduction also was found in pancreatic edema, neutrophil infiltration, serum amylase and lipase levels, serum cytokine levels, and mRNA expression of multiple inflammatory mediators in [10].

44.3.3 Neuroprotective Effects of Gardenia jasminoide

Geniposide and its aglycon genipin, isolated from *Gardenia jasminoide*, have potent neuritogenic activity in PC12 cells [11, 12]. Lee et al. [5] recently also reported that geniposide could protect from neuronal death in a rat hippocampal slice culture system withoxygen and glucose deprivation [13]. Liu et al. identified that geniposide was a novel agonist for GLP-1 receptors, causing the neuronal differentiation of PC12 cells via the MAP kinase pathway by the activation of the GLP-1 receptor [14]. Additionally, pretreatment with geniposide also prevented neurons from oxidative stress via phosphatidylinositol 3-kinase (PI3 K) signaling pathway [15, 16]. Geniposide also up-regulated insulin-degrading enzyme expression to antagonize the cytoxicity of Aβ in primary cultured cortical neurons [17].

44.3.4 Antitumoric Activity of G. jasminoides

Gardenia jasminoides Ellis (GJE) extract and its constituents, such as ursolic showed acid-neutralizing capacities, antioxidant activities, and inhibitory effects on the growth of *Helicobacter pylori* (*H. pylori*). In addition, the GJE extract and ursolic acid had cytotoxic activity against AGS and SUN638 gastric cancer cells. The genipin and ursolic acid inhibited significantly HCl/ethanol-induced gastric lesions, meanings that genipin and ursolic acid may be useful for the treatment and/or protection of gastritis [18].

44.3.5 Antihyperlipidemic Effects of Gardenia jasminoides

Traditionally used as a treatment for diabetes in Chinese herbal medicine, *gardenia* extract contains an iridoid genipin. Researchers at Harvard Medical School found that genipin inhibits the functions of an enzyme which increases the risk of type 2 diabetes.

It was shown that *Gardenia jasminoides* water extract could inhibit pancreatic lipase activity. Isolated from *Gardenia jasminoides* water extract, crocetin and crocin were shown as inhibitors of pancreatic lipase with an IC_{50} value of 2.1 and 2.6 mg/ml (triolein as a substrate). The increase of serum TG level was significantly inhibited by crocin and crocetin in corn oil feeding-induced triglyceridemic mice, as well as that of serum triglyceride and total and LDL cholesterol levels in Triton WR-1339-induced hyperlipidemic mice. These compounds also showed hypolipidemic activity in hyperlipidemic mice induced by high cholesterol, high fat or high carbohydrate diets for 5 weeks. The results suggest that the hypolipidemic activity of *Gardenia jasminoides* and its component crocin may improve hyperlipidemia [19].

44.3.6 Antifibrotic Effects of G. jasminoides

Glutathione helps determine the modulation of immune response, including cytokine production and is an important immune system amino acid. Geniposide from *Gardenia jasminoides* could enhance glutathione content in rat livers [20].

Gardenia jasminoides remarkably reduced liver mRNA and/or protein expression of transforming growth factor beta1 (TGF-beta1), collagen type I (Col I) and alpha-smooth muscle actin (alpha-SMA). The up-regulation of TGF-beta1, Col I and alpha-SMAwere significantly suppressed by *Gardenia jasminoides* in LX-2 exposed to recombinant TGF-beta1. Moreover, *Gardenia jasminoides* inhibited TGF-beta1-induced Smad2 phosphorylation in LX-2 cells. Therefore, *Gardenia jasminoides* exerts antifibrotic effects in the liver fibrosis and may be a potential novel antifibrotic agent [21].

44.3.7 Antithrombotic Effect of Gardenia jasminoides

The aqueous extract of *Gardenia jasminoides* (GJ-ext) (67, 133 and 266 mg/kg) and aspirin (50 mg/kg), respectively, decreased the length of tail thrombus with average thrombus inhibition rate of 21.9, 55.7, 65.8 and 57.6 % at 48 h and 19.0, 54.5, 69.3 and 56.9 % at 72 h after carrageenan injection on the models of carrageenan-induced tail thrombosis and arteriovenous shunt thrombosis. Meanwhile, improved thrombosis induced by arteriovenous shunt (silk thread) with 36.3, 45.5, 86.4 and 63.7 % inhibition rate of thrombus respectively, and the ED(50) of GJ-ext was 160.8 mg/kg. Furthermore, GJ-ext (67 mg/kg) and geniposide (20 mg/kg) significantly suppressed platelet aggregation induced by thrombin/collagen with 45.1/19.3 % and 52.8/26.2 % aggregation rate. Geniposide (10–40 mg/kg) and genipin (5–20 mg/kg) inhibited venous thrombosis induced by tight ligation of the inferior vena cava, their ED(50) values were 18.4 and 8.6 mg/kg, respectively.

Herein, GJ-ext and geniposide demonstrated remarkable antithrombotic activities and supported their therapeutic uses for thrombotic diseases [22].

44.4 TCM Applications and Dietary Usage

44.4.1 TCM Applications

Gardenia jasminoides fruit is used within traditional Chinese medicine to "drain fire" and thereby treat certain febrile conditions. Since the Han dynasty (25–220 AD), the use of gardenia in Chinese horology, or herbal medicine, was recorded. *Gardenia* leaves, flowers and fruits were included in several canon or formulas, which are mostly remedies for the common cold. In Asia, gardenia is known as the 'happiness herb' because it is said to detoxify the liver, thereby releasing negative emotions. This may results in the relationship between gardenia and love, healing and spirituality.

The dried ripe fruit of *Gardenia jasminoides* Ellis is a traditional Chinese medicine used as a diuretic, antipyretic, antihepatic, and anti-inflammatory agent. Additionally, when used externally it can also act as antithrombotic and neurito-genic and can be used for treating ulcers of the skin and sprains.

Gardenia fruit extract is also used in traditional concentrated pharmaceutical herbal products and the Chinese medicine for the treatment of irritability in febrile dis-decoction. Herbal products have been widely adopted for clinical use in Taiwan, Japan, China, Korea and other Asian countries, and even in certain European.

44.4.2 Dietary Usage

44.4.2.1 Teas

In China, *Gardenia jasminoides* Ellis flowers are popularly used as flavor herbal teas, often in combination with other herbs and flowers such as chrysanthemums. Gardenias infused teas are known to detoxify the blood, relieve congestion and help lower LDL cholesterol.

44.4.2.2 Dye

Another application of *Gardenia jasminoides* Ellis is used as dye for the presence of many phytochemicals found in the color pigments of gardenia fruits and flowers. Indeed, carotenoids including crocin and crocetin isolated from gardenia fruits,

which were also found in the Crocus species of plant such as saffron. Aside from their ability to add a subtle yellow color to foods, the carotenoids have numerous health benefits.

44.4.2.3 Culinary Uses

Gardenia flowers can be added to salads, used as garnish, and the fruits can be eaten out of hand. However, *Gardenia jasminoides* Ellis is primarily valued for its natural yellow coloring, which was used in the food industry as a less expensive substitute for the spice, Saffron.

44.5 Clinical Evidences

Zhizi has been used for Heat-Clearing and Detoxifying for several centuries. Zhizi combined with soya bean could pure heart and relieving restlessness. When combined with Huanglian (rhizome of *Coptis chinensis*) and Guanhuangbai (bark of *Phellodendron amurense*), Zhizi could reduce fire and detoxify. When combined with *Cogongrass rhizome* and Sanqi (root of *Panax notoginseng*), Zhizi could stop bleeding. When combined with Jinyinhua (flower of *Lonicera japonica*) and lianqiao (fruit of *Forsythia suspense*), Zhizi could dissipate furuncle.

Yinchenhao Tang (YCHT) is an aqueous extract derived from three herbs: Yinchenhao (herb of *Artemisia capillaries* Thunb), Zhizi (fruit of *Gardenia jasminoides* Ellis) and Dahuang (root and rhizome of *Rheum officinale*) with a ratio of 4:3:1 in weight. YCHT decoctions have long been used as anti-inflammatory, antipyretic, choleretic and diuretic agents for liver disorders and jaundice. Several studies provide clinical evidence of its functions in the treatment of various liver diseases [2].

44.6 Safety Evaluation and Toxicity Issue

The safety and efficacy of this herbal medicine has been demonstrated by pharmacological investigation and clinical applications for centuries. The safety of geniposide the major active compound from *Gardenia jasminoides*, was determined using hepatotoxicity in rats. This was evaluated using liver enzymes in serum and histopathology ultrastructural preparation. The lethal dose, 50 % (LD_{50}) of oral geniposide was 1431.1 mg/kg. The acute toxicity study indicated geniposide at a dose of 574 mg/kg or more could cause hepatic toxicity in rats and the hepatotoxicity often appeared at 24–48 h after the oral administration. The hepatotoxicity was associated with oxidative stress with a decrease of total superoxide dismutase activity and increase of malondialdehyde concentration in rats' livers. Subchronic

toxicity study showed geniposide did not cause hepatotoxicity at the doses of 24.3 and 72.9 mg/kg orally for 90 days in rats. Thus, acute hepatotoxicity of geniposide at high doses was likely to be linked to oxidative stress, while geniposide at normal dose of 24.3 mg/kg or less did not cause hepatotoxicity even in the repeated dosing study [23].

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Chapter 45
Ginkgo biloba L. 银杏
(Yinxing, Baiguo, Ginkgo)

Yingqin Li and Chun Hu

45.1 Botanical Identity

Ginkgo biloba is the only genus and species of the botanical family Ginkgoaceae, and is one of the best-known examples of a living fossil. This family of prehistoric trees once included several species which grew in abundance throughout the world (141–98 million years ago), but disappeared from the western North American fossil record (24–7 million years ago) [1]. Today, it is native only to China, with an annual production of 14,000 tons of ginkgo nut and 20,000 tons of ginkgo leaf primarily from Jiangsu, Shandong, Zhejiang, Hubei, Anhui and Guangxi provinces [2].

The ginkgo genus name comes from the Japanese pronunciation of the Chinese name for the plant-Gin Kyo or silver apricot. Its species name *biloba* reflects the often 2-lobed nature of the leaf. According to the Chinese Pharmacopoeia, both ginkgo nuts and leaves are considered to have medicinal uses [3]. Baiguo (ginkgo nut or seed) is used in traditional Chinese medicine as food and medicine, and ginkgo leaf extract is a well known dietary supplement and pharmaceutical ingredients in global markets. The *Ginkgo biloba* L. tree is a deciduous tree that can grow up to 40 m high and 3–4 m in diameter. Ginkgo is cultivated as an ornament worldwide in cool to sub-tropical regions, but is only cultivated medicinally in China. In the Chinese Pharmacopoeia, ginkgo nuts are harvested in the fall and are processed by removing their outer fleshy sacrotesta and followed by washing, steaming or blanching, and drying. Ginkgo leaves are typically used in extract forms, produced from green leaves harvested between May and July when ginkgo leaves contain high amounts of active compounds. Leaves from young trees contain higher amount of active compounds than older trees [4]. The fresh leaves are dried

Y. Li · C. Hu (✉)
Nutrilite Health Institute, 5600 Beach Blvd, Buena Park, CA 90621, USA
e-mail: charles.hu@amway.com

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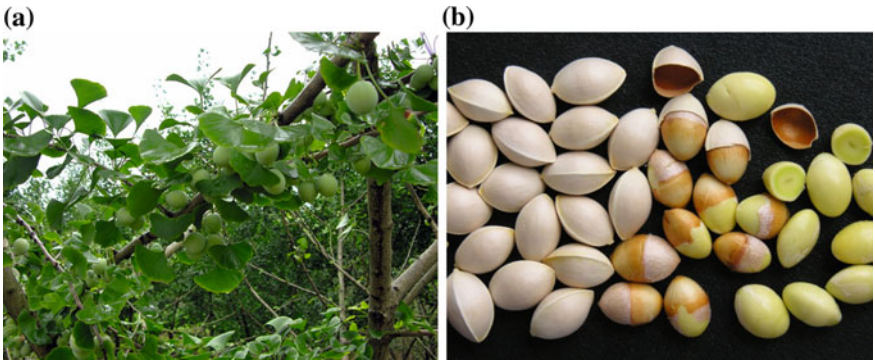


Fig. 45.1 Ginkgo tree with fruits and fresh leaves (**a**) and Ginkgo nuts (**b**)

immediately, extracted, purified through various methods, and followed by drying processes. Depending on the quality of the leaves and the processing procedures, in general, one kg of ginkgo leaves extract is produced from 35–67 kg of dried leaves (with an average of 50:1) (Fig. 45.1).

45.2 Chemical Constituents

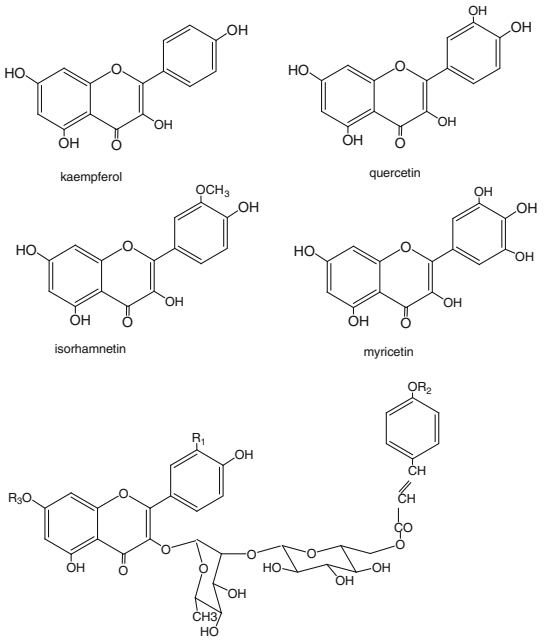
Ginkgo nuts are listed as an edible food in the Chinese Food Composition Table (2002) and as medicine in the Chinese Pharmacopioea. Ginkgo nuts contain 13.2 % (dry weight) protein, 1.3 % fat and 72.6 % carbohydrates. Ginkgo starch granules are oval or spherical, and while their amylose and pectinamymlose ratio and degree of polymerization vary among cultivars, a large portion of ginkgo starch is slowly digestible resistant starch [5]. Major phytochemicals in the nut include polyacetate derivatives such as alkyl phenolic acids and alkyl phenols, ginkgotoxin (4′-O-methyl pyridoxine), cyanophoric glycosides, phytohormone cytokine like components, gibberellin and asparagin. Ginkgo nuts contain same flavonoids as ginkgo leaves, but at lower contents (less than 0.1 %), however they contain the same terpene lactones as the leaves at higher contents [6].

Ginkgo nut oil contains high levels of unsaturated fatty acids [7], including palmitic acid (5.7–6.7 %), palmitoleic acid (3.2–3.9 %), stearic acid (0.9–1.3 %), oleic acid (35.0–36.9 %), linoleic acid (40.4–42.9 %) and linolenic acid (1.7–5.5 %).

Both ginkgo leaf and its extract are listed as medicinal ingredients in the Chinese Phamacopoeia. Their primary phytochemicals are flavonoids and terpene lactones. Minor compounds include polyacetate derivatives such as alkyl phenolic acids and alkyl phenols, ginkgotoxin, and miscellaneous organic and inorganic compounds.

45.2.1 Flavonoids

Flavonoids are rare in gingko nuts [8], but abundant in ginkgo leaves. More than 30 flavonoids have been identified [9]. Flavonol glycosides from ginkgo include mono-, di- and tri-glycosides of quercetin, kaempferol, and isorhamnetin, myricetin and 3′-methylmyricetin with glucose and rhamnose as sugar units (Fig. 45.2).



R_1	R_2	R_3	
H	H	H	3-*O*-(2”-*O*-(6”’-*O*-(*p*-hydroxyl-*trans*-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl) kaempferol
H	Glucose	H	3-*O*-(2”-*O*-(6”’-*O*-(*p*-(β-D-glucosyl) oxy-*trans*-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl) kaemferol
OH	H	H	3-*O*-(2”-*O*-(6”’-*O*-(*p*-hydroxyl-*trans*-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl) quercetin
OH	Glucose	H	3-*O*-(2”-*O*-(6”’-*O*-(*p*-(β-D-glucosyl) oxy-*trans*-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl) quercetin
OH	H	Glucose	3-*O*-(2”-*O*-(6”’-*O*-(*p*-hydroxyl-*trans*-cinnamoyl)-β-D-glucosyl)-α-L-rhamnosyl)-7-*O*-(β-D-glucosyl) quercetin

Fig. 45.2 Flavonol and acylated flavonol aglycones, mono-, di- and tri-glycosides found in ginkgo leaf

Quercetin and kaempferol are the predominant aglycones and their 3-O-rutinoside and 3-O-biloside, acylated flavonol derivatives are the primary constituents of ginkgo leaves. The Chinese Pharmacopoeia requires minimum of 0.4 % ginkgo flavonol glycoside in dried leaves, and minimum 24 % in ginkgo leaf extract. Due to market competition and limited resources of feedstock, ginkgo leaf extract is known to be adulterated by non-ginkgo flavonoids to achieve commercial advantage. Adulteration can be identified by using the quantitative ratio of quercetin: kaempferol at 0.8–1.5:1 and HPLC fingerprinting of natural occurring flavonoids fractions [10]. Ginkgo leaves also contain fair amounts of biflavones including amentoflavone, 7-methyoxyamentoflavone, bilobetin, 5′-methyoxybilobetin, ginkgetin, isoginkgetin, and sciadopitysin (Fig. 45.3) [11]. Minor flavonoids in leaves

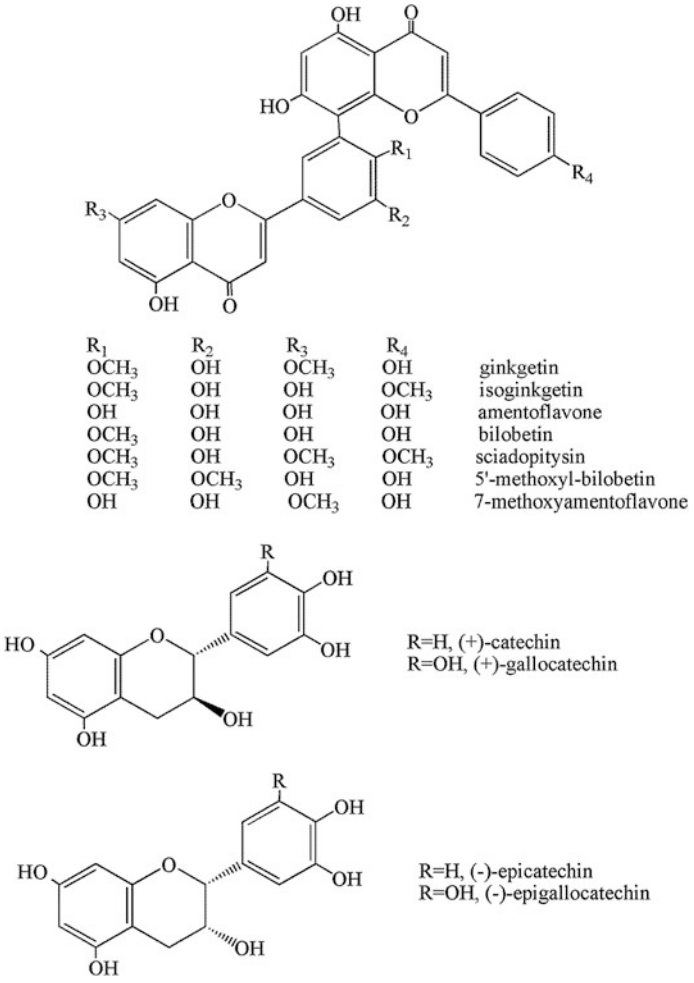


Fig. 45.3 Structure of biflavonoids and catehins in ginkgo leaf

include apigenin, luteolin and their glycosides, (+)-catechin, (−)-epicatechin, (+)-gallocatechin and (−)-epigallocatechin (Fig. 45.3).

45.2.2 Alkyl Phenolic Acids and Alkyl Phenols

Alkyl phenolic acids (anacardic acids), known as ginkgolic acids, are 6-alkylsalicyclic acids with alkyl residues of the size 13–19 carbon and with up to three double bonds. Ginkgolic acids are more abundant in ginkgo nuts than in leaves. Five ginkgolic acids are often found at 0.48–2.51 % in dry leaves depending on the season it was collected and 5–10 ppm in leaf extract, with a typical breakdown of C13 (12 %), C15 (48 %) and C17 (40 %) (Fig. 45.4). Leaves harvested from younger trees in May and June contain higher amount of ginkgolic acids [12]. Since regulations limit ginkgolic acid concentrations to 5–10 ppm in ginkgo extracts in pharmacopoeias, total ginkgolic acids are often removed by different manufacturing processes such as solvent extraction, supercritical CO_2 extraction or column chromatography. In addition to ginkgolic acids, ginkgo nuts also contain hydroginkgolic acid, ginnol, ginkgols, bilobols, cardanol, and ginkgotoxin [8]. Ginkgo nuts and leaves also contain 3-alkylphenols (cardanols, or ginkgols) and related 5-alkyl resorcinols (cardols, or bilobols) shown in Fig. 45.4.

45.2.3 Terpenes

Ginkgo leaves contain a number of different types of terpenes, namely terpene trilactones (ginkolides A, B, C, J and bilobalide) (Fig. 45.5), tripernenes (steroids,

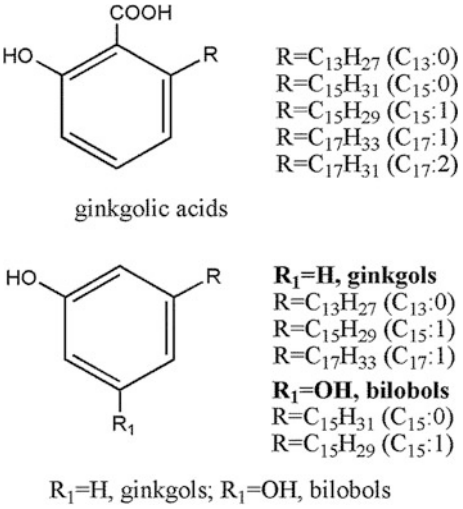
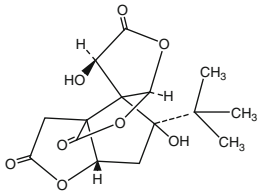
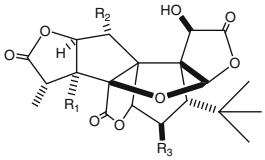


Fig. 45.4 Alkyl phenolic acids and alkyl phenols in ginkgo seed and leaf



bilobalide



gingkgolide

	R_1	R_2	R_3
Ginkgolide A	OH	H	H
Ginkgolide B	OH	OH	H
Ginkgolide C	OH	OH	OH
Gingkgolide J	OH	H	OH
Ginkgolide M	H	OH	OH

Fig. 45.5 Terpene lactones in ginkgo seed and leaf

phytosterols), carotenoids (α-carotene, γ-carotene, lutein, zeaxanthin), polyprenols (sioprene units with a structure of w-t_2-C_n–OH), and volatile mono- and sesquiterpenes. The terpene trilactones are considered unique to ginkgo. The Chinese Pharmacopoeia requires that dried Ginkgo leaves contain at least 0.25 % of ginkgolide A, B, C and bilobalide, and standardized ginkgo leaf extract should contain at least 6 % ginkgo terpene lactones [3]. No terpenes are found in ginkgo nuts [8].

45.3 Pharmacological Studies

Compared to ginkgo leaves, studies on ginkgo nuts are limited. The antioxidant capacity of ginkgo nuts was identified using the ABTS radical model, it was observed that antioxidant capacity was reduced by 40 % after heating due to the loss of vitamin C [13]. The lipid soluble fraction of ginkgo nuts down-regulated the apo-B protein secretion and its mRNA expression in HepG2 cells and reduced the hepatic cholesterol level in cholesterol fed mice, suggesting this fraction may help in cholesterol management [14]. An albumin type antioxidant protein has been identified in ginkgo nuts, consisting of two peptides with similar molecular weights linked by a disulfide bond [15]. Ginkgo nuts and their extracts inhibit fungi and

bacteria due to the existence of salicylic acid derivatives and other phenolic acids [6, 8]. Ginkgo leaf extract has also been reported to exhibit neuroprotective, cardioprotective, stress alleviating, memory enhancing, and anti-tumor effects as well as possible effects on tinnitus, geriatric complaints and psychiatric disorders.

The therapeutic properties of ginkgo leaf extract for cognitive function are suggested to be due to its antioxidant activities toward cellular and molecular targets in the CNS. Its effectiveness include the protection of cell membranes and mitochondria during hypoxia and reoxygenation, the improvement in peripheral circulation in conditions related to cerebrovascular insufficiency, alleviate pAOD, the regulation of gene expression and synthesis of various proteins associated with dementia and cognitive decline such as β-amyloid and increase α-secretase, and the enhancement of cerebral circulation through inhibiting platelet activating factor. Additional effects include anti-inflammation, remedying deficiencies of cytochrome oxidase, neuron death prevention, post-lesion neuron recovery enhancement, and effects on nerve growth factors and growth-associated proteins.

Animal and in vitro studies suggest that ginkgo leaf extract acts on the cardiovascular system, including vasorelaxant effects, the inhibition of cyclic nucleotide phosphodiesterase, releasing and preserving production of PGI_2, reducing activity of nitric oxide synthase, enhancing vasoconstriction effects, and increasing capillary resistance and tissue perfusion [16].

While ginkgo flavonoids are generally regarded as the primary antioxidants, ginkgo terpenes have also been shown to possess cardioprotective effects [17]. Although ginkgolic acids, cardanols and bilobols have been reported to be responsible for undesirable allergic skin reactions, they are also reported to have anti-HIV and anti-bacterial properties [18].

45.4 TCM Applications and Dietary Usage

45.4.1 TCM Applications

In traditional Chinese medicine, the ginkgo nut is considered sweet, bitter and astringent, and acts on lung and kidney meridians [3]. Ginkgo nuts are used to treat lung and kidney disorders, alone or in combination with other herbs based on TCM theory. It can astringe the lung to stop wheezing associated with coughing, act as an antidiuretic, and is effective in treating sexual conditions like nocturnal emission, virginal discharge and uterine fluxes [19]. Topical application can treat brandy nose, ringworm sores, and carious tooth. Before consumption, the hard shell must be removed to reach the edible kernel (nut-like hametophytes). Recommended daily consumption of ginkgo nut is 5–10 g [3]. However, the sascotesta of raw ginkgo fruit has a foul smell and is toxic; thus, ginkgo should not be consumed raw.

Throughout history, ginkgo has been used to treat a variety of conditions, including as a topical remedy for freckles, an oral treatment for diarrhea and dysentery, for fullness and oppression of the chest, cardiac pain and palpitations.

45.4.2 Dietary Usages

Ginkgo nuts are particularly valued in Asia for their wellness and anti-aging properties. Benefits are thought to include lightening skin, improving skin tone, as well as maintaining cardiovascular, gynecological, lung and mental acuity. The nut-like gametophytes are the most commonly eaten. Ginkgo nut has a plain taste, is compatible with various foods ingredients, and can be cooked in many ways such as boiling, steaming, roasting, simmering, stewing, frying, in hot meals such as congee soup, in cold dishes, and in deserts or beverages. Typical dose is 10–20 nuts per day for an adult.

Ginkgo leaf extract has grown to be one of the top 10 dietary supplements in last 20 years globally. The most well-known ginkgo leaf extract is EGb 761, invented by Dr. Willmar Schwabe GmbH, which was studied using numerous experiments and human clinical trials for its effects on the circulatory system and mental acuity [20, 21]. A specifically characterized ginkgo leaf extract (24 % flavonol glycosides; 6 % terpene trilactones; <5 ppm ginkgolic acids) is the most popular and widely prescribed herbal and over the counter (OTC) drug medications and dietary supplement in many countries (e.g. German, France, Japan, United Kingdom, Canada, United States, China, Korea). These ginkgo extracts are manufactured by two major processes, a solvent-solvent partition process in Europe and a porous resin column process in China. Ginkgo extract has a characteristic bitterness, so the most common delivery forms are tablets, capsules and soft gels at a dosage of 120–240 mg per day, which are taken for 4–52 weeks. Ginkgo leaf extract is often used alone, or in combination with natural ingredients such as gotu kola, eleutherococcus, omega-3, choline, or with synthetic pharmaceutical ingredients such as vinpocetine (Table 45.1).

In China, the State Food and Drug Administration is responsible for the approval of functional foods and dietary supplements using a series of function and safety evaluation protocols for health benefits, and only products approved by government agency are permitted to be marketed as functional foods with functional claims. By the end of 2012, while there were 329 products approved in China containing ginkgo leaf or leaf extracts, there were only 10 products containing ginkgo nuts. Nearly half of these approved products claimed “to assist in modulating blood lipids”, followed by claims related to immunity, hypoxia endurance, memory and blood sugar regulation etc.

Table 45.1 Comparison of ginkgo leaf extract specification of pharmacopoeias

Items	EP 7.5 (2012) [22]	USP 35-NF30 [23]	ChP 2010 [3]
Manufacturing process	Organic solvents extraction followed by purification	Acetone or other solvents extraction	Ethanol extraction followed by resin purification
Total flavonol glycosides	22.0–27.0 %	22.0–27.0 %	24.0 % min
Total terpene lactones	5.4–6.6 %	5.4–12 %	6.0 % min
Bilobalides	2.6–3.2 %	2.6–5.8 %	Not specified
Ginkgolides	2.8–3.4 %	2.8–6.2 %	Not specified
Ginkgolic acids	5 ppm max	5 ppm max	10 ppm max
AUC ratio between kaempferol/ quercetin	Not specified	≥0.7	0.8–1.2, isorhamnetin/ quercetin > 0.15
Quercetin/ kaempferol	Not specified	Not specified	0.8–1.5
Isorhamnetin/ quercetin	Not specified	≥0.1	>0.15

45.5 Clinical Evidence

For therapeutic applications, the oil soaked ginkgo nuts is used to treat tuberculosis [8]. The widespread positive results in the majority of randomized, double-blind, placebo-controlled clinical trials give compelling evidence for the effectiveness of ginkgo leaf extract in alleviating the symptoms of vascular, neurodegenerative and mixed forms of dementia. But, there are mixed results regarding the efficacy of ginkgo leaf extract in treating depressive moods associated with cerebrovascular insufficiency or cognitive impairment [16]. However, there is good evidence to indicate that ginkgo leaf extract can improve cognitive function in healthy humans and in patients with impaired cognitive function that do not have dementia; it is also effective for treating symptoms of premenstrual syndrome and preventing altitude sickness [24]. Most clinical studies used EGb761 and LI 1370 (24 % flavonoids, 6 % terpene lactones, 5 ppm ginkgolic acids). Daily dose varies depending on use; single dose ranges from 320 to 600 mg while lower long-term dose (120–240 mg) are taken for 8 weeks for dementia, 120–160 mg dose is taken for 6 weeks for intermittent claudication, and 120–160 mg doses are taken for 12 weeks for vertigo, tinnitus of vascular and involutional origins. In a recent randomized double-blind, placebo-controlled, multi-centered 24 week trial (n = 200 in treatment; n = 202 in placebo), taking 240 mg EGb761 once per day significantly improved cognition, psychopathology and function measurements in patients with mild to moderate dementia (Alzheimer's disease or vascular dementia) associated with neuropsychiatric symptoms [25]. On the other hand, a five-year clinical trial, conducted in the older population (>70 years old) who spontaneously reported memory

complaints, failed to demonstrate that EGb761 significantly reduced the risk of progression to Alzheimer's disease compared to placebo [26]. On the other hand, a Chinese-based ginkgo leaf extract tablet clinically improved the episodic memory in patients with mild cognitive impairment over 6 month with daily dose of 57.6 mg [27].

45.6 Safety Evaluation and Toxicity Data

Ginkgo nuts can cause acute poisoning and have been documented in ancient compendiums. The Chinese Pharmacopoeia lists the ginkgo nut as poisonous when eating raw [3], and limits its daily consumption of less than 5–10 g. Fresh nuts are more toxic than steamed ones. Ingestion of fresh nuts or a large amount of heat processed nuts may cause adverse reactions associated with the central nervous system, observed within 1–12 h of consumption; symptoms include vomiting, comas, fear, convulsions, mental sluggishness, difficulty breathing, fevers and loss of consciousness [8, 28]. 4′-O-methodypyridoxine (MPN) and MPN-5′-glucoside are both responsible for ginkgo seed poisoning, though the latter is more prevalent in heat-treated ginkgo nuts [28]. The neurotoxin 4′-O-methylpyridoxine (ginkgotoxin) was found as high as 360 ng/ml in serum from a toddler poisoned from eating ginkgo nuts [29], compared to 181 ppm in raw seeds, and 50 ppm in leaf extracts [30]. Ginkgotoxin and its glucoside can be reduced via heat treatment in nuts, confirmed by LC/MS analysis [31]. In addition, a 32.12 kDa glycoprotein (MW 31 kDa) with protein to sugar ratio as 20.56:1 was identified as an allergen in ginkgo nut [32].

Little to no adverse events have been reported using ginkgo leaf extracts in 54 clinical studies reviewed in a monograph, or the adverse incidence was equal between the treatment and placebo groups with various doses, including a high single dose of 600 mg [18]. In a 3-month drug-monitoring study with 10,815 patients treated with ginkgo leaf extract LI1370, 183 subjects (1.7 %) experienced adverse events, including nausea (0.3 %), headache (0.2 %), stomach problems (0.1 %), diarrhea (0.1 %), allergies (0.9 %), anxiety and/or restlessness (0.07 %), problems sleeping (0.06 %), and other unspecified effects (0.6 %) [33]. However, the in vitro blood-thinning effect is not supported by human clinical data. Hemorrhagic events may be associated with taking anticoagulant medications (e.g. aspirin, warfarin). No allergic sensitization is expected when ginkgo leaf extract contains <5 ppm ginkgolic acids for human oral consumption, although cytotoxic, embryotoxic and neurotoxic effects have been observed in vitro. When rats were administrated ginkgo extract EGb 761 at daily dose of up to 100 mg/kg for 2 years, there was not an increase in tumor incidence in the treatment group when compared to the control group [34]. On the other hand, in a recent 2-year study, a ginkgo leaf extract (not the widely recognized EGb761) was fed to F344 rats at 1000 mg/kg and B6C3F1 mice at 2000 mg/kg, results showed higher carcinogenic incidence in the treatment group compared to the placebo group [35]. However there is still active debate on the validation of this safety concern, not only for the validation of the

materials used in this study, but also because such high doses aren't realistic for normal consumption. Therefore, without further risk assessments, it is too early to link the results between this national toxicology program study with human safety concerns, though further research is necessary to validate any potential carcinogenic risk for human consumption of ginkgo leaf extract.

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Chapter 46
Hippophae rhamnoides L. 沙棘
(Shaji, Common Sea-buckthorn)

Yingqin Li and Chun Hu

46.1 Botanical Identity

The common sea-buckthorn (*Hippophae rhamnoides* Linnaeus, also known as *Elaeagnus rhamnoides* (Linnaeus) A. Nelson, or *Rhamnoides Hippophae* Moench) is a species of flowering plants of the family *Elaeagnaceae*, native to the dry temperate and cold desert areas of China, Russia, Mongolia, India, Pakistan, Nepal, Europe and North America. Comprising of eight subspecies, sea buckthorn is by far the most widespread species of the genus [1]. The most common subspecies are *H. rhamnoides L. subsp.rhamnoides* (found in coastal North Europe), *H. rhamnoides L. subsp. sinensis Rousi*, *H. rhamnoides L. subsp. gyantsensis Rousi, H. rhamnoides* L. *subsp. tibetana* (Schlechtendal) *Servettaz* (found in China), and *H. rhamnoides L. subsp. turkestanica Rousi* (found in India, Afghanistan, Kazakhstan, Kyrgyzstan, Mongolia, Pakistan, Tajikistan, Turkmenistan and Uzbekistan).

The Latin name Hippophae is derived from the Latin word 'Hippo'—meaning 'horse'—and 'Phaos'—meaning 'shine'. The common name, sea buckthorn, refers to how it often grows near the sea and its many spines and thorns. It is known as 'cold desert gold' due to its high potential as a bio-resource for land reclamation, helping reduce soil erosion and possessing multifarious uses. For medicinal use, it's referred to by a variety of common names, such as Shaji, Culiu, Suanci, Dhar-bu (Tibetan medicine, Star-bu), sallow thorn, sanddorn, Siberian pineapple, and sea berry. Most plants are wild crafted, but cultivation has been carried out in a wide range of soil and adverse weather conditions in Asia and Europe [2]. In China, more than 50 % of sea buckthorn is from Tibetan plateau.

Sea buckthorn usually forms a shrub or a small tree 3–4 m in height. The female plants produce orange, yellow, and red berry-like fruit 5–8 mm diameter that are

Y. Li · C. Hu (✉)
Nutrilite Institute of Health, 5600 Beach Boulevard, Buena Park, CA 90621, USA
e-mail: Charles.hu@amway.com

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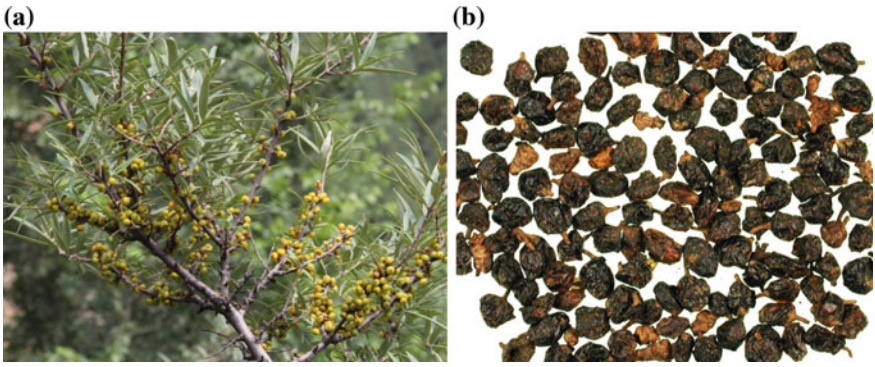


Fig. 46.1 Fruiting plant (**a**) and crude drug (**b**) of *Hippophae rhamnoides* L

aromatic and rich in oil. The seeds are dark brown, sometimes nearly black. Dried fruit is used in traditional Tibetan and Mongolian medicine [3]. Mature fruit is harvested in autumn and winter, dried naturally, and is sometimes steamed slightly before drying (shown in Fig. 46.1). As an herbal material, its moisture content is required to be less than 15 %, ash content less than 6.0 % and total flavonoid content not less than 1.5 % (measured as rutin by spectrophotometry based on dry weight) and isorhamnetin at least 0.10 % (by HPLC method based on dry weight) [3]. Fruit yield, size, sensory, phytochemical profile and content vary significantly by subspecies, origins, harvest time, and processing methods. Its fruit oil is one of most recognized ingredients in the dietary supplement industry [4].

46.2 Chemical Constituents

Sea buckthorn is reported to be a natural reservoir of many nutrients including vitamins, essential polyunsaturated fatty acids, carotenoids, phytosterols, essential volatiles, flavonoids, phenolics, organic acids (e.g. hydrobenzoic acid derivatives), and amino acids—including 8 essential amino acids [5]. Bioactive compounds composition and content vary significantly with fruit maturity, fruit size, subspecies, geographic locations, climate and extraction methods [6, 7].

46.2.1 Fatty Acids and Phytosterols

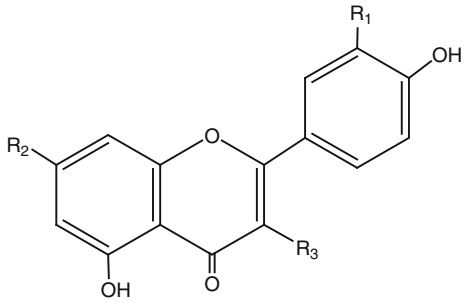
Both seeds and flesh (pulp) of sea buckthorn berries are rich in lipids [4], and the oil content in berries varies with subspecies, from 4–20 % in ssp. *sinensis*, to 16–28 % in ssp. *mongolica,* and 23–34 % in ssp. *caucasica* (dry pulp) [4]. In addition, the fatty acid profiles in pulp oil and seed oil are different. The predominant fatty acids

in seed oil are 30–40 % linoleic acid (C18:2ω-6), 20–35 % α-linolenic acid (C18:3ω-3), 13–30 % oleic acid (C18:1ω-9), 15–20 % palmitic acid (C16:0), 2–5 % stearic acid (C18:0) and 2–4 % vaccenic acid (C17:1 ω-7); the predominant fatty acids in the pulp oil are 16–54 % palmitoleic acid (C16:1ω-7), 17–46 % palmitic acid, and 2–35 % oleic acid [4]. The uniqueness of fatty acids makes the sea buckthorn oil popular in the dietary supplement industry.

Sea buckthorn oil typically contains 0.1–0.2 % total phytosterol in seeds and 0.02–0.04 % in pulp [4]. Campesterol, clerosterol, lanosterol, sitosterol, β-amysin, sitostanol, Δ^5-avernsterok, $\Delta^{24(28)}$-stigmasta-en-ol, α-amyrin, $\Delta^{5,24,(25)}$-stigmasta-dienol, lupeol, gramisterol, Δ^7-stiosterol, cycloartenol, cycleucalenol, Δ^7-avenasterol, 28-methylbtusifoliol, 24-mehtylenecycloartanol, erythrodiol, citrostadienol, uvol and oleanol aldehyde were identified from *H. rhamnoides* L. seeds [8], with sitosterol and Δ^7-avenasterol being most abundant phytosterol in seed oil extract.

46.2.2 Flavonoids and Phenolics

Flavonoids are a group of important bioactive phytochemicals related to the health benefits of sea buckthorn berries. The primary flavonoides in berries are glycosides of isorhamnetin, quecertin, and kaempferol (Fig. 46.2), with minor amounts of anthocyanins, proanthocyanins, catechin and epicatechin. Among flavonoid



R_1	R_2	R_3	
H	OH	OH	kaempferol
OH	OH	OH	quercetin
OCH_3	OH	OH	isorhamnetin
H	rhamnose	sophorose	kaempfereol-3-O-sophoroside-7-O-rhamnoside
OH	rhamnose	sophorose	quercetin-3-O-sophoroside-7-O-rhamnoside
OCH_3	rhamnose	sophorose	isorhamnetin-3-O-sophoroside-7-O-rhamnoside
H	rhamnose	OH	kaempferol-7-O-rhamnoside
OH	OH	glucose	quercetin-3-O-glucoside
OH	OH	rutinose	quercetin-3-O-rutinoside (rutin)
OCH_3	OH	glucose	isorhamnetin-3-O-glucoside
OCH_3	OH	rutinose	isorhamnetin-3-O-rutinoside

Fig. 46.2 Flavonoids in *Hippophae rhamnoides* L

glycosides, quercetin-3-O-rutinoside, isorhamnetin-3-O-rutinoside and isorhamnetin-3-O-sophoroside-7-O-rhamnoside are the major ones at 5.9, 4.9 and 3.7 % respectively [9]. Flavonoids profile and content change with subspecies and harvest time. For example, subspecies *H. rhmanoides* ssp. *rhamnoides* contains higher amounts of isorhametin-3-O-glucoside-7-O-rhmnoside and isorhamnetin-3-O-glucoside and lower amounts of rutin and quercetin-3-O-glucoside in the berries than subspecies *H. rhmanoides* ssp. *sinensis* and ssp. *mongolica*. The authors of the study also found that the peak time of flavonoid glycosides in the cultivated berry was slightly earlier than those from the wild, though flavonol glycoside contents in both decreased after October [10]. Acylated isorhamnetin, quercetin, and kaempferol glycoside were identified from berries and leaves of *H. rhamnoides* ssp. *sinensis* [11]. Quercetin-7-O-rutinoside, isorhamnetin-3-O-rutinoside and isohamnetin-3-O-sophroside-7-O-rhamnoside were found as the principal flavonols glycosides of the antioxidants of the *H. rhamnoides* seed [9].

Various phenolic acids in both hydroxybenzoic acid and hydrocinnamic acid derivatives were identified in sea buckthorn berries and seeds, including salicylic acid, gallic acid, 2,5-dihydroxybenzoic acid, p-hydroxybenzoic acid, pyrocatechuic, 3,4-dihydroxycinnamic, vanilic acid, varatric, caffeic acid, *m*-coumaric acid, *o*-coumeric acid, *p*-coumeric acid, *p*-hydroxyphenyl-lactic acid, quinic acid, ferulic acid, hydroxycaffeic acid and cinnamic acid [12, 13]. The phenolic acids profile varies by genotypes, present in the form of free acids, ester and glycosides [12, 13]. salicylic acid is the predominate phenolic acid accounted for 55–74 % of total phenolic acids in berry pulps from commerical sea buckthorn cultivated in Poland [12], whilst gallic acid was the predominant phenolic acid in *H. rhamnoides* ssp. *turkestanica* from the Himalayan region, accounting for 65 % of total phenolic acids in berry pulp [13]. The phenolic acids content was higher in seeds than in berry pulp, and the leaves contained the least [13].

46.2.3 Vitamins

Sea buckthorn seeds and pulp are considered good sources of vitamin E. The tocopherols and tocotrienols content vary within the range of 100–300 ppm in seeds and 10–150 ppm in fresh berries, ranging from 0.1–0.3 % in seed oil depending on the origin, harvest time and postharvest process [4]. α-Tocopherol is the primary vitamin E in pulp, the α- and γ-tocopherols are the primary ones in seeds. The tocopherol content varies not only between parts of berries, but also between subspecies, apparently ssp. *sinensis* berries contains higher levels of tocopherols than ssp. *mongolica* and *rhamnoides*. Tocopherols and tocotrienols also vary with ripeness; α-tocopherol level is higher during early ripening periods, while δ-isomer level increases later [14].

Sea buckthorn is a good source of vitamin C, accounts for up to 2 % in fresh fruit depending on subspecies, origin, harvest time, and processing conditions [15], with a wide range of variation among subspecies and cultivars [16].

The orange-yellow color of sea buckthorn berry reflects the existence of carotenoids. Generally, carotenoid content increase during the ripening season. Total carotenoid content was found within 1.5–18.5 mg/100 g in fresh berries, depending on the cultivar, harvest time, and production year [17]. Typically, carotenoids content is much lower in seeds than in pulp [4]. β-Carotene is the primary carotenoid, while others include α-carotene, γ-carotene, lycopene, lutein, zeaxanthin, canthaxanthin, β-cryptoxanthin esters etc. [4, 18, 19]. The β-cartoene is served as a quality check point for sea buckthorn oil in some countries [19].

Inositol and methylinostol were also found in sea buckthorn berries.Wild Chinese berries (*H. rhamnoides* ssp. *sinensis*) contained higher levels of 1L-2-O-methyl-*chiro*-inositol methy-*myo*-iinositol than Finnish (*H. rhamnoides* ssp. *rhamnoids*) and Russian berries (*H. rhamnoides* ssp. *mongolica*) [20].

46.3 Pharmacological Studies

Sea buckthorn berries have been traditionally used to treat asthma and infectious lung disorders, gastric ulcers, skin diseases, poor blood circulation, and cardiovascular diseases. A broad range of pharmacological researches was conducted and results support use of sea buckthorn berries for these clinical applications. Immunomodulatory activities include anti-inflammation, anti-cancer, anti-viral, anti-radiation, and antioxidant activities.

46.3.1 Antioxidant Activities

Antioxidant activity of the sea buckthorn has been widely studied in multiple mechanisms of oxidative damage in vitro and animal models. Sea buckthorn oil stabilized the membrane structure by inhibiting lipid oxidation and improved antioxidant enzyme activities when orally administrated to experimental animals [4]. The presence of abundant antioxidant vitamins (vitamin E, vitamin C and carotenoids), flavonoids and phenolic acids contributed to antioxidant activities [19, 21]. Chen et al. [11] found acylated flavonol glycosides from *H. rhamnoides* ssp. *sinensis* berries exhibited free radical scavenging capabilitieson diphenyl-1-picrylhydrazyl (DPPH) radical and 2,2′-azino-bis-3-benzothiozoline-6-sulphoneate (ABTS) radicals. Seed fractions rich in flavonols also exhibited free radical scavenging capacities on DPPH, ABTS, superoxide, and hydroxyl radicals [9]. Isorhamnetin inhibited hydrogen peroxide-induced apoptoic damage in H9c2 cardiomycotes by suppressing the production of reactive oxygen species and activating ERK and p53 [22], in addition to the inhibition of the overproduction of ox-LDL-induced reactive oxygen species in endothelial cell Eahy926 [23]. Sea buckthorn fruit feeding alleviated oxidative stress-induced skin damage in mice exposed to UV irradiation [24]. Sea buckthorn seed oil

displayed hepatic protection in a carbon chloride induced mice model by improving their antioxidant defense system and suppressing lipid oxidation [25].

46.3.2 Cardiovascular Protection

Various studies have reported the cardioprotective effects related to the health benefits of rich flavonols content and unique fatty acids in sea buckthorn. Isorhamnetin pretreatment significantly improved cell viability of endothelial cell Eahy 926 medicated by oxidized-LDL (ox-LDL); the flavonols of sea buckthorn inhibited the ox-LDL-induced down-regulation of eNOS, up-regulation of letcin-like-ox-LDL receptor-1, phosphorylation of the p38MARK and translocation of NF-κB, suggesting anti-atherosclerotic benefits [23]. In a small human trial, 8 weeks of flavonol rich sea buckthorn (equivalent to 355 mg flavonoids/day) led to a moderate decrease in the susceptibility of LDL to oxidation ex vivo, though TC and TG were not significantly affected [26]. In addition, Xu et al. [21] summarized the cardioprotective effects of sea buckthorn flavonols, which include increasing circulating lipid markers, preventing cardiac cell death from oxidative stress and injury, and improving cardiac cell health. Sea buckthorn oil was also investigated for its benefit in cardiovascular health for its high amount of polyunsaturated fatty acids, known for their anti-atherogenic, hypocholesterolemic and antiplatelets aggression effects [21].

In animal studies with sea buckthorn fruit powder and seeds, hypertensive stroke-prone rats showed improvement in their metabolic processes and reduction of hypertensive stress; sucrose-fed rats showed decreases in blood pressure, hyperinsulinemia, and dyslipidemia; dogs with acute heart failure showed strengthened cardiac pump functions; rabbits fed with high cholesterol diets showed reduction in LDL atherogenic index, increase in HDL and vasorelaxant activities. Sea buckthorn is also found to decrease fasting blood sugar levels, triglycerides, and nitric oxide in diabetic rats [21]; possible processes to achieve this include improving insulin secretion and sensitivity, increasing liver glycogen, and down-regulating glyconegoensis [27]. Together, sea buckthorn berries may also contribute to metabolic syndrome management.

46.3.3 Skin and Mucosa Health

UV radiation causes oxidative stress and oxidative photo-damage on skin, which leads to skin aging including wrinkling, roughness, laxity and hyperpigmentation. A high antioxidant fruit blend containing sea buckthorn and blueberry fed to hairless mice suffering from UV irradiation resulted in a reduction of wrinkle formation and transdermal moisture loss. Sea buckthorn administration reduced the overly expressed matrix metalloproteinase (MMP) MMP-1 and MMP-9 induced by irradiation, and improved SOD avidity dramatically [24]. The dermal healing and

anti-apoptotic effects of sea buckthorn fruit and oil for acute and chronic skin problems have been extensively investigated in various animal models with wounds, burns, and scalds [19, 28]. Topical application of sea buckthorn preparation increased neovascularization, tissue regeneration, collagen synthesis, up-regulated gene expression of collagen type-III, and decreased in lipid peroxide levels in wound granulation tissues [19].

Evidence in both animal and human clinical studies showed protective effects of sea buckthorn oil on mucosa membrane in gastric ulcer models, where pulp oil is more effective than seed oil [4]. Oral administration of supercritical CO_2-extracted seed and pulp oils (7.0 ml/kg bw/day) significantly reduced ulcer formation in water-immersion ($p < 0.05$) and reserpine-induced ($p < 0.01$) models in rats. In addition, administration of seed and pulp oils (3.5 ml/kg bw/day) significantly reduced the index of pylorus ligation-induced gastric ulcer ($P < 0.05$) and sped up the healing process of acetic acid-induced gastric ulcers ($P < 0.01$). The results suggested that sea buckthorn oil has protective and curative effects against experimental gastric ulcers in rats [29]. Another study showed that sterol may promote the packing of adjacent unsaturated phospholipid molecules of either the cell membrane or a putative extracellular hydrophobic lining of the gastric epithelium to protect the mucosa against luminal acid [30].

46.3.4 Liver Protection

Sea buckthorn seed oil administration was found to attenuate CCl_4-induced haptic damage in ICR mice, not only reducing the elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALT), but also improving the activities of antioxidant enzymes and liver histopathology [25]. The same preparation was also found to improve liver glutathione, SOD, and catalase, and to reduce hepatic toxicity induced by oxidized LDL in mice [31].

46.4 TCM Applications and Dietary Usage

46.4.1 TCM Applications

Sea buckthorn was first recorded in the Tibetan medicine compendium 1200 years ago and formally appeared in Chinese Pharmacopoeia in 1977. Primary applications in Tibetian and Mongolian folk medicine include treatment of lung diseases, slow digestion, stomach disorders, pain, amenorrhea, and virginal dryness [32]. In modern traditional Chinese medicine practices, sea buckthorn has been used to treat cardiovascular problems, liver injuries, tendon and ligament injuries, oral mucositis, rectum mucositis, virginal mucositis, cervical erosion, radiation, scalds, duodenal ulcers, gastric ulcers, chilblains and skin ulcers caused by malnutrition. Its effectiveness for

diabetes treatments is not only due to its function in lowering fasting blood glucose and 2 h postprandial blood glucose, but also in treating complications [27].

Sea buckthorn is often used alone or formulated with other herbs as a concentrate, syrup, tablet, or powder drink etc. A well-known classic Mongolian traditional medicine formula, Wuwei Shaji San containing sea buckthorn, Muxiang (root of *Aucklandia lappa* Decne.), Zhizi (fruit of *Gardenia jasminoides* Ellis), Gancao (root of *glycyrrhiza uralensis* Fisch.), and grape is effective to treat coughing caused by lung infections such as bronchitis and tuberculosis. The fruit oil has been traditionally used topically to treat all kinds of skin diseases, burns, frostbite, dermatitis and eczema. These skin-healing qualities have led to the suggestion that sea buckthorn be used as a natural treatment for radiation poisoning.

Recommended daily dose of dried fruit is 3–10 g. Leaves and twigs are not generally used for human consumption, though there is some research on the benefits of leaves [6, 19, 21].

46.4.2 Dietary Use

Sea buckthorn berries have long history of food consumption. It has grown rapidly in last decades as a new "superfruit" for wellness and beauty because of its unique blend of vitamins, essential fatty acids, amino acids and other phytochemicals. Their high ascorbic acid content places the sea buckthorn berry among one of the richest sources of vitamin C.

Sea buckthorn oil is the most popular preparation form and is well researched. For example, sea buckthorn pulp oil standardized to 30 % omega-7 (palmitoleic acid) was reported to help avoid weight gain and maintain a slim physique. Different extraction methods were compared for their phytochemical recovery of seed and pulp oil products. One study found that supercritical CO_2 extraction is more effective in oil production than conventional hexane extraction and cold pressing, supercritical CO_2 extraction produced the highest total sterol levels in oil (1640 mg/100 g oil) and cold pressing produced the lowest (879 mg/100 g oil) [8]. However, another study reported similar recovery in fatty acids among supercritical CO_2, petroleum ether extraction, screw press, and aqueous extraction [33]. Standardized fruit extracts to flavonoids, and vitamin C, and vitamin E are widely used in dietary supplements for their benefits as antioxidant and for heart health [26], anti-aging in skin, dry eye, anti-inflammation and general wellbeing [19].

46.4.3 Beverages and Foods

Fresh fruit is acidic (astringent) and unpleasant to eat raw, unless "bletted" (frosted to reduce the astringency) and/or mixed with sweeter fruit juices, such as apple or grape juice, in drinks. The juice provides a nutritious beverage, high in suspended

solids and very high in vitamin C and carotenes. The pulp remaining after juicing provides feedstock for extraction of "sea buckthorn yellow", a pigment that has potential use as a food coloring material. The fruit can be used to make pies, jams, preserved fruits, fruit wines, and liquors. To date, sea buckthorn yellow (*Hippophae rhamnoides* yellow) is a food colorant listed under China national food additive hygiene standard GB2760-2011.

46.4.4 Beauty

Sea buckthorn oil extract is popularly used in cosmetics, beauty products, creams and lotions for cleaning, detoxifying, rejuvenating, restoring and softening skin.

46.5 Clinical Evidences

Most clinical studies have been conducted using sea buckthorn oil for patients with various conditions, such as liver fibrosis, mucous membrane [34], heart diseases, skin problem and weight management [35].

Thirty liver cirrhosis patients (25 hepatitis B cirrhosis and 5 alcoholic) aged 20–70 years old, orally took 5 g sea buckthorn extract 3 times daily for 6 months. The serum levels of laminin, hyaluronic acid, collagen types III and IV, and total bile acid decreased significantly as compared with those in the control group consisting of 20 liver cirrhosis patients (17 hepatitis B cirrhosis and 3 alcoholic) taking 6 vitamin-B complex tablets daily. The sea buckthorn notably shortened the duration for normalization of aminotransferases [36].

Traditional use of sea buckthorn oil to promote the recuperation of skin injuries and to support the treatment of skin diseases align with clinical findings. In a double blind placebo controlled study, 5 g of sea buckthorn pulp oil administration by 49 atopic dermatitis patients for 4 month significantly improved their dermatitis and increased their HDL levels [37]. Other studies showed significant improvement in skin collagen synthesis, wrinkling, elasticity, surface roughness, luminosity, and cutaneous thickness after oral doses of 2 g of seed oil daily or topical cream for 3 months in females subjects age 50–70 years old [38]. Another 8-week study applied a cream containing 1 % sea buckthorn berry to 21 healthy subjects, results showed increases in skin hydration level and significant decreases in skin trans-epidermal water loss which indicated anti-wrinkle effects [39]; 151 burned patients received the treatment with sea buckthorn oil dressing every other day showed more obvious exudation reduction, pain relief, faster epithelial cell growth, and wound healing compared to the control group which was treated with vaseline gauze [40].

In a double-blind placebo controlled crossover study by Sumodela et al., 14 healthy nonsmoking males 35–53 years old, with slightly elevated total cholesterol levels, took sea buckthorn orally with meals for 4 weeks. It was found that flavonols

from sea buckthorn extraction were absorbed, particularly when co-ingested with a small amount of sea buckthorn oil; however, no significant effects were found on low-density lipoprotein oxidation, C-reactive protection, and homocysteine [41]. The increased circulating of flavonol from sea buckthorn consumption was confirmed in a three month trial in human subjects, the consumption of 28 g sea buckthorn did not lead to significant effects on the serum total cholesterol, LDL, HDL, and triglyceride [42]. In another study, 12 healthy normolipidemic men were assigned to take 5 g/day sea buckthorn oil or fractionated coconut nut oil (control) for 4 weeks with a 4–8 week wash-out. The sea buckthorn oil group displayed clear decreases in the rate of adenosine-5′-diphosphate-induced platelet aggregation and maximum aggregation, though phospholipid fatty acids, plasma lipids, and glucose were not affected by the treatment; the data suggested that sea buckthorn may have beneficial effects on blood clotting [43].

In a 90-day randomized double blind placebo controlled trial, healthy volunteers (254 subjects) were assigned to receive sea buckthorn daily (28 g frozen sea buckthorn puree) or a placebo. Although there were no significant differences in the number or duration of common colds or digestive tract infections between the treatment and placebo groups, the serum C-reactive protein (CRP) concentration decreased significantly in sea buckthorn group ($P < 0.05$) [44].

Lehtonen et al. evaluated the benefits of sea buckthorn on metabolic diseases in overweight/obese women by using test material for 33–35 days followed by a 30–39 day wash-out. The authors found that sea buckthorn reduced the subjects' waist circumference by an average of 1.2 cm ($p < 0.05$) though no weight loss effect was found, suggesting the sea buckthorn consumption may possess slight health benefits related to manage metabolic syndromes [45].

In a more recent randomized crossover study, overweight women consumed sea buckthorn, sea buckthorn oil, and sea buckthorn phenolic fraction for 30 days; the authors found that the use of these sea buckthorn products led to a significant ($p < 0.01$) effect on the subjects' overall metabolic profiles. Sea buckthorn oil induced a decreasing trend in the serum total cholesterol, intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) [46].

46.6 Safety Evaluation and Toxicity Data

Sea buckthorn berries have a long history as food. Seed oil, pulp oil, and juice have proven to be relatively safe by toxicological studies in animal models. The investigation includes acute and chronic toxicity in blood, liver-kidney functions, and heart health as well as mutagenicity and teratogenicity of ingested oil [4].

Acute toxicity studies showed that LD50 of a single ig for mice is 20.4 ± 2.6 g/kg juice concentrate; mice displayed reduced heart rates when given 30 g/kg juice concentrate. Mice died 40 days after given sea buckthorn oil at a dose of 15 g/kg via intragastic daily. In several chronic toxicity studies, neither toxic reactions nor visible pathological changes were found when mice were orally administrated with a single

strength juice at a dose of 520 ml/kg daily for 6 months, or administrated 0.3 g/kg daily for 12 months respectively [5]. Sea buckthorn oil was found safe in rabbits when administrated intramuscularly at a dose of 1.5 ml/kg daily for 7 weeks [47]. It was also found to be safe at an oral dose of 2.5 ml/kg body weight, and at a dose of 200 μL when applied for 7 days on experimental burn wounds in rats [28].

Since sea buckthorn was found to slow blood clotting [43], it is recommended to stop using sea buckthorn at least two weeks before and after surgery.

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Chapter 47
Hovenia dulcis Thunb. 枳椇子 (Zhijuzi, Oriental Raisin Tree Seed)

Tongxiang Liu, Shengyu Hua and Zongwei Wang

47.1 Botanical Identity

Zhijuzi, the ripe fruit or seed of *Hovenia dulcis* Thunb., has frequently been used in traditional Chinese medicine (TCM) and was originally documented in early publications of the Materia Medica of Tang (Xinxiu Bencao). It is also referred to as papaya, orange dates and calligonum as it has a curved stalk. The mature fruit is typically harvested in later fall between October and November. Cleaned and dried fruit or seeds can be stored and marketed as commercial products [1, 2].

Hovenia dulcis Thunb. (commonly known as honey raisin tree, honey tree, Japanese raisin tree, or Chinese raisin tree) is a deciduous arbor tree which belongs to a small genus of Rhamnaceae. It is mainly found in the east and southwest of China, but is also found throughout Japan, Korea and the Himalayas, up to an altitude of 2000 m. This tree prefers growing in full sunlight on moist sandy or loamy soils [3, 4]. It also occurs in the montane forests of north Thailand and north Vietnam [5]. This plant is mainly cultivated in China, and has been introduced as a rare ornamental in the USA, Brazil, Cuba, Australia, New Zealand, North and Central Africa, and Europe [3, 5, 6].

Hovenia dulcis Thunb. is characterized by broadly ovate, glassy dark green foliage and sweet, fleshy and swollen peduncles. It is a glabrous tree with lenticular branches, and can grow up to 10 m in height. The membranous leaves, which are 6–12 cm wide and 8–15 cm long, are broadly ovate and arranged spirally. They

T. Liu
Institute of Chinese Minority Traditional Medicine, Minzu University of China, Beijing 100081, China

S. Hua
Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China

Z. Wang (✉)
Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
e-mail: zwang0@mgh.harvard.edu

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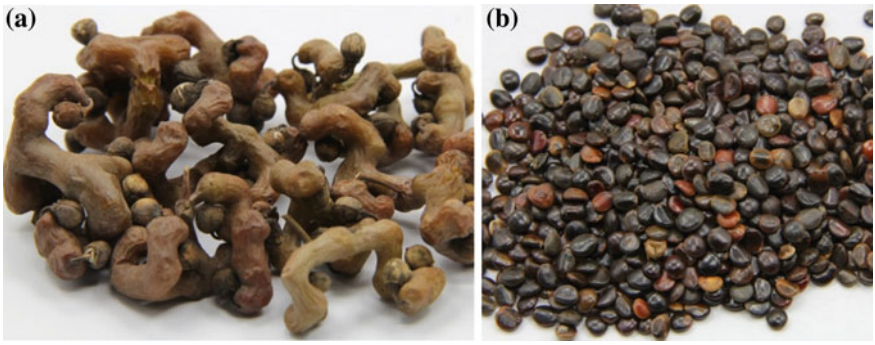


Fig. 47.1 The fresh fruit with stalk (**a**) and the dried seeds (**b**)

have a papery texture and are acuminate in shape at the tip and rounded to shallowly cordate at the base, with opaquely triangular obtuse teeth. The top side of the leaves is green, whereas the bottom is a pale green, becoming deep brown when dry. The petioles can be up to 6 cm long. The globose fruits, about 7 mm in diameter, are initially green before transforming into reddish-brown drupe with 3 seeds. The end of the fruit stalks swell to form the accessory fruit [3, 5]. The fresh fruits with stalk and the dried seeds are both illustrated in Fig. 47.1.

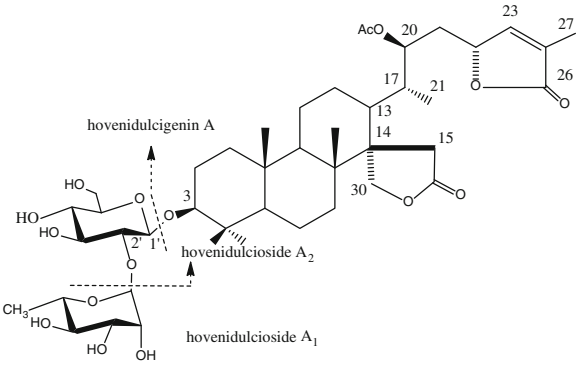
47.2 Chemical Constituents

The seeds of *Zhijuzi* contain perlolyrine, β-carboline, hovenoside C, D, G, G′, and hovenic acid. The fruit contains protein, fat, glucose, potassium nitrate, and potassium malate [7]. The fruit stalk and rachis contains glucose, fructose and sucrose [8–10].

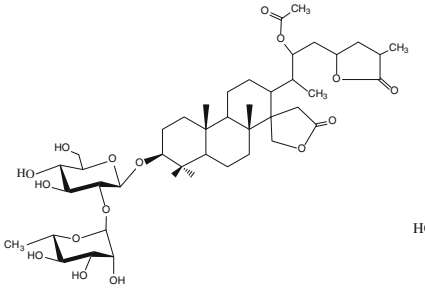
The peduncles contain high levels of sugar and organic acids [11], whereas the leaves contain sugar [12], dammarane-type sweetness inhibitors [13, 14], triterpenoid sweetness inhibitors [6], flavonoids [15] and saponins [16].

Triterpene glycosides are the major bioactive compounds of *H. dulcis*, which include hovenoside A, B, C, D, G, G′, H and I. All these compounds were found to inhibit the histamine release induced by compound 48/80 and calcium ionophore A-23187 in rat peritoneal exudate cells. Hovenidulciosides A1, A2, B1 and B2 (Fig. 47.2) showed more potent antiallergic activity [11].

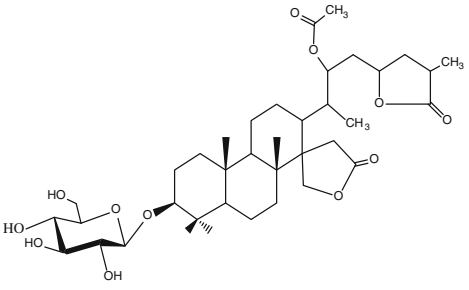
Hovenitin I and ampelopsin, which isolated from the seeds and fruits of *H. Dulcis*, have a hepatoprotective effect, and inhibit alcohol-induced muscle relaxation in rats [7].



Hovenidulciosides A1, A2



Hovenidulcioside B1



Hovenidulcioside B2

Fig. 47.2 Chemical structures of triterpenoids from Zhijuzi

47.3 Pharmacological Studies

The seeds of *H. dulcis* exhibit alcohol detoxifying, hepatoprotection, anti-anoxia, and anti-fatigue [17] properties. The seeds have historically been used in TCM to relieve intoxication with excessive drinking. Studies have shown that the seed extract of *H. dulcis* or its complex formulas can remarkably decrease alcohol concentration in blood, promote the clearing of alcohol, eliminate excessive free radicals, block lipoperoxidation, and thereby alleviate alcoholic liver damage [18]. For instance, oral administrating of water extract of the seeds of *H. dulcis* 30 min before alcohol in rats lowered 40 % of the maximum alcohol concentration in blood. When the extract was used in humans, the expiratory alcohol concentration at 1 h after beer drinking was significantly decreased from 1.72 to 0.24 mg L^{-1} [18], possibly via inhibiting the gastrointestinal absorption of alcohol [19].

Additionally, when exposed mice to alcohol, the level of alanine aminotransferase (ALT) in serum could be lowered by the ethyl acetate extract of seeds of *H. dulcis.*, The enzyme activities of alcohol dehydrogenase (ADH), acetaldehyde

dehydrogenase (ALDH), MDA, SOD, and GSH in liver could be regulated too [20, 21]. The aqueous extract of seeds of *H. dulcis* also exhibited a remarkable hepatoprotective effect, via improving the inflammatory in liver and lowering the hepatic biochemical injury index [22]. In D-GalN/LPS-induced liver injury, the methanol fraction of the seed and fruit of *H. dulcis* showed a hepatoprotective function too. In addition, the aqueous extract could not only significantly prolong the survival time of mice under hypoxia environment, both in cold (−20 °C) and hot (56 °C) conditions, but also improve the exercise endurance, increase the glycogen storage in the body, and ameliorate biochemical markers of fatigue induced by overexercise [23].

47.4 TCM Applications and Dietary Usage

47.4.1 TCM Applications

There has been a long history for Zhijuzi using as a food supplement and traditional medicine in China. In the Compendium of Materia Medica (Bencao Gangmu), Zhijuzi was described as sweet and sour in flavor, neutral in nature, and non-toxic. It was noted that Zhijuzi functioned as heat clearing, diuresis promoting and alcohol detoxifying, and was traditionally used for lingering intoxication, thirsty, emesis, urinal disorder, and constipation. Some of the above functions are similar to honey [24].

Zhijuzi is frequently used for sobering up and tranquilizing after ingestion of alcohol, most likely since of the high content of glucose and organic acid induced by Zhijuzi increasing the blood volume of the whole body, and preventing hangover induced by alcohol. Zhijuzi is also used to treat urinal disorder and constipation, which might be attributed to the large amount of glucose, inorganic salts and lipids promoting urine excretion and accelerating intestinal peristalsis. In addition, Zhijuzi has the function of dispelling wind and removing obstruction in the meridians, possibly because of the high concentration of calcium and saponin, which inhibit the central nervous system, act as an anti-convulsant and prevent tetany of hands and feet. A composite prescription of Zhijuzi has been reported to ameliorate gout [25]. The large amount of glucose, sucrose, fructose, organic acids, inorganic salts, and vitamins in Zhijuzi has also been shown to help quench thirst in diabetic patients. Recent studies further found that the bioactive ingredients perlolyrine, β-carboline, hovenoside C, D, G and H could lower blood pressure and might be beneficial for hypertension [26].

47.4.2 Dietary Usage

47.4.2.1 Zhijuzi and Swine Lung Soup

Fresh Zhijuzi fruit (120 g), one swine lung, brown sugar (30 g) and 1000 ml of water can be simmered for 1 h and then consumed to combat dehydration and restlessness in those who are intoxicated and vomiting.

47.4.2.2 Zhijuzi Wine

The mixuture of dried fruit and stalk of Zhijuzi is soaked in 500 ml of mild wine and sealed for one week. 20 ml of Zhijuzi wine can be served twice daily to disperse pathogenic wind. Zhijuzi wine is also recommended to treat rheumatoid arthritis. Similar herbal wines made from Zhijuzi alone or combined with other herbs have the function of promoting blood flow, eliminating blood stasis, dispelling dampness, and relieving asthma, and are beneficial to rheumatoid numbness and traumatic injury.

47.4.2.3 Zhijuzi Cooked with Chicken Liver

Two dried fruits with stalk of Zhijuzi are ground and steamed with one chicken liver for 20 min. This dish has the function of invigorating the spleen and can be used for infantile malnutrition.

47.5 Clinical Evidence

The compound preparation containing Zhijuzi has been reported to treat gout. Zhiju Tongfeng decoction is composed of Zhijuzi (15 g), Huangbai (*Phellodendron chinense*, 12 g), Yiyiren (*Coix lacryma*, 30 g), Rendongteng (*Lonicera japonica*, 30 g), Huainiuxi (*Achyranthes bidentata*, 15 g), Tufuling (*Smilax glabra*, 30 g), Tianqi (*Panax notoginseng*, 10 g), Bixie (*Dioscorea septemloba*, 15 g), and Cheqianzi (*Plantago asiatica*, 10 g). A clinical study reported that the patients with gout were divided into two groups; one group was treated with the Zhiju Tongfeng decoction twice per day, and the control group was treated with 7.5 mg of Meloxicam twice per day. After one week of treatment, the parameter of edema, pain and the total efficient rate between two groups was not significantly different ($P > 0.05$) [25].

The oral decoction of Zhijuzi (fruit with stalk, 0.125 g/ml, 100 ml twice per day) has been reported to treat hyperlipidemia. The efficient rate in 46 patients was 87.0 %, which was similar to that of the Xuezhikang-treated control group in 40 patients ($P > 0.05$) [27].

47.6 Safety Evaluation and Toxicity Data

In an animal experiment, mice were given an oral administration of Zhijuzi seeds (22 g/kg body weight). Although this dose was 36.6 times higher than the tested effective dose, there was not any toxicity or side-effects were found in experimental animals [28].

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Chapter 48
Lycium barbarum L. 枸杞子 (Gouqizi, Wolfberry)

Jin Yang

48.1 Botanical Identity

Gouqizi or GouqiBerry, the dried ripe fruit of *Lycium barbarum* L., is one of the most popular traditional Chinese medicines, and also a common ingredient in tonic food. The common name "wolfberry" comes from the word "gou", meaning wolf or dog. Although the fruit is from two different, but closely related plants, *L. barbarum* and *L. chinense* are used interchangeably. *L. barbarum* is the legal resource recorded in the Pharmacoepia of People's Republic of China [1, 2]. This plant occurs naturally in Asia, primarily in the Northwest regions of China, including Ningxia, Xinjiang, Qinghai, Gansu and Inner Mongolia. However, this plant is also found as far east as Hebei and west to Tibet. Cultivated along the fertile aggradational floodplains of the Yellow River for more than 600 years, Gouqizi from the Ningxia region has earned a reputation throughout Asia as premium quality, sometimes described commercially as "red diamonds".

L. barbarum is a deciduous woody perennial plant, growing 0.5–1.5 m high. Stem tufted with short spines. The leaves form on the shoot either in an alternating arrangement or in bundles of 2–4, each having a lanceolate or ovate sharp. The lavender or light-purple flowers grow in groups of one to three in the leaf axils, held with bell-shaped or tubular calyx. The ellipsoid berry is red or orange-red, and 1–2 cm long. When ripe from July to October, the oblong, red berries are tender and must be picked carefully or shaken from the vine into trays to avoid being damaged. The fruits are preserved by drying them in full sun on open trays or by mechanical dehydration to yield the market herb. The elliptic or spindly Gouqizi is 1.5–2 cm long and 4–8 mm in diameter, and bright red to kermesinus in color with irregular wrinkles, and a white fruit stalk. The fresh fruits can be squeezed for their juice for future use in making various beverages [2].

J. Yang (✉)
Beifang University of Nationalities, Yinchuan, Ningxia, China
e-mail: youngkin@126.com

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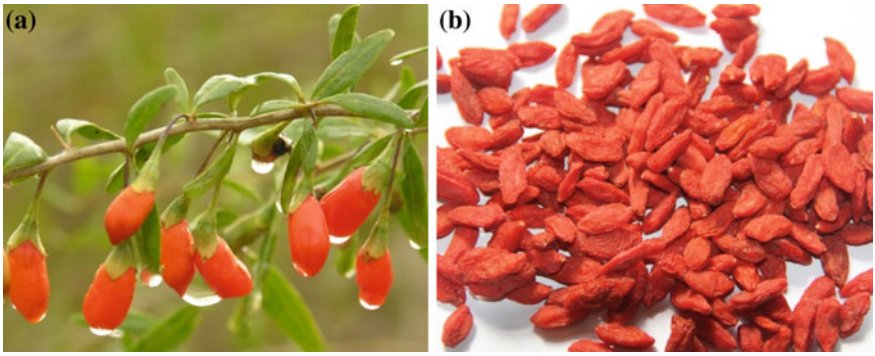


Fig. 48.1 Fruiting plant (**a**) and crude drugs (**b**) of Gouqizi

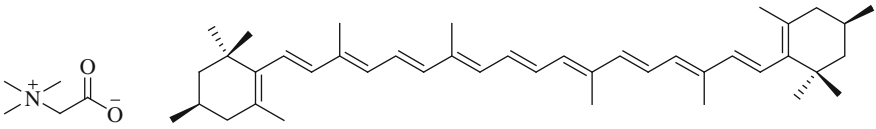
Historically, the tender leaf, flower and root cortex called Digupi (Cortex Lycii), can also be used as herbal medicines. During the past decade, the tender leaf had been developed as a tea, named as Gouqiya Tea ("ya" is used to describe young shoots and/or tender leaves), and the whole over ground seedling is a raw material for making salad. A fruiting plant (a) and commercial Gouqizi (b) of *Lycium barbarum* are shown in Fig. 48.1.

48.2 Chemical Constituents

Polysaccharides and carotenoids are two major classes of component isolated from the fruit of *L. barbarum* L.

48.2.1 Polysaccharides

Although betaine (**1**) serves as the primary marker compound to control the quality of crude drug Gouqizi in the Pharmacopoeia of People's Republic of China, the phytochemical investigation indicates that polysaccharides, which make up 5–8 % of the dried fruits [3], are a major contributor to all bioactivities of this herbal medicine. Although referred to as polysaccharides, the functional immune-regulating constituent is actually a polysaccharide-peptide mixture, in which the amino acid chains play a critical role in the polysaccharide structures [4]. The detailed structures of these polysaccharides reported in previous literatures should be further understood [5].



1 2

Fig. 48.2 The marker compound and main carotenoid isolated from Gouqizi

48.2.2 Carotenoids

The color components of Gouqizi are a group of carotenoids, which make up only 0.03–0.5 % of the dried fruit [6]. The predominant carotenoid is zeaxantin (2, see Fig. 48.2), which is present mainly as zeaxanthin depalmitate (physalien or physalin). Gouqizi is considered to be one of the best food sources of zeaxanthin. It has been reported that this compound may help to protect the macula from degeneration, which can be induced by excessive sun exposure (UV light) and by other oxidative processes [7]. These pigments help to understand the bioactive mechanism of Gouqizi for its improving eyesight according to TCM theory.

48.3 Pharmacological Studies

In China, Gouqizi is usually prescribed by TCM doctors for the treatment of a variety of deficiency syndromes. The immunological impacts of this herbal medicine, especially polysaccharides, have been the primary focus of modern pharmacological studies. The ability of Gouqizi polysaccharides (LBP) to promote immune system function has been observed in laboratory animals and isolated cells [7]. A clinical evaluation of increasing immune activity of cancer patients who consumed polysaccharides orally has been done and yielded positive results, although further investigation is needed [8]. Gouqizi and LBP are reported to display anti-aging and neuroprotective effects against toxins in aging-related neurodegenerative diseases [9]. Gouqizi and LBP exhibit some bioactivities including stimulation of metabolism, cardiovascular benefits, and anti-diabetes effects; these were recently summarized and listed by Amagase [7].

48.4 TCM-Applications and Dietary Usage

48.4.1 TCM Application [10]

According to TCM theory, the dominant attributes of Gouqizi are nourishing the *Yin* of the kidney and enriching the *Yin* of liver. This herbal medicine can also

improve eyesight and moisten the lung. There have been a few reports of using Gouqizi as a single herb in a clinical recipe. Gouqizi is always combined with other herbs for treatment of conditions such as consumptive disease accompanied by thirst, dizziness, diminished visual acuity, and chronic cough. For example, Qiju Dihuang Pill, a derivative of Liuwei Dihuang Pill, can treat dizziness and diminished visual acuity because of the deficiency of liver's *Yin*.

48.4.2 Dietary Usages

48.4.2.1 Soups

Gouqizi, traditionally, is used as a tonic food in China and needs to be cooked before consumption. It is often added to rice congee and almond jelly, as well as Chinese tonic soups, in combination with chicken or pork, vegetables, and other herbs such as Huangqi (*Astragalus membranaceus*) and Danggui (*Angelica sinensis*). The recommended dose for Gouqizi is 8–10 g daily.

48.4.2.2 Teas

In Northwest China, Gouqizi, along with sugar, red jujubes, raisins, dried apple slices, sesame, dried longan pulp and walnut kernel, is boiled as a tea. This herbal tea, known as "Eight Treasures Tea" (Babao Tea), gets it's name from the fact that there are eight components in the tea. Eight Treasures Tea can easily be made at home. In addition, herbal tea made of Gouqizi alone or mixed with chrysanthemum flowers is the most common way to consume Gouqizi.

48.4.2.3 Wines or Drinks

Gouqi wine is a variety of Chinese alcoholic beverage made from Gouqizi. This pick-me-up has a long history in China and is recorded in Han dynasty. There are three distinct varieties of Gouqi wine: distilled, fermented, and those produced by soaking Gouqizi in Chinese spirit. Commercially distilled and fermented Gouqi wines are readily available for purchase, and soaked wine can easily be prepared at home. One recipe for soaked Gouqi wine includes steeping Gouqizi (200 g) in 1 kg Chinese spirit for more than two weeks. To consume, it is recommended to drink a 10–50 mL serving twice daily.

48.5 Clinical Evidences

As previously mentioned, Gouqizi is used to promote immune system functions. A clinical study of 171 cancer patients who consumed Gouqi polysaccharides orally indicated that the bioactive constituents could increase immune activity of chemotherapy-caused immunosuppression patients [8]. Commercial Gouqi polysaccharides, which is a dietary supplement known as Qisheng Capsule, is available over-the-counter. There are also many clinical reports and observations published on the effects of Gouqizi for anti-aging and decreasing blood lipid levels [11].

48.6 Safety Evaluation and Toxicity Data

As an edible food, Gouqizi is considered non-toxic. It has been used traditionally as a food and herbal medicine for over 2500 years without any specific toxicity. Modern toxicity investigations showed that 2 g/kg of Gouqizi extract by subcutaneous application in mice did not cause adverse reactions. The ip LD_{50} is determined to be approximately 8.3 g/kg [12].

Atropine, a toxic muscle relaxation alkaloid contained in Gouqizi and some members of the Solanaceae family could be a potential safety hazard. It is reported that atropine concentrations are trace (in concentrations of maximally 3 ppb (w/w)) in tested samples collected from China [13].

Potentially harmful interactions may also occur if Gouqizi is consumed while taking other medications, such as those metabolized by the cytochrome P450 liver enzymes. Two published case reports have indicated that patients who consumed Gouqizi and warfarin at the same time had an increased risk of bleeding [14, 15]. It is worth noting that there are no modern pharmacologist studies indicating or confirming the side effects of Gouqizi overdose, although folklore suggests nosebleeding is a common side effect.

Although Gouqizi is considered to be a safe herbal medicine and food material, it is strongly recommended to talk to a doctor before consumption, especially if you are planning to use more than the recommended amount, or to use Gouqizi for an extended period of time.

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Chapter 49
Siraitia grosvenorii Swingle 罗汉果 (Luo Han Guo)

Chun Li

49.1 Botanical Identity

Luohanguo, a famous edible herbal medicine, specifically refers to the dried ripe fruit of *Siraitia grosvenorii* (Swingle) C. Jeffrey ex A. M. Lu et Z. Y. Zhang [1]. It has been used in Chinese folk medicines for more than 300 years. Due to the definite curative effects in treating pertussis, chronic bronchitis, pharyngitis and gastrointestinal diseases, Luohanguo has been recorded in the successive editions of Pharmacopoeia of China since 1977. It is also one of the first varieties listed as both edible and medicinal resources published by the Ministry of Health of China. Furthermore, Luohanguo is one of the traditional export commodities of China and has been sold to more than twenty countries and regions, such as America, Japan, Hong Kong, southeast Asia and so on.

Siraitia grosvenorii is a perennial vine of the Cucurbitaceae Family growing in the tropical and subtropical mountainous area. It's birthplace and main production area is Northern Guangxi, especially in *Yongfu* and *Lingui* counties, its cultivation history is more than 200 years. Also, it is distributed in Guizhou, Hunan, Guangdong and Jiangxi provinces in China. There are approximately seven species of the genus *Siraitia* recorded in the world, and four species are found in China [2]. Among the four species, *Siraitia grosvenorii* and *Siraitia siamensis* (Craib) C. Jeffrey are traditionally used as herbal medicines, but only *Siraitia grosvenorii* is the legal resource of Luohanguo in China. Due to the confusion of the plant classification (Luohanguo was initially classified into genus *Momordica*, then classified into genus *Thladiantha*), Luohanguo had been written as *Momordica grosvenorri* fruit or *Thladiantha grosvenorii* fruit in early papers. By authoritative identification, Luohanguo was classified into genus *Siraitia* and its legal name was

C. Li (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: yujiaolong1977@aliyun.com

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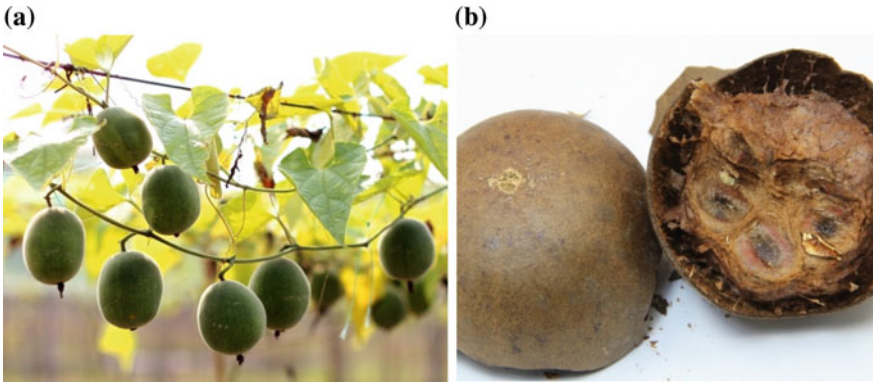


Fig. 49.1 The fruiting plant (**a**) and crude drug (**b**) of Luohanguo

changed to be *Siraitia grosvenorii* fruit in Chinese Pharmacopoeia (Edition 2010, Ch P 2010).

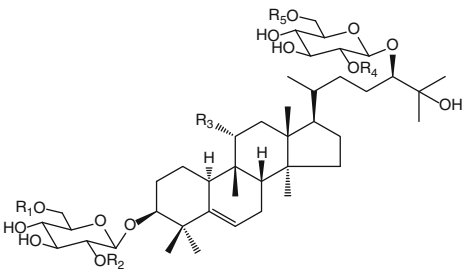
Luohanguo is collected during the autumn when the fruits are ripe. After harvested, the fruits should be placed in dry and well-ventilated area for 7–10 days to become fully ripe, and then baked with soft fire at 45–65 °C for 7–8 days until the peel is yellowish-brown and the pulp becomes sticky and sweet. The fruit is ovoid, elliptical or sphereical, 4.5–8.5 cm long and 3.5–6 cm in diameter. It is externally brown, yellowish-brown or greenish-brown, marked with dark-colored patches and covered with yellow fine hairs, some exhibiting 6–11 longitudinal lines. The traditions believe high-quality Luohanguo has the following characteristics: a round shape, externally yellowish-brown, no sound when shaking, whole shell, unburned and sweet. The original plant and the crude drug of Luohanguo are shown in Fig. 49.1.

49.2 Chemical Constituents

Luohanguo contains triterpene glycosides, flavonoids, proteins, vitamins, sugars, inorganic elements, volatile oil and so on.

49.2.1 Triterpene Glycosides

Cucurbitane-type triterpene glycosides are not only the main components, but also the active ingredients of Luohanguo. Ever since Takemoto et al. isolated mogrosides IV, V, and VI from Luohanguo in 1983, a total of thirty-seven similar compounds have been obtained from the fruit [3]. Most of these compounds taste sweet, so they are collectively called mogrosides. Mogrosides are the main active



	R_1	R_2	R_3	R_4	R_5
1	β-D-glc	H	OH	H	β-D-glc
2	β-D-glc	H	OH	β-D-glc	H
3	β-D-glc	H	OH	β-D-glc	β-D-glc
4	H	H	OH	β-D-glc	β-D-glc
5	β-D-glc	H	O	β-D-glc	β-D-glc
6	β-D-glc	β-D-glc	OH	β-D-glc	β-D-glc

Fig. 49.2 Representative triterpene glycosides isolated from Luohanguo

components of Luohanguo [4], and they account for about 4 and 1 % of the weight of dry and fresh fruits, respectively. The major sweet components from Luohanguo includes mogroside IV [including mogroside IVa (1) and mogroside IVe (2)], mogroside V(3), siamenoside I (4), 11-oxo-mogroside V(5) and mogroside VI (6) (Fig. 49.2), and their relative sweetness were 392, 425, 563, 125 and 84 times as potent as that of sucrose, respectively. At present, mogrosides have been approved as food additive in the following countries and regions: China, USA, UK, Japan, Korea, Singapore, Hongkong and Taiwan [4]. Mogroside V is a representative ingredient and quality evaluation marker in Ch P 2010, and its content is generally in 0.5–1.4 %. According to Ch P 2010, the quality control method of Luohanguo medicinal materials is to use high performance liquid chromatography to determine the range of content of mogroside V which should not be less than 0.5 %.

49.2.2 Flavonoids

Flavonoid is another kind of important chemical constituents from Luohanguo. So far, total of four flavonoid compounds have been isolated from Luohanguo and they are kaempferol 3-O-α-L-rhamnopyranoside-7-O-[β-D-glucopyranosyl (1 → 2)]-α-L-rhamnopyranoside, kaempferol 3, 7-di-O-α-L-rhamnopyranoside, kaempferol 7-O-α-L-rhamnopyranoside and kaempferol [5, 6]. The content of total flavones determined by HPLC was about 5–10 mg in a fresh fruit of Luohanguo [7].

49.2.3 Other Ingredients

In addition, there are abundant nutritional ingredients in Luohanguo [3]. It is reported that the content of crude protein in Luohanguo was between 8.67 and 13.35 %. Furthermore, the hydrolysis products of Luohanguo contained eighteen kinds of amino acids, including eight kinds of essential amino acids. Among the eighteen amino acids, the content of aspartic acid was the highest (939–1125 mg/

100 g dried fruits) and that of γ-aminobutyric acid was the lowest (15.9–35.6 mg/100 g dried fruits). Luohanguo is rich in vitamin C. The content of vitamin C reached 339–461 mg/100 g in the fresh fruits, but decreased to 24.6–38.7 mg/100 g in the dried fruits. Additionally, Luohanguo contained large quantity of fructose and glucose, and their total content were between 16.11 and 32.74 % in it. Luohanguo also contained sixteen essential trace elements and a wide variety of inorganic elements. Among these inorganic elements, potassium, calcium and magnesium had high contents, with a ratio of 1.229, 0.667 and 0.55 %, respectively. What is more, the content of Se in Luohanguo reached 0.1864 mg kg^{-1}, which was 2–4 times higher than that in grains. The seed oil of Luohanguo contained a number and large quantity of fatty aldehydes, such as fagni aldehyde, valeraldehyde, hexanal, and nonanal, and the content of fagni aldehyde in the oil reached 52.14 %. The volatile oil content in the dried Luohanguo was about 0.2–0.3 %, and *n*-Hexadecanoic acid (45.609 %) and 9, 12-octadecadienoic acid (36.151 %) were the most abundant in the essential oil from Luohanguo.

49.3 Pharmacological Studies

The pharmacological and clinical investigations carried out during the last 30 years have shown that extracts and individual compounds isolated from Luohanguo had a wide variety of biological effects, including anti-tussive and expectorant [8–10], stimulating immunity [8, 11, 12], liver protection [8, 13, 14], eliminating free radicals [15], regulating blood sugar and blood fat levels [15–18], anti-inflammatory [19], anti-carcinogenic [20], and anti-fatigue [21] effects, etc.

49.4 TCM Application and Dietary Usage

49.4.1 TCM Applications

Luohanguo was first recorded in the *Lingnan Caiyao Lu*, an important herbalism monography on the folk herbs in Lingnan region (mainly referring to Guangxi and Guangdong provinces) written by Budan Xiao in 1932. According to the theory of TCM, Luohanguo is sweet in taste and cool in nature, and it has the functions of moistening lung, relieving cough, lubricating intestines and urging purgation. So, Luohanguo is often used alone or together with other herb medicines to treat whooping cough, acute and chronic bronchitis, asthma, hypertension and diabetes.

Here are some commonly used therapeutic prescriptions: (1) A Luohanguo fruit, dried persimmon 25 g, decocted in water for oral dose; this prescription is used to treat pertussis; (2) Luohanguo 15 g, Baihe (bulb of *Lilium lancifolium*) 9 g, decocted in water for oral dose; this prescription has certain curative effect on the

senile chronic cough; (3) Luohanguo, Baibu (root of *Stemona sessilifolia*), Tiandong (root of *Asparagus cochinchinensis*), Kuxingren (seed of *Prunus armeniaca* var. *ansu*) and Sangbaipi (root bark of *Morus alba*), each 15 g, decocted in water for oral dose; this is effective in treating bronchitis; (4) Luohanguo 15 g, Baihe (bulb of *Lilium lancifolium*) 12 g, Cebaiye (leaf of *Platycladus orientalis*) 6 g, Chenpi (fruit pericarp of *Citrus reticulata*) 3 g and Mahuang (herb of *Ephedra sinica*) 3 g, decocted in water for oral dose; this prescription is effective and commonly used in treating pediatric whooping cough; (5) Two Luohanguo fruits, take the flesh and seed (smashed), decocted in water for oral dose, once daily before bedtime, can treat the senile constipation; (6) Two Luohanguo fruits, smashed and then decocted in water, left to cool, slowly swallow the decoction twice a day (morning and afternoon), has curative effect on acute and chronic pharyngitis and aphonia.

49.4.2 Dietary Usages

Luohanguo can be used as food except the traditional medicine. Now in Chinese market there are many health products made from Luohanguo, such as Luohanguo herbal tea, Luohanguo teabag, Luohanguo concentrated juice and various Luohanguo buccal tablets with health function of relieving cough, reducing sputum and relaxing the bowels, etc. In food industry Luohanguo can be used to make sugars, desserts, milk products and various kinds of drinks. Additionaly, Luohanguo can be used as a kind of condiment in all kinds of stews and soups.

The following listed are the most common and easiest ways to use Luohanguo in ordinary life.

49.4.2.1 Luohanguo Teas

The typical procedure of making Luohanguo tea is as following: a Luohanguo fruit is smashed or sliced, and then steeped in boiling water for 15 min, next the solution is drunk like an ordinary tea. It was often used as adjuvant therapy of hoarseness, cough, sore throat and constipation. Luohanguo Wuhua tea is another famous herbal tea and prepared as following: one Luohanguo fruit, Jinyinhua (flower bud of *Lonicera japonica*) 15 g, Huaihua (flower of *Sophora japonica*) 15 g, Gehua (flower of *Pueraria lobata*) 15 g, Jidanhua (*Plumeria rubra* cv. *acutifolia*) 15 g, Mumianhua (flower of *Gossampinus malabarica*) 15 g, brown sugar 20 g, all these materials are put into a marmite and washed two times with fresh water, and then they are cooked in proper amount of water for 20 min, after cooled, the solution is drunk as an ordinary tea. The tea has the following functions: eliminating phlegm, reducing internal heat, clearing away dryness and moistening lung.

49.4.2.2 Luohanguo Candy Drink

Luohanguo candy drink is prepared as follows: 250 g of Luohanguo is crushed, and then decocted in water for three times and each time for half an hour, next the decoction is filtered and the filtrate is concentrated to syrup. After left to cool, the syrup is stirred in white sugar, mixed very well, sun dried, smashed and stored in a bottle. Each time, brew 10 g of the powder with boiling water, stew for 3–5 min and then drink.

49.4.2.3 Luohanguo Gruel

Luohanguo gruel is a very popular food in Guangxi province of China. A common production method is to heat 250 g of crushed Luohanguo with boiling water three times, each time lasting 10–15 min, and then remove the residue of crude drug by filtration. Next, 50 g of japonica rice is added to the boiling mixture until a thick porridge is formed. The taste can be adjusted by the amount of added salt and Monosodium glutamate (MSG).

49.4.2.4 Luohanguo Soup

Luohanguo pig lung soup is very famous and first recorded in the Lingnan Caiyao Lu. The concrete practices are: a Luohanguo fruit smashed and 250 g of pig lung are prepared, the pig lung is cut into pieces and the foam inside is squeezed out, and then these materials are put into appropriate amount of water and cooked for half an hour, then the soup is seasoned with MSG and salt. This soup can nourish the Lung Yin and clear the pharynx.

49.5 Clinical Evidences

Although Luohanguo has been used in folk medicines in China for hundreds of years, there are few reports on the clinical use of Luohanguo and the related preparations. At present, a lot of single and compound China patent medicines containing Luohanguo are used for relieving cough and resolving phlegm in clinic, such as Luohanguo cough syrup and Luohanguo anti-asthma tablet, etc.

49.6 Safety Evaluation and Toxicity Issue

There was little clinical report on the toxicity and side effect directly related with Luohanguo and its related preparations. Animal tests also didn't show clear toxicity for various organs through oral administration. After single oral administration of 100 g/kg of Luohanguo water extract in mice, no death was observed and all the mice showed normal in seven days [8]. Acute toxicity test result showed that the LD_{50} of mogrosides by i.g. to mice was more than 10 g/kg, and the Ames test result of mogrosides was also negative [22]. No matter domestic dogs were consecutively given 3 g/kg of mogrosides by i.g. for four weeks, or Wister rats were repeatedly given 5 % of Luohanguo extract by gavage administration for thirteen weeks, or dogs were orally delivered 10 mL/kg bw/day of PureLo® (a non-caloric sweetener derived from Luohanguo) aqueous solution for 28 and 90 days, there were no significant adverse effects on any of the measures including clinical observations, body weight, food consumption, hematology, blood chemistry, urinalysis, gross necropsy, organ weight and histopathology [22–24]. These results showed both Luohanguo and mogrosides are basically non-toxic.

In conclusion, as an endemic economic crop of China, Luohanguo contains a lot of nutritious ingredients and has various pharmacological effects, so it not only can be used as a herbal medicine, but also as a functional food additive in food industry. Especially high-sweetness, low-caloric and non-toxic mogrosides, as new alternatives to sugar and synthetic sweeteners, have broad application prospect.

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Chapter 50
Myristica fragrans Houtt.
肉豆蔻 (Roudoukou, Nutmeg)

Ping Ding

50.1 Botanical Identity

Roudoukou, belonging to the family of *Myristicaceae*, is a medium-sized evergreen tree cultivated in tropical regions. The medicinal part is the seed of *Myristica fragrans* Houtt., which is one of the most popular medicinal materials, and also frenquently used in diet and cosmetic products. There are 120 species of genus *Myristica* in the world, but only a few species with similar botanical features are used as Roudoukou. *M. fragrans* Houtt. is the major and legal source recorded in the Pharmacoepia of People's Republic of China [1] and all historical records of Chinese herbal works. Typically, *M. fragrans* grows to the height of 12–20 m. Leaves alternat, elliptic lanceolate or oblong lanceolate. Flowers are creamy yellow in color and fragrant. Fruits are yellow colored, globose with fleshy pericarp that splits into two halves on maturity. Seeds are obtuse, oblong and shiny. The arillus isolated from seeds of Roudoukou is called as mace, which has similar odour and taste to the seed [2].

Foreign imports and cultured plants are the main sources of clinical supply. The seed is harvested twice a year between June–August and October–December after growing for 6–7 years. One tree of *M. fragrans* can produce an average of 3000–4000 nuts every year at the age of 25, and some of them even bear 8000 fruits or more within one year. Once cleaned and dried, the semen can be stored and marketed as raw material. For further processing, the raw material is roasted with 40 % wheat bran for about 15 min at 150–160 °C, until the wheat bran turns focal yellow and the seeds show a brown color with crack on the surface [1]. There are also other processing methods for some specific medicinal purposes, including

P. Ding (✉)
School of Chinese Materia Medica, Guangzhou University of Chinese Medicine, Guangzhou 510406, China
e-mail: dingpinggz@126.com

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Fig. 50.1 The fruit (**a**) and crude drug (**b**) of Roudoukou

Roudoukou steamed with water steam, roasted with flour, sauted with flour, roasted with talcum powder, and roasted with loess, etc. [3] (Fig. 50.1).

50.2 Chemical Constituents

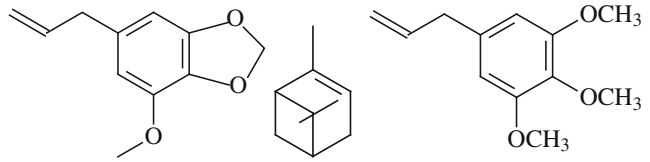
Essential oils and neolignans are two major classes of bioactive compounds found in the seeds of *M. fragrans* Houtt. [4, 5].

50.2.1 Essential Oil

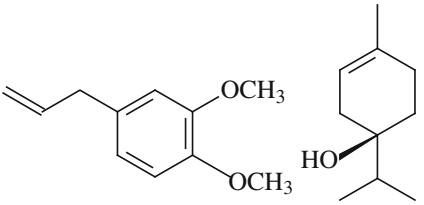
As the major class of bioactive compounds, Roudoukou essential oil (EO) has been extensively studied over the last decades [6, 7]. EO is the main source of its fragrance so it has been used as a popular spice since ancient times in Indonesia. Roudoukou EO is made up of monoterpenes, oxygenated monoterpenes, sesquiterpenes, phenolic ether, etc., and monoterpenes account for the majority. Myristicin (**1**), α-pinene (**2**), elemicin (**3**), methyleugenol (**4**), and terpine-4-ol (**5**) are representative components found in a relatively high content and used as the main compounds for analysis of essential oil from Roudoukou (Fig. 50.2).

50.2.2 Neolignan

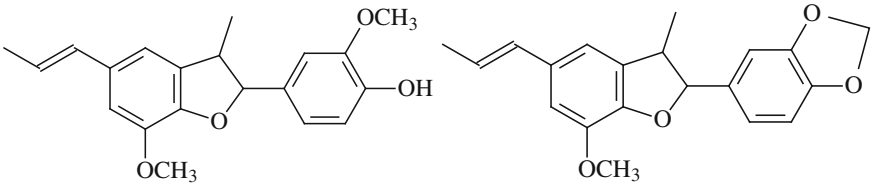
Neolignan is another major class of bioactive compounds in Roudoukou. Because of the significant antioxidant activity and inhibitory effects on the growth of the tumor cells, neolignan has become a new factor to further understand the in vitro



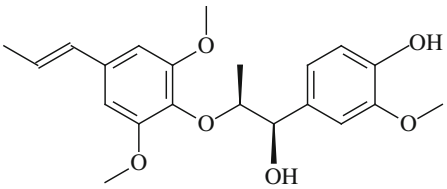
Myristicin, 1 **α-pinene,2** **Elemicin,3**



Methyleugenol, 4 **Terpine-4-ol, 5**



Dehydrodiisoeugenol,6 **Licarin B, 7**



Myrislignan,8

Fig. 50.2 Representative compounds from essential oil and lignins isolated from Roudoukou

metabolism of Roudoukou. More than 60 neolignan compounds were isolated and identified from Roudoukou so far [8]. Dehydrodiisoeugenol (**6**), licarin B (**7**), and myrislignan (**8**) are representative components and dehydrodiisoeugenol (**6**) is used as the standard compound for evaluation of the quality of Roudoukou in Chinese Pharmacopoeia.

50.3 Pharmacological Studies

Roudoukou is a popular herbal medicine, and has a long history in traditional Ayurvedic, Chinese, and Thai medicine system due to its antimicrobial, antipyretic, abortifacient, and stomachic effects. Pharmacological research revealed various activities like antioxidant, anti-depressant and improved learning and memory functions, anti-diabetic, antibacterial, anticancer, aphrodisiac, hypolipidemic, hepatoprotective, analgesic, anti-inflammatory, anti-diarrhoeal, etc. [9, 10]. Myristicin from the essential oil was found to be responsible for the hepatoprotective effect due to inhibition of TNF-α release from macrophages. The compound myristicin has cytotoxic and apoptotic effects in certain cells. Activities in cardiovascular and blood systems are related to methyleugenol for its direct effect on vascular smooth muscle. It also showed activity of anti-inflammation, anti-bacterial, antitussive, expectorant, sedative, and analgesic qualities.

50.4 TCM Applications and Dietary Usage

50.4.1 TCM Applications

Roudoukou is a traditional common herb used in TCM. As a famous herb for antidiarrheal and certain gastrointestinal diseases, it exerts therapeutical actions in the following three aspects: warming and promoting the circulation of *Qi*, helping digestion and astringing intestine to stop diarrhea, alleviating distending pain and controlling nausea and vomiting. Roudoukou could be used as single form or in combination with other herbs based on TCM theory [11].

Roudoukou is commonly used as an associate drugs in different forms, e.g. Sishen Pills. The Sishen Pill is composed of four herbal components: *Myristica fragrans*, *Psoralea corylifolia*, *Schisandra chinensis*, and *Tetradium ruticarpum*. It is mainly used for the treatment of diarrhea and bad appetite.

The essential oil of Roudoukou has anti-inflammatory, anesthetic, and antioxidant properties, which can be easily mixed with other preparation or used singely.

Preparations made from active components including myristicin and dehydrodiisoeugenol are also in the market as chemical drugs [12].

50.4.2 Dietary Usages

Roudoukou has been used in the diet since ancient Indonesia. The following introduction contains information about the dietary use of Roudoukou.

50.4.2.1 Spice

The use of Roudoukou including nutmeg and mace as a spice has been well known since ancient Indonesia. They can be used in expelling the smell of meat, and giving special taste to pudding and chocolate.

50.4.2.2 Essential Oil

Essential oil is extracted from kernel of Roudoukou. It exerts therapeutical and health-maintaining actions in the following three aspects: helping digestion and controlling nausea and vomiting, dispelling bromopnea and preventing astriction.

50.4.2.3 Roudoukou Tea

Roudoukou Tea is a health-maintaining product composed of Roudoukou, Pugongying (*Taraxacum officnala*), and Jiaosanxian (scorched *Hordeum vulgare*, *Crataegus pinnatifida*, and medicated leaven). Metal pots are not recommend to make the herbal tea.

50.5 Clinical Evidences

As a therapeutic medicine, Roudoukou is often used in combination with other herbal medicines, such as Buguzhi (*Psoralea corylifolia*) or Hezi (*Terminalia chebula*), to enhance the effect of warming the middle or astringency. For example, Sishen Pills and ZhenrenYangzang decotion. For Sishen Pills, the clinical reports showed that the preparation could cure ulcerative colitis, encopresis, and rectal prolapse [13]. For the ZhenrenYangzang decotion, clinical observation indicated that it can cure ulcerative colitis in 44 cases (47.73 %), and only 4 cases (9.52 %) relapse within half of year, which was better than control groups [14].

Clathrating with β-cyclodextrin can improve the solubility of essential oil, and reduce irritation.

50.6 Safety Evaluation and Toxicity Data

Roudoukou is subject to abuse because of its psychotropic effects. Acute psychosis has been reported with a variety of symptoms. These effects occur due to the metabolic products of the ingredients of Roudoukou, namely elimicin, myristicin

and Safrole [6]. A one-time dose of 0.5–1 g of Roudoukou powder and 1–3 drops of essential oil are considered to be safe. Toxic overdose has been observed be equal or greater than 5 g [15].

Some clinical reports show toxicity reactions on various body systems as follows.

50.6.1 Cardiovascular Reaction

It may lead to tachycardia, hypertension or hypotension in certain cases, and Chest pains or tightness in the chest has also been observed [16, 17].

50.6.2 Neurological Reaction [17, 18]

Side effects on the central nervous system includes severe headaches, drowsiness several hours or fitful sleep after taking Roudoukou, convulsions, hallucinations (predominantly visual) and distortion may also occur. In the Peripheral nervous system, initial stimulation after administration of Roudoukou is found. For example, a strong tingling in the fingers and toes shortly after snuffing some Roudoukou drugs can be experienced. Numbness in the hands and feet after snuffing for half an hour is observed and limb reflexes become less prominent. There is lots of sweating, which may act as an amphetamine type reaction in autonomic nervous system.

50.6.3 Effects on Liver

Hepatic necrosis is seen in cases of heavy poisoning. Fatty degradation of liver has also been observed. Safrole has been shown to produce hepatic carcinoma in mice [19].

50.6.4 Toxicity Data

Animal studies show noticeable toxicity for various organs through i.v. and oral administration. According to the toxicity data quoted in Duke [20], the LD_{50} of myristic acid when administered to mice intravenously was 43 mg. Nutmeg oil (expressed) when administered to rats orally showed LD_{50} of 3640 mg. Nutmeg oil (volatile) showed LD_{50} of 2620 mg.

As narrated above, the excessive doses can result in considerable harm, so paying attention to the correct dose of Roudoukou is needed. Attention must be paid when you decide to use this herb personally. It is strongly suggested to ask your doctor whether Roudoukou is proper for you.

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Chapter 51
Phyllanthus emblica L. 余甘子 (Yuganzi, Indian Gooseberry)

Yanze Liu and Fan Liu

51.1 Botanical Identity

Phyllanthus emblica Linn. (syn. *Emblica officinalis*), commonly known as Yuganzi in Chinese and Indian gooseberry or amla in English, is a Phyllanthaceaeous plant indigenously grown in the area of Nepal, India, Sri Lanka, throughout South-East Asia to southern China. It is also widely cultivated for its fruits throughout its natural area of distribution, particularly in southern China and India. All parts of the plant are used for medicinal purposes, especially the fruit, which has been used in traditional Chinese medicine and Indian Ayurveda for the treatment of diarrhea, jaundice, and inflammation. Modern pharmacological researches revealed its antidiabetic, hypolipidemic, antibacterial, antioxidant, antiulcerogenic, hepatoprotective, gastroprotective, and chemopreventive properties. The fruit of the plant is also used as a tonic to build up lost vitality and vigor with its highly nutritious and abundant phenolic compounds, tannins, flavonoids, vitamins, amino acids, and minerals [1, 2].

The family Phyllanthaceae comprises about 2000 species, grouped into 54–60 genera. The genus *Phyllanthus*, one of the largest genera of flowering plants, with over 1200 species, has more than half of the species in the family. Previously, Phyllanthus was included in the family Euphorbiaceae under the subfamily Phyllanthoideae [3, 4].

Y. Liu (✉)
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, 100193 Beijing, China
e-mail: yzliu@implad.ac.cn

F. Liu
China-ASEAN Traditional Medicine Exchange and Cooperation Center, Guangxi Botanical Garden of Medicinal Plant, Nan'ning 530023, China

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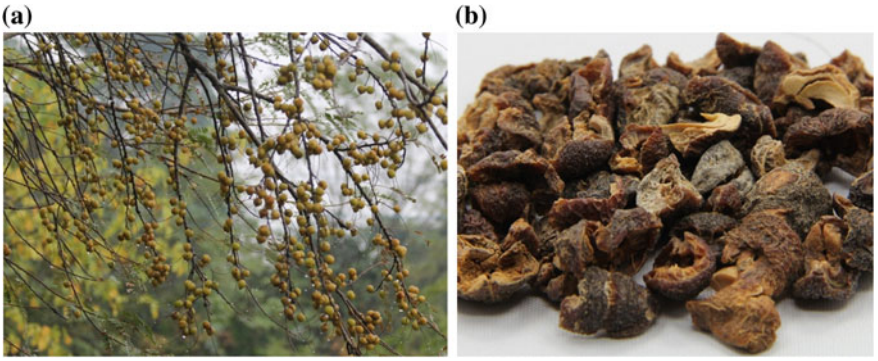

Fig. 51.1 The fruiting plant (**a**) and crude drug (**b**) of Yuganzi

The *Phyllanthus emblica* plant is a tree of small to medium in size, reaching 8–18 m in height, with a crooked trunk and spreading branches. The branchlets are glabrous or finely pubescent, 10–20 cm long, usually deciduous; the leaves are simple, subsessile and closely set along branchlets, light green, resembling pinnate leaves. The flowers are greenish-yellow. The fruit is nearly spherical, light greenish yellow, quite smooth and hard on appearance, with six vertical stripes or furrows. The berries are harvested when ripe in autumn. The taste of the fruit is sour, bitter and astringent, and the texture is quite fibrous [5] (Fig. 51.1).

51.2 Chemical Constituents

Either in the family Phyllanthaceae or Euphorbiaceae, tannins and polyphenols are known as the representative components. More interestingly, Yuganzi contains very similar tannins with *Terminalia chebula* (Combretaceae), such as chebulinic acid, chebulagic acid, corilagin, and chebulic acid etc., which are used in similar applications in Chinese medicine and Ayurveda [6].

51.2.1 Tannins and Related Polyphenols

Hydrolysable tannins, including $^{4}C_{1}$ form galloyl glucoses, $^{1}C_{4}$ form chebulloyl and/or hexahydroxdiphenyl (HHDP) glucoses, are the major polyphenolic compounds and the origin of the astringency of Yuganzi fruit meat. Chebulinic acid (1), chebulagic acid (2), corilagin (5), and chebulic acid are the typical tannins isolated from the plant and explained the most of the biological activity and clinical applications [7]. Putranjivain A (8) was later found to be a very active tannic compound against HIV-1 from Yuganzi, which is one of five active herbal extracts screened from 41 Egypt medicinal plants [8, 9]. Other representative hydrolysable tannins are

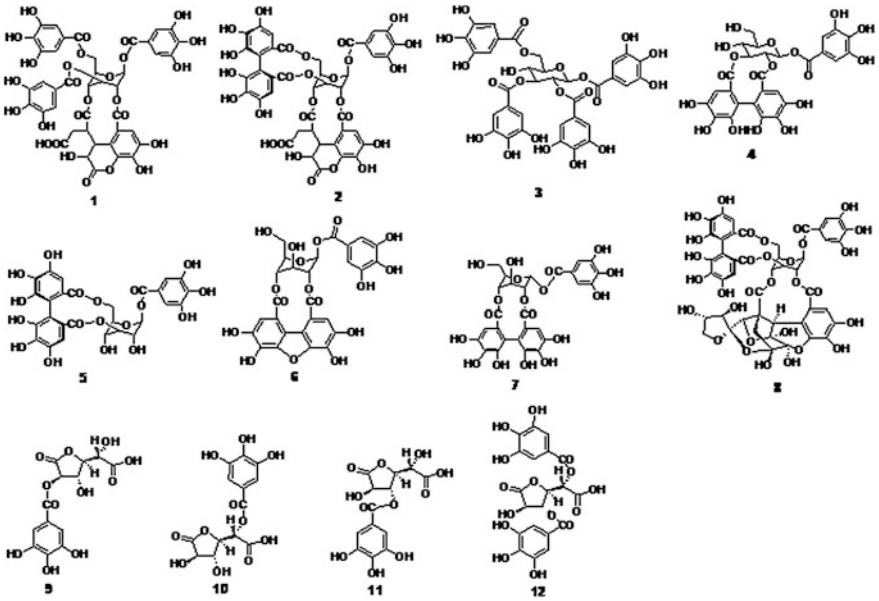

Fig. 51.2 Representative hydrolysable tannins and related phenolic acids from Yuganzi

1,2,3,6-tetra-O-galloyl-β-D-glucose (3), 1-O-galloyl-2,3-HHDP-β-D-glucose (4), Phyllannemblinin A (6), and Phyllannemblinin B (7) [10]. Figure 51.2 depicts the structures of some typical hydrolysable tannins from Yuganzi.

51.2.2 Phenolic Acids

Yuganzi tastes sour-sweet with astringency. Abundant vitamin C was thought to be the principle source of the sour, but later evidence proved that most of the acidity comes from the rich content of the gallates of vitamin C derivatives, such as mucic acid-1,4-lactone 2-O-gallate (9), mucic acid-1,4-lactone 5-O-gallate (10), mucic acid-1,4-lactone 3-O-gallate (11), and mucic acid-1,4-lactone 3,5-di-O-gallates (12) etc. [11]. Gallic acid, ellagic acid, and chebulic acid were also reported as the building blocks of the hydrolysable tannins from Yuganzi.

51.2.3 Nutritious Components

As general nutritious components, amino acids, vitamins, and mineral elements may take a very important position. Nine free amino acids, i.e. ASP, GLU, SER, ARG, GLY, THR, PRO, ALA, and PHE were analysed by RP-HPLC and the

contents of them were 0.0042–0.5666 mg/g (dry material), while the PRO took the highest position between 0.2809–0.566 6 mg/g and GLY 0.0113–0.0344 mg/g in four varieties [12]. Vitamin C was thought to be the most nutritious component and make the fruit more nutritious by comparison with apple (160 times higher) and other fruits [2, 13, 14]. But, recent report from Indian scientists suggested that the existance and content of vitamin C is questionable based on the evidence of HPLC analysis [15]. The so-called or ascorbic acid-like peak on HPLC chromatogram is just a small shoulder peak of a main peak. Further separation of the main peak by changing the HPLC condition resulted in the separation of four peaks, three of them were identified as a pair isomers of mucic acid 2-O-gallate and mucic acid-1,4-lactone 5-O-gallate (10). Other vitamins includes vitamin B1, B2, A, pp, and carotene. The seeds of Yuganzi contain about 26 % of fatty acids including linolenic acid, linoleic acid, oleic acid, stearic acid, palmitic acid, and myristic acid etc. Selenium, zinc, calcium, iron, phosphorus, and potassium are main mineral elements of the fruits detected. Flavonoids are thought to be popular biological and nutritional components widely distributed in various herbs and foods. Quercetin is one of main flavonoids with a content of 0.086 mg/g in dry material [16].

51.3 Pharmacological Studies

Antioxidant and free radical scavenging, immunomodulatory, and anticancer activities are the most prominent and typical activities of Yuganzi, which could be easily linked to its important position either in Chinese medicine, especially Tibet medicine or Indian Ayurveda. Vitamin C derivatives, tannins, and flavonoids are thought to be responsible components for these activities [13]. Gallic acid as a basic structural unit of hydrolysable tannin showed the highest DPPH radical scavenging activity among all the compounds tested including ethyl acetate extract of Yuganzi, cinnamic acid, quercetin, ellagic acid, and BHT, TBHQ, and vitamin C as positive control [17].

Baliga et al. [18] summarized the pharmacological properties of *P. emblica* in a review, in which a lot of preclinical studies had shown that amla possesses antipyretic, analgesic, antitussive, antiatherogenic, adaptogenic, antianemia, antihypercholesterolemia, wound-healing, antidiarrheal, cardioprotective, gastroprotective, hepatoprotective, nephroprotective, and neuroprotective properties. Further experimental studies had shown that amla and some of its components such as gallic acid, ellagic acid, pyrogallol, corilagin, geraniin, chebulinic acid, and chebulagic acid also possesses antineoplastic effects [13, 18]. Additionally, amla had also been reported to possess radiomodulatory, hemomodulatory, chemopreventive, and anti-inflammatory efficacies for the treatment and prevention of cancer [2].

Antibacterial and antiviral properties are the most important and representative biological activities of tannins. Rich content of hydrolysable tannins in the fruits of *P. emblica* well explained its antivirus activity. Among 41 medicinal plants used in Egyptian folk medicine screened for anti-HIV activity, *P. emblica* is the most active one within five effective plants. By bio-guided fractionation and repeated column

chromatography over Sephadex LH-20, a hydrolysable tannin with $^{1}C_{4}$-form glucose, putranjivain A (8) was isolated as a potent inhibitory substance with IC_{50} = 3.9 μM for HIV-1 [8].

Aimed at the management of Alzheimer's disease, the effects of *Emblica officinalis* on memory, total serum cholesterol levels, and brain cholinesterase activity in mice were investigated. *E. officinalis* was administered orally in three doses (50, 100 and 200 mg/kg) for fifteen days to different groups of young and aged mice. The results showed that *E. officinalis* (50, 100 and 200 mg/kg, p.o.) produced a dose-dependent improvement in memory scores of young and aged mice. Furthermore, it reversed the amnesia induced by scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). Interestingly, brain cholinesterase activity and total cholesterol levels were reduced by *E. officinalis* administered orally for 15 days. So, *E. officinalis* could be a useful remedy for the management of Alzheimer's disease on account of its multifarious beneficial effects such as, memory improving property, cholesterol lowering property, and anticholinesterase activity [19].

51.4 TCM Applications and Dietary Usage

Yuganzi has an even longer history of medicinal use in Ayurveda, with 6000 years, than in traditional Chinese medicine. Yuganzi was first officially recorded in Xinxiu Bencao written in *Tang* dynasty in A.D 657 and was thought to be introduced from India or other southwest countries [20]. The Chinese name Yuganzi describes the fruit's specific taste, first sour-astringent and then sweet. The fruit is traditionally used as food and medical purpose.

51.4.1 TCM Applications

As previously mentioned, Yuganzi is a typical Tibetan medicine used singly or combined with other herbs to make certain formula. 25 Wei Yuganzi Wan, composed of 25 herbs including *Terminalia chebula* and *T. belerica*, and Yuganzi is one of the major components, is a very typical and well known Tibet formula and a patent Chinese medicine used for the treatment of hypertension, liver and gallbladder pain, hoarse, red eyes, thirst, lips purple, and irregular menstruation. Chinese Pharmacopeia [21] described that the fruit is used for heated-blood and bloodstasis, indigestion, bloating, cough, sore throat, and dry mouth by its function of clearing the evil heat and cooling the blood, helping the digestion and enhancing the stomach, generating the body-fluid to stop thirst. 3–9 g is recommended to be used in the pills or powder and 15–30 g is for decoction. The lozenge made from Yuganzi extract and borneol, menthol is a licensed herbal product used for dry throat with pain and becoming more and more popular [22]. The fresh juice is also sometimes used for above purpose.

51.4.2 Dietary Usages

As a popular and functional fruit, Yuganzi is more widely used in fresh or dry form. The following popular ways are recommended as required.

51.4.2.1 Fresh Fruits

There are many ways to use fresh fruits of Yuganzi [23]: (1) Flavoured fruit: Fresh fruit sprinkled with salt and pepper to be eaten directly, which aids the function of digestion; (2) Fruit jam: The fruit meat is homogenized with different seasonings depending on preferences; (3) Pickled fruit: The fresh fruits are soaked with salty water and vinegar, ginger, and cinnamon, which can be reserved and eaten for a whole year. (4) Direct eat: For sore throat, direct eating of the fresh fruit is recommended.

51.4.2.2 Fruit Juice

The fresh fruit juice can be made at home or commercially in a factory. Because of the strong sour and astringent taste, sugar, honey, or other fruit or vegetable juice is sometimes added for different purposes and tastes. Daily administration of the fruit juice with honey is used for anti-aging purposes. For diabetes patients or to lower the blood sugar, 5 ml fresh juice mixed with 250 ml bitter melon juice is recommended for daily use for two months. For diarrhea, it is suggested to drink the fresh juice mixed with lemon juice.

51.4.2.3 Yuganzi Succades

The basic formula for succades (candied peel) is to combine Yuganzi and sugar at a ratio of 10:6 and boil together until the content of sugar reached 60 %. The taste and color are helpful for enhancing the appetite and digestion [24].

51.4.2.4 Yuganzi Wine

Fresh or dry Yuganzi can be used to make an herbal wine. The alcohol content, concentration of Yuganzi, and taste can be adjusted based on personal preference. The wine is used as an anti-inflammatory and for detoxication.

51.5 Clinical Evidences

Although there are 6000 years' experience in Ayurveda and more than a thousand years in Chinese medicine, mostly it was used in certain formula combined with other herbs, except when used as food. It's also mostly used together with other two closely related fruits *Terminalia chebula* and *T. belerica*, called Indian or Tibet Three-fruits.

Triphla [1] is an herbal mixture composed of equivalent *P. emblica*, *Terminalia chebula* and *T. belerica*. According to Ayurvedic practitioners, daily use of Triphala promotes appetite, ensures good digestion, increases red blood cells and hemoglobin, and helps in removal of undesirable fat. It's also used in other prescriptions for the treatment of cancer, diabetes, heart disease, liver disease, anemia, ulcers, hypercholesterol, fever, atherosclerosis, bronchitis, and Alzheimer's disease etc. [1]. Qingpeng Gao is an external paste used for the removal of bone and joint pain in Tibet medicine since 16th century. The medicine is composed of nine herbs including above Tibet Three-fruits and tannins in these three-fruits were thought to be effective substances for the relief of inflammation. Clinical study of Qingpeng Gao showed that the test group gave 80 % efficacy and positive control group with Diclofenac Sodium Enteric-coated Tablets (Novartis) 66 % [25, 26]. Another early report about the clinical observation of Yugan Chongji (instant extract powder) for hepatitis B showed 89.9 % efficiency and 46.6 % of them was cured after 90 days treatment [27]. Unfortunately, there was no detailed design of clinical trial and control tests.

Above all, there is almost no scientific clinical trial data and mechanism study for Yuganzi and its main preparations. More studies focused on the controlled clinical trial and molecular mechanism, especially in the single Yuganzi form or simpler formula, is required in order to better use Yuganzi and for new drug discovery.

51.6 Safety Evaluation and Toxicity Data

There is little clinical evidence to show the toxicity or side effect of Yuganzi and related products, which is in consistence with long historical record. An animal acute toxicity test with mice showed that the LD_{50} was 35.16 ± 2.5 g/kg, which is 163–188 times of clinical dose (60 kg body weight, 8–12 g daily), indicating the good safety with normal use [28]. Another report with rat for long term toxicity test resulted in that when three dosages of 3.6, 7.2, and 10.8 g/kg were ig given for 60 days, there was no any visible toxicity or side effect observed by comparing with blank control [29].

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Chapter 52
Piper nigrum L. 黑胡椒 (Heihujiao, Black Pepper)

Jianhui Liu and Fei Yin

52.1 Botanical Identity

Piper nigrum is a flowering vine in the family *Piperaceae*, cultivated for its fruit, which is usually dried and used as a spice and seasoning. The fruit, known as a peppercorn when dried, is approximately 5 mm (0.20 in) in diameter, dark red when fully mature, and, like all drupes, contains a single seed. Peppercorns, and the powdered pepper derived from grinding them, may be described simply as pepper or more precisely as black pepper (cooked and dried unripe fruit), green pepper (dried unripe fruit) and white pepper (dried ripe seeds).

P. nigrum is native to south India, and is extensively cultivated there and elsewhere in tropical regions. Currently Vietnam is the world's largest producer and exporter of pepper, producing 34 % of the world's *P. nigrum* crop as of 2008.

The plant of *P. nigrum* is a perennial woody vine growing up to 4 m (13 ft) in height on supporting trees, poles, or trellises. It is a spreading vine, rooting readily where trailing stems touch the ground. The leaves are alternate, entire, 5–10 cm long and 3–6 cm across. The flowers are small, produced on pendulous spikes 4 to 8 cm long at the leaf nodes, the spikes lengthening up to 7–15 cm as the fruit matures. The plants bear fruit from the fourth or fifth year, and typically continue to bear fruit for seven years. The cuttings are usually cultivars, selected both for yield and quality of fruit.

A single stem will bear 20–30 fruiting spikes. The harvest begins as soon as one or two fruits at the base of the spikes begin to turn red, and before the fruit is fully mature, and still hard; if allowed to ripen completely, the fruit lose pungency, and

J. Liu (✉) · F. Yin
College of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, China
e-mail: jhliu@cqut.edu.cn

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Fig. 52.1 Growing plant (**a**) and dietary black pepper (**b**) from *Piper nigrum*

ultimately fall off and are lost. The spikes are collected and spread out to dry in the sun, and then the peppercorns are stripped off the spikes (Fig. 52.1).

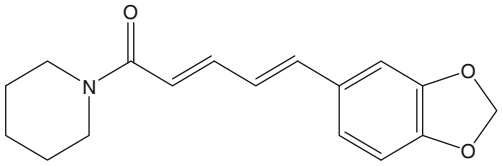
52.2 Chemical Constituents

52.2.1 Amide Alkaloids

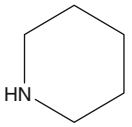
As an herb, *P. nigrum* contains 5–10 % pungent acid-amides (pseudoalkaloids), with piperine (1) as its main compound and several others including piperyline (2), piperoleines (3), and piperamine (4) [1]. Piperine is representative component and used as standard compound for evaluation of the quality of crude drug *P. nigrum* and related pharmaceutical or natural health preparations containing *P. nigrum* (Fig. 52.2).

52.2.2 Essential Oils

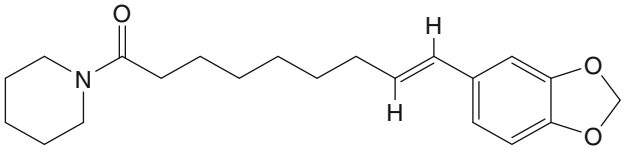
The sharp aroma of *P. nigrum* is due to its essential oil content. *P. nigrum* contains approximately 1.2–3.5 % essential oil. Its key chemical constituents include: (R)-Limonene (up to 20 %) (5), α-pinene (6), β-pinene (7), sabinene (8), β-caryophyllene (9) and δ-3-carene (10) [2] (Fig. 52.3).



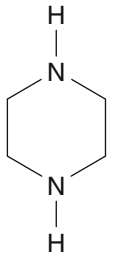
Piperine, 1



Piperidine, 2

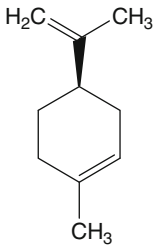


Piperoleine, 3

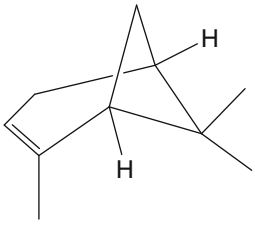


Piperamine, 4

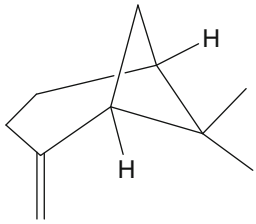
Fig. 52.2 Representative alkaloids compounds isolated from *P. nigrum*



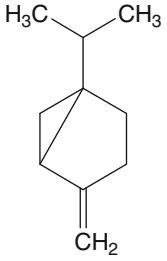
(R)-Limonene, 5



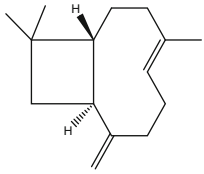
α-pinene, 6



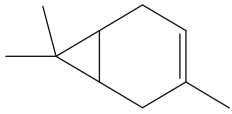
β-pinene, 7



Sabinene, 8



β-caryophyllene, 9

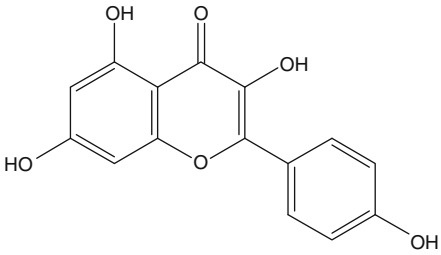


δ-3-carene, 10

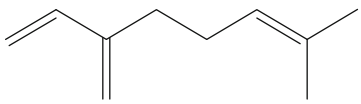
Fig. 52.3 Terpenoids isolated from essential oils of *P. nigrum*

52.2.3 Other Components

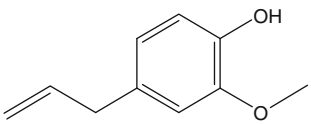
The other constituents of *P. nigrum* include kaempferol (11), myrcene (12), eugenol (13), quercetin (14), rutin (15), etc. [1, 3] (Fig. 52.4).



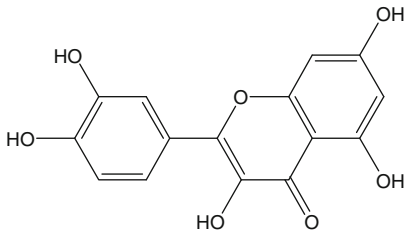
Kaempferol, 11



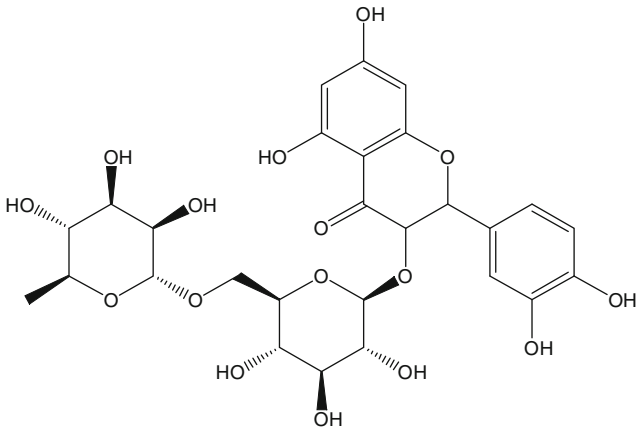
Myrcene, 12



Eugenol, 13



Quercetin, 14



Rutin, 15

Fig. 52.4 Some other active compounds isolated from *P. nigrum*

52.3 Pharmacological Studies

P. nigrum is one of the most widely used among spices, which is famous as the species king due to its pungent quality. *P. nigrum* is used not only in human dietaries but also for other purposes such as medicinal, as constipation, diarrhea, earache, gangrene, heart disease, hernia, hoarseness, indigestion, insect bites, insomnia, joint pain, liver problems, lung disease, oral abscesses, sunburn, tooth decay, and toothaches.

52.3.1 Effects of P. nigrum *on Digestion*

It was reported that orally administration of *piperine*, one kind of pungent compound from *P. nigrum* could increase the production of saliva and gastric secretions and bile acid secretion [4]. And ingestion of *P. nigrum* increases the production and activation of salivary amylase, which probably stimulates liver to secrete bible, and further to digest food substances. Furthermore, a large number of references suggested that intake of peppercorn in food items and oral administration of active compounds of *P. nigrum* such as piperine, piperamides, piperamines and pipene enhanced the enzymes activation of pancreas, liver and small intestinal mucosa [5].

52.3.2 Antioxidant Activity of P. nigrum

Studies have also indicated that various spice principles form an important group as antioxidants. Piperine has been demonstrated in vitro experiments to protect against oxidative damage by inhibiting or quenching free radicals and reactive oxygen species and inhibit lipid peroxidation [6].

The increasing data shows that intake of *P. nigrum* could prevent the intestine induced oxidative stress, inhibit lipid peroxidation, arresting different radicals such as hydroxyl and oxides radicals, decrease induced lung carcinogenesis and inhibit human lipoxygenase, and the antioxidative activity of *P. nigrum* might be associated with the presence of flavonoids and phenolic contents [7].

52.3.3 Antidiarrhoeal Property of P. nigrum

Until now, the antidiarrhoeal property of this plant has been reported by several different groups. Piperine, the most important component of *P. nigrum* has been shown to minimize the antidiarrheal activity induced by the supplementation of various chemical activators and oil in experimental animals' model. To deeply

explore the mechanisms about that, the researchers identified that piperine preventing the secretion and accumulation to show the antidiarrhoeal activity might be associated with its regulation on the capszaepine-sensitive vanilloid receptors during castor oil induced situation [8].

52.3.4 Antimutagenic and Antitumor Activity of P. nigrum

Beside with using in perfumery, *P. nigrum* also plays an essential role on some fatal diseases caused by mutations. It was reported that *P. nigrum* could reduce the mutation on *Drosopjila* melanogaster induced by the exposure to promutagen-ethyl carbamate. And, *P. nigrum* and peppercorn extract have also been reported to inhibit the formation of tumor in some experimental models. One report showed that peperine could prevent and inhibit lung metastasis in mice induced by the exposure of melanoma cells. Moreover, piperine also inhibited lung cancer by modulating lipid peroxidation by activation of antioxidative enzymes [9].

52.3.5 Anti-inflammatory Activity of P. nigrum

The anti-inflammatory activity of piperine isolated from *P. nigrum* has been proved in different acute and chronic experimental models. Singh and Duggal reported that piperine inhibited adhesion of endothelial monolayer to neutrophils, and blocked the expression of some cell adhesion molecules including intercellular adhesion molecule-1, vascular cell and E-selection. They also showed that administration of piperine dramatically reduced pro-inflammatory cytokines, including GM-CSF, IL-6, TNF-α and IL-1β [8]. Another study suggested that piperine could dose-dependently inhibit the collagen matrix invasion of melanoma cells, and block the phosphorylation and degradation of IκBα by attenuating tumor necrosis factor-α induced IκB kinase activity [7].

52.3.6 Antihypertensive Effect of P. nigrum

P. nigrum is mostly administrated orally as food additives. But, when administrated by different means, it showed different effects. It was introduced that piperine, the major active component of *P. nigrum,* when administrated intravenously, decreased pressure in arteries in normotensive anesthetized rats, and caused a partial reduction of force, contraction of tissues and blood flow in coronary vessels in vitro on rat rabbit heart. Additionally, in rabbit aortic ring, piperine partially inhibited phenylephrine and high K^+ pre-contractions due to blockade Ca^{2+} channel [8, 10].

52.3.7 Antibacterial Effects of P. nigrum

P. nigrum has been extensively applicated in antibacterial preparations belonging to Ayurvedic system of medicine. A bioguided extraction and fractionation of the petroleum ether extract of the berries of *P. nigrum* afforded 2E, 4E, 8Z-N-isobutyleicosatrienamide, pellitorine, trachyone, pergumidieneandisopiperole. And all the isolated compounds were active against *Bacillus subtilis, Bacillus sphaericus*, and *Staphylococcus aureus* amongst Gram +ve bacteria, and Klebsiellaaerogenes and Chromobacteriumviolaceum among Gram −ve bacterial strains [11].

In an in vitro study, the researchers found that using 12 different genera of bacterial populations isolated from the oral cavity of 200 individuals, an aqueous decoction of black pepper (*P. nigrum*) exhibited 75 % antibacterial activity as compared to aqueous decoction of bay leaf (53.4 %) and aqueous decoction of aniseed (18.1 %), at the concentration of 10 mL/disc [8].

52.3.8 Other Activities

In an in vitro study using whole-cell patch-clamp electrophysiology, piperine, a pungent alkaloid found in *P. nigrum*, had similar agonist effects on the human vanilloid receptor TRPV1 as capsaicin. However, piperine could induce greater receptor desensitization and exhibit a greater efficacy than capsaicin [12].

Piperine, as a thermogenic compound in *P. nigrum,* enhances the thermogenesis of lipid and accelerates energy metabolism in the body and also increases the serotonin and beta-endorphin production in the brain [13].

Piperine and other components from *P. nigrum* may also be helpful in treating vitiligo, although when combined with UV radiation should be staggered due to the effect of light on the compound [14].

52.4 TCM Applications and Dietary Usage

52.4.1 TCM Application

In traditional Chinese medicine, black pepper is considered to be pungent and hot. It is indicated for the Stomach and Large intestine meridians. Black pepper warms the stomach and spleen, disperses cold-stomach cold, and is used to treat vomiting, diarrhea, and abdominal pain due to cold invading the stomach. It is contraindicated when there is heat present due to Yin deficiency.

According to India Herbal Medicine (Ayurveda), *P. nigrum* possesses anti-tumourigenic, immunostimmulatory, stomachic, carminative, anticholestrolemic and again known for its strong phytochemical activities.

Like all eastern spices, *P. nigrum* was historically both a seasoning and a medicine. The pungency in *P. nigrum* is due to the piperine compound. *P. nigrum* have featured in traditional remedies in Ayurveda, Unani and Siddha medicine in India for centuries and in Jamu preparations in Indonesia. It has been prescribed for illnesses such as constipation, diarrhea, earache, gangrene, heart disease hernia, indigestion, insect bites, insomnia, joint pains, lung disease, liver problems, tooth decay and toothache. Various sources also recommend pepper to treat eye problems, often by applying salves or poultices made with pepper directly to the eye (From Edible Medicinal and Non-medicinal Plants-Volume 4, fruits).

52.4.2 Dietary Usage

P. nigrum is famous as the species king due to its pungent quality, which can be used for different purposes such as human dietaries, as medicines, as preservatives, as biocontrol agents.

Pepper oil is a "Charlie" of Revlon and "Posion" of Christian Dior. In the past, Egyptians used it in embalming mixture and also as an air-purifier. Its insecticide properties are also being exploited for household use and agriculture.

Once the peppercorns are dried, pepper spirit & oil can be extracted from the berries by crushing them. Pepper spirit is used in famous beverages like Coca-Cola and many medicinal and beauty products. Pepper oil is also used as ayurvedic massage oil and used in certain beauty and herbal treatments.

52.5 Clinical Evidences

In a clinical study of intestinal peristalsis in 16 healthy volunteers, consumption of 1.5 g of *P. nigrum* in capsules increased the orocecal transit time from 90 ± 51 min to 122 ± 88 min ($p = 0.09$) [15].

P. nigrum essential oil may be as effective as the alcohol extract in helping smokers quit. According to a study carried out in North Carolina, 48 cigarette smokers took part in a 3 h study during which they were not allowed to smoke and were instead given dummy cigarettes impregnated with *P. nigrum* extract, or with mint/menthol (placebo 1), or with nothing (placebo 2) [16]. Those who inhaled the *P. nigrum* reported that their craving for cigarettes was significantly reduced.

According to research by Ebihara et al. [17], Nasal inhalation of *P. nigrum* essential oil, which can activate the insular or orbitofrontal cortex, was found to improve the reflexive swallowing movement caused by dysphagia, which could be effective regardless of the individual patients level of consciousness or physical and mental status.

"Black pepper infused oil or ghee, applied into the nose, can be a wonderful decongestant to the sinuses blocked with Kapha or ama." In Ayurvedic medicine

black pepper, a pungent herb is used to treat the digestive, respiratory, circulatory and excretory channels. It is indicated for sluggish digestion, abdominal pain, toxins or ama and anorexia (appetite stimulant). For the lungs, *P. nigrum* is indicated for cold, wet, damp, Kapha conditions with white sticky mucus and a productive cough. It is used for asthma, bronchitis, pneumonia and sore throats. *P. nigrum* is also used to increase microcirculation in the capillaries and is indicated for skin diseases with signs of stagnant blood.

52.6 Safety Evaluation and Toxicity Data

P. nigrum is not a commonly allergenic food, is not included in the list of 20 foods that most frequently contain pesticide residues, and is also not known to contain goitrogens, oxalates, or purines. For people used to have flaring up of inner fire, manifesting red eyes, sore throat or thirst, pepper is contraindicated.

It was reported that piperine, the major active component of *P. nigrum*, is acutely toxic to mice, rats and hamsters. The LD50 values for a single i.v., i.p., s.c., i.g., and i.m. administration of piperine to adult male mice were 15.1, 43, 200, 330, and 400 mg/kg body wt, respectively. The i.p. LD50 value was increased to 60 mg/kg body wt in adult female and 132 mg/kg body wt in weanling male mice. In adult female rats, the i.p. LD50 value was 33.5 mg/kg body wt whereas the i.g. LD50 value was increased to 514 mg/kg body wt. Most animals given a lethal dose died of respiratory paralysis within 3–17 min. In subacute toxicity studies, the rats died within 1–3 days after treatment. Histopathologic changes included severe hemorrhagic necrosis and edema in gastrointestinal tract, urinary bladder and adrenal glands. Death of these animals may be attributable to multiple dysfunctions in their organs [18]. But, non-toxic *P. nigrum*, its oleoresin, or its active principle piperine fed to rats at doses 5–20 times normal human intake did not cause any adverse effect on.

Earlier studies indicated that no adverse effect was caused by feeding *P. nigrum* or piperine at levels equivalent to normal human intake or as much as 250 times as indicated by growth, organ weights, and blood constituents [19]. *P. nigrum*, its oleoresin, or its active principle piperine, fed to rats at doses 5–20 times normal human intake did not cause any adverse effect on growth, food efficiency ratio and organ weights, blood cell counts, and the levels of blood constituents like hemoglobin, total serum proteins, albumin, globulin, glucose and cholesterol, activities of serum aminotransferases and phosphatases, fat, and nitrogen balance [20]. The non-genotoxic nature of piperine was evidenced in latter studies using four different test systems, namely, Ames test using Salmonella typhimurium, micronucleus test, sperm shape abnormality test and dominant lethal test using Swiss albino mice [21]. In the Ames test, six different doses of piperine, in the range of 0.005–10 μ mol/plate, did not induce his + revertants, with or without metabolic activation, indicating its non-mutagenic nature. In the bone narrow micronucleus test using two doses (10 and 20 mg/kg body weight), piperine itself was non-mutagenic. Like in

somatic cells, piperine (10 and 50 mg/kg body weight) failed to induce mutations in male germ cells of mice as assessed by using the sperm shape abnormality and dominant lethal tests. Piperine thus appears to be a non-genotoxic chemical. The immuno-toxicological effects of piperine were investigated in Swiss mice, gavaged at a dose of 1.12, 2.25, or 4.5 mg/kg body weight for five consecutive days. All these dose levels had no overt toxic effect, while the lowest dose had no immunotoxic effect.

All in all, it seems that more likely than not, *P. nigrum* has positive health benefits. But before you start loading *P. nigrum* onto every single meal, realize that there are possible negatives, as well.

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Chapter 53
Prunella vulgaris L. 夏枯草 (Xiakucao, Common Selfheal)

Li-mei Lin, Hui-Min Gao and Jing-jing Zhu

53.1 Botanical Identity

Xiakucao is distributed chiefly in the temperate zone and tropical mountains of Europe and Asia. It is mainly found in Jiangsu, Anhui, Zhejiang and Henan provinces in China, usually on wasteland or the thick patches of grass at roadsides. The dried spica of Prunella vulgaris is used in traditional medicine.

The characteristics of the plant are as follows. Stems 20–30 cm, ascending, base much branched, purple-red, sparsely strigose or subglabrous. Petiole 0.7–2.5 cm, upper ones shorter; leaf blade lanceolate to ovate, glabrous to sparsely villous, base truncate to broadly cuneate-decurrent, margin undulate to entire, apex obtuse to rounded. Spikes 2–4 cm, sessile; floral leaves similar to cauline leaves, sessile or short petiolate, subovate; bracts purplish, broadly cordate, cuspidate, veins sparsely hispid. Calyx campanulate, sparsely hispid, tube ca. 4 mm; upper lip suboblate, subtruncate; lower lip narrower, teeth acuminate. Corolla purplish or white, slightly exserted, glabrous; tube ca. 7 mm, base ca. 1.5 mm wide, gradually dilated to ca. 4 mm wide at throat; upper lip subcircular, ca. 5.5 mm in diam., ± galeate, emarginate; lower lip ca. 1/2 as long as upper lip, middle lobe subobcordate, fringed; lateral lobes oblong, spreading, minute. Anterior stamens very long. Nutlets oblong-ovoid.

Xiakucao is collected when it looks brown-red, any foreign matter is removed, and the Xiakucao is dried. The raw material for medicine is clavate and slightly flat, light brown or reddish brown with 1.5–8 cm of length and 0.8–1.5 cm diameter. The ear is made of several or 10 rounds of persistent calyx and bracts, there are

L. Lin
School of Pharmacy, Hunan University of Chinese Medicine, Changsha 410208, China

H.-M. Gao · J. Zhu (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: zhujj15@163.com

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Fig. 53.1 The flowering plant (**a**) and crude drug (**b**) of Xiakucao

2 opposite bracts in each round. There are 3 flowers in each bract with 4 small nuts. The product is light and crisp with mild fragrance. The optimal product is purple brown with large spike (Fig. 53.1).

53.2 Chemical Constituents

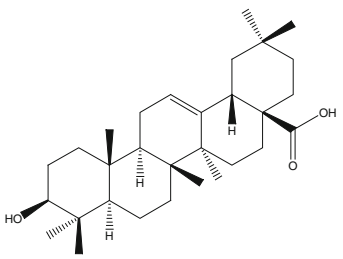
Xiakucao contains a variety of active chemical components, including triterpenoids, flavonoids, steroids and coumarins [1–3].

53.2.1 Triterpenoids and Their Saponins

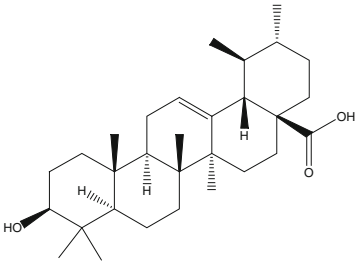
Oleanolic acid (1), ursolic acid (2), methyl oleanolate (3) and methyl ursolate (4) are the main pentacyclic triterpenoids [1–4]. Three mainly triterpenoid saponins, named prunelloside A (5), vulgarsaponin A (6) and vulgarsaponin B (7) are isolated from Xiakucao [5–9] (Fig. 53.2).

53.2.2 Flavonoids

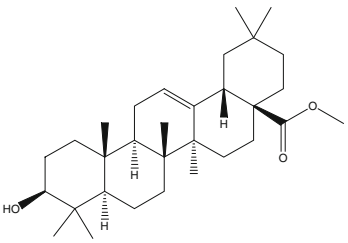
In addition to rutin, luteolin, homoorientin and luteolin are isolated from Xiakucao [5, 6].



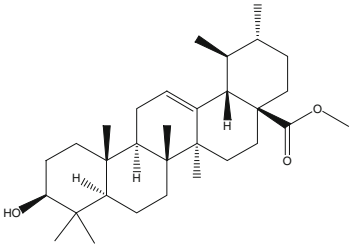
Oleanolic acid, 1



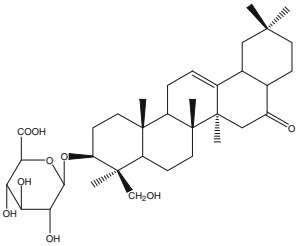
Ursolic acid, 2



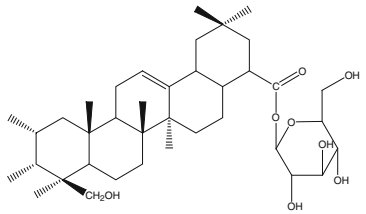
Methyl oleanolate, 3



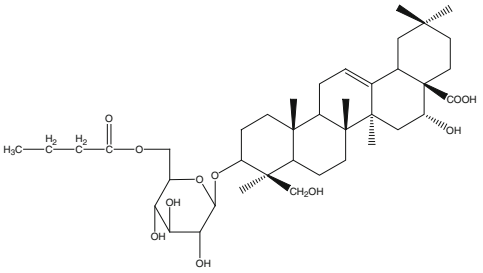
Methyl ursolate, 4



Prunelloside A, 5



Vulgarsaponin A, 6



Vulgarsaponin B, 7

Fig. 53.2 The structures of triterpenoids and their glycosides from Xiakucao

53.3 Pharmacological Studies

Xiakucao has exhibited properties of lowering blood sugar, cardioprotecting, antioxidant, antiviral, antibacterial, and anticancer activities. Thus it has a potential efficacy against various cardiovascular diseases, diabetes, HIV, cancer and other chronic illnesses. It has also been proven that Xiakucao possesses therapeutic effects including reduction of blood pressure, suppression of symptoms associated with type II diabetes and multiple sclerosis, inhibition of human immunodeficiency virus (HIV) replication, antipyretic, anti-inflammatory, antibacterial, antiasthmatic and analgesic effects, as well as use in prevention and treatment of cancer [10–15]. Current pharmacological research is focused on Xiakucao's cardiovascular protection and suppression of symptoms associated with type II diabetes.

53.4 TCM Applications and Dietary Usage

53.4.1 TCM Application

The action of Xiakucao is to quench Fire of the Liver and counteract inflammation of the eyes, reduce nodulation, and induce subsidence of swelling. It is mainly used for treatment of eye inflammation, ophthalmalgia at night, headache and dizziness; scrofula, goiter, mastitis with swelling and pain, hyperplasia of breast; and hypertension in Chinese medicine.

Xiasangju granule is a famous preparation in Southern China, composed of Xiakucao (fruit spike of *Prunella vulgaris*), Sangye (leaf of *Morus alba*) and Yejuhua (flower head of *Chrysanthemum indicum*), and used for clearing liver and improving vision, and clearing Heat and toxic material.

53.4.2 Dietary Usages

In China, Xiakucao has been used as food for nearly a thousand years. It was first recorded that Xiakucao was edible in *Materia Medica Yanyi*, an ancient medicinal material works in 1116. It recorded the primary leaves of Xiakucao should be soaked to remove the bitter taste and then cooked.

53.4.2.1 Xiakucao Teas

Xiakucao is used widely in herbal teas or beverages such as Wong Lo Kat, Xiasangju and Heqizheng, which can remove Heat and have a cooling effect.

53.4.2.2 Xiakucao Wine

The dried Xiakucao (500 g) is rehydrated with some boiled water, added to rice wine (1000 g) and steamed till no wine taste remains, then filtered. The filtered juice can clear heat, cool blood, stop bleeding and improve eyesight.

53.4.2.3 Xiakucao Foods

Cold dish of Xiakucao: Fresh tender stem and leaves of Xiakucao is put into boiling water, rapidly removed and cooled, then cut into segments. Salt, soy sauce and sesame oil are added and mixed well. The dish can make skin smooth and improve vision.

Rabbit meat stewed with Tufuling and Xiakucao: Tufuling (rhizome of *Smilax glabra* Roxb., 30 g), Xiakucao (fruit spike of *P. vulgaris* L., 45 g), Mizao (fruit of Ziziphus jujube Mill., 5 fruits), rabbit meat (400 g), pig bone (200 g) and ginger (3 pieces) are prepared. Both Tufuling and Xiakucao are washed and slightly immersed. Mizao without seed is soaked. The cracked pig bone and the clean rabbit meat were put into boiling water, and rapidly removed. These ingredients, together with soup condiments, are put into pot and added boiled water 1500 ml, and then stewed for 3 h. Salt is added before eating. The soup smells delicious and serves the functions of clearing Heat and removing Dampness, nourishing the Liver and detoxification. It is a beneficial soup in hot and humid weather for the people of all ages and both sexes.

Xiakucao Lean pork soup: Xiakucao (fruit spike of *P. vulgaris* L., 6–24 g) plus lean pork (30 g) are cooked. The meat and soup can be eaten to clear Heat and lower blood pressure. Normally it is effective to take twice or three times.

53.5 Clinical Evidences

Xiakucao is widely used for prevention of influenza, hypertension and summer heat in clinic. The preparations with single Xiakucao cream or oral solution were used for the treatment of hyperthyrea or goiter. Two case reports described the efficacy of Xiaokucao oral solution as an adjuvant drug [16, 17]. All patients were randomized into two groups. Group A treated by classical therapy, Group B by Xiakucao oral solution based on classical therapy. It is indicated that combined treatment of Chinese medicine (using Xiakucao oral solution) and Western medicine is superior to Western medicine alone in treating hyperthyrea or goiter with different states of thyroid function.

53.6 Safety Evaluations

Toxicity of Xiakucao in humans is very low. When it is over prescribed or inappropriately used, patients will suffer from diarrhea. Acute toxicity in mice is also low. The LD_{50} in adult mice by intragastric administration with crude Xiakucao extract was 21.5 g/kg (equivalent to 169.6 g/kg of Xiakucao); and when SD rats were administered by oral dose with 11.73 g/kg of Xiakucao extract (equivalent to 92.58 g/kg of Xiakucao) for 90 days, it was found there was not significant toxicity in the appearance of signs, feces and urine, body weight, food intake, blood morphological and biochemical indexes [18]. Although Xiakucao is a relatively safe herbal medicine often used as the food and tea, it is still strongly recommended to use it under the proper supervision.

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Chapter 54
Prunus armeniaca L. 苦杏仁 (Kuxingren, Apricot)

Feng Zhang, Yin Lu, Wenhui Qian and Zifan Pei

54.1 Botanical Identity

Kuxingren, the kernel or seed of Rosaceous plants, including *Prunus armeniaca* L. var. *ansu* Maxin., *Prunus sibirica* L., *Prunus armeniaca* L. or *Prunus mandshurica* (Maxim.) Koehne. The ripe fruit is usually harvested in summer; pulp removed and stone opened to obtain the kernel and dry it. Kuxingren is mainly produced in China's Inner Mongolia, Liaoning, Hebei, and Shandong provinces. The kernel, also called bitter apricot pit or bitter almond, is a flat heart-shaped seed with yellowish brown to dark brown surface; one end pointed, and the other end rounded and hypertrophy. The kernel has left-right asymmetry, while its tip side has a short-term form of hilum and the other round combined end is full of dark brown veins which point to the tip. The seed has a thin layer of skin, and is milky white and full of oil [1] (Fig. 54.1).

54.2 Chemical Constituents

The main chemical compositions of Kuxingren include cyanohydrin glycoside amygdalin (**1**) and volatile components such as linalool (**2**), β-ionone (**3**), γ-decanolactone (**4**), hexanal, (E)-2-hexenal, (E)-2-nonenal, (E)-2-noenal, terpineol, geraniol, and tetradecanoic acid. Eight fatty acids are found in Kuxingren, of which oleic acid (**5**), linoleic acid (**6**), and palmitic acid are the major ones. It also contains stearic acid, linoenic acid, tetradecanoic acid, palmitoleic acid and eicosenoec acid.

F. Zhang · Y. Lu (✉) · W. Qian · Z. Pei
Department of Pharmacology, Nanjing University of Chinese Medicine,
138 Xianlin Avenue, Nanjing 210023, Jiangsu, China
e-mail: luyingreen@126.com; nucmzf@163.com

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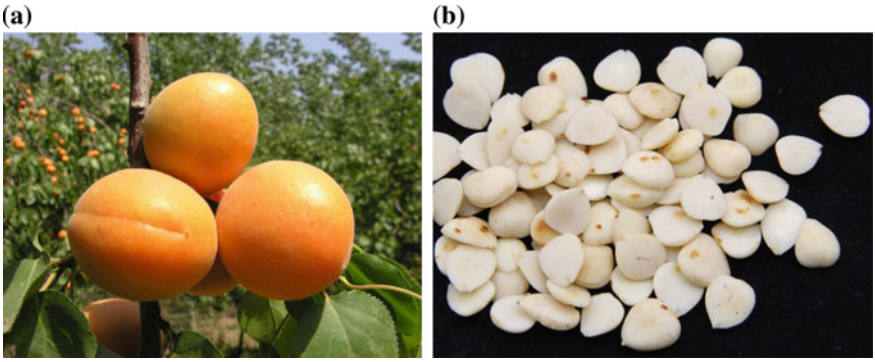

Fig. 54.1 The fruit-bearing apricot plant (**a**) and the crude drug (**b**) of Kuxingren

Furthermore, Kuxingren also contains proteins and amino acids, and glutamic acid is found as the most abundant amino acid [2]. Representative structures of these constituents are shown in Fig. 54.2.

54.3 Pharmacological Studies

Currently, most pharmacological studies on Kuxingren have focused on the biological activities of the characteristic cyanohydrin compound amygdalin. Studies showed that amygdalin could attenuate the development of atherosclerosis by suppressing inflammatory responses and promoting the immunomodulation function, and that the effects of amygdalin ultimately resulted in enlarged lumen area and loss of atherosclerotic plaque, indicating the therapeutic potential of amygdalin in management of atherosclerosis [3]. In a rat model of obstructive nephropathy, following ureteral obstruction, treatment with amygdalin immediately eliminated the accumulation of extracellular matrix in kidney tissue and alleviated the renal injury. Amygdalin attenuated kidney fibroblast activation and renal interstitial fibrosis in rats, suggesting that amygdalin could be a potent antifibrotic agent that may have therapeutic potential for patients with kidney fibrotic diseases [4]. Amygdalin has also been found to effectively alleviate responses to lipopolysaccharide treatment in RAW 264.7 cells and carrageenan-induced arthritis in rats, and could serve as an analgesic for relieving inflammatory pain [5]. Furthermore, many studies have shown that amygdalin had potent anti-tumor activities, for example, amygdalin administration inhibited the growth of HeLa cell xenografts through induction of apoptosis, suggesting that amygdalin may offer a new therapeutic option for patients with cervical cancer [6].

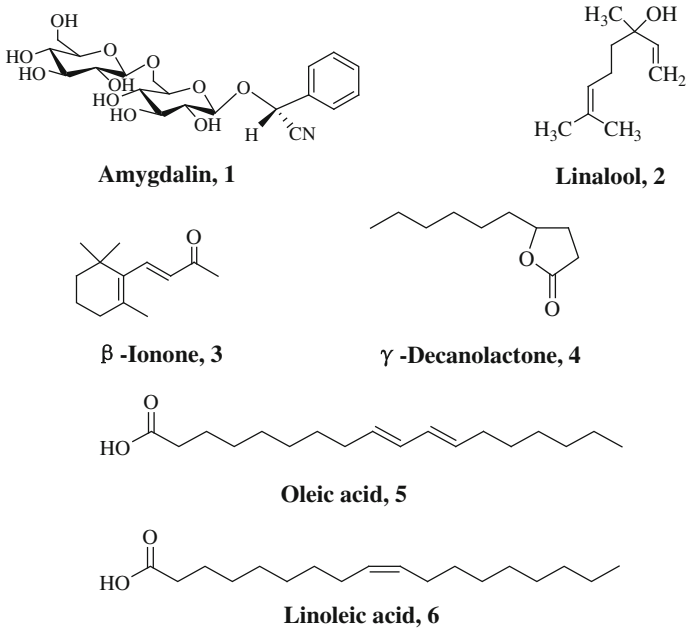

Fig. 54.2 Chemical structures of major constituents in Kuxingren

54.4 TCM Applications and Dietary Usage

54.4.1 TCM Applications

As well-documented in TCM literature, Kuxingren has the functions of removing phlegm, relieving asthma and arresting cough, and is clinically used for the treatment of respiratory diseases, cough and asthma [7]. It also has laxative effect, for example, it is used in combination with Mahuang (stem of *Ephedra sinica*) and Gancao (root and rhizome of *Glycyrrhiza uralensis*) to treat cold cough. Another formula "Sangju Yin" consisting of Kuxingren, Sangye (leaf of *Morus alba*) and Juhua (flower of *Chrysanthemum morifolium*), is applied for "wind-heat" cough. On the other hand, "Sangxing" decoction, which consists of Sangye (leaf of *Morus alba*), Zhebeimu (bulb of *Fritillaria thunbergii*) and Shashen (root of *Adenophora tetraphylla*), is used for the treatment of hot and dry cough. Kuxingren is applied in clinical treatment of postpartum constipation for the elderly.

54.4.2 Dietary Usages

Kuxingren is one of the most popular Chinese herbal medicines in clinical context, and is also widely applied in daily diet. The following dietary forms can be easily made at home.

54.4.2.1 Xingsu Cake

Take 15 g of Kuxingren, peel after soaking, then grind and press into powder. Add appropriate brown sugar and mix well, scatter this mixed powder on the surface of the pieces of dough. The cake is covered with fresh Zisuye (leaf of *Perilla frutescen*) and steamed. Cough can be relieved by taking the cake 1 or twice a day.

54.4.2.2 Honey and Almond Pellet

Prepare walnut (50 g), Kuxingren (50 g), ginger (50 g) and appropriate amount of honey. Soak the walnut and Kuxingren in water and then peel. Wash, chop and smash the ginger. Add some honey to the mixture, knead into pellets, and divide into 10 doses in total. It is used for the treatment of cough, asthma, physically weak and hyperactivity. Take it before sleeping.

54.4.2.3 Almond Sesame Powder

Pound or grind black sesame (50 g) and Kuxingren (50 g) into powder, then put them into 300 mL of water and bring to boil, and then add some sugar. It is used for senile constipation and is taken daily.

54.5 Clinical Evidence

Amygdalin is the main component of Kuxingren, and has been reported for its antitumor effect. In an early study, 178 patients with cancer were treated with amygdalin plus a "metabolic therapy" program consisting of diet, enzymes, and vitamins. The great majority of these patients were in good general health before treatment. None were totally disabled or in preterminal condition. One third had not received any chemotherapy previously. The pharmaceutical preparations of amygdalin, the dosage, and the schedule were representative of past and present Laetrile practice. No substantive benefit was observed in terms of cure, improvement or stabilization of cancer, improvement of symptoms related to cancer, or extension of life span. The hazards of amygdalin therapy were evidenced in several

patients by symptoms of cyanide toxicity or by blood cyanide levels approaching the lethal range. Patients exposed to this agent should be instructed about the danger of cyanide poisoning, and their blood cyanide levels should be carefully monitored [8].

54.6 Safety Evaluation and Toxicity Issues

Kuxingren has moderate toxicity, mainly due to the fact that amygdalin can decompose into hydrogen cyanide. Relatively large amount of hydrogen cyanide in medulla oblongata vital center would have an effect of excitement before paralysis, and can inhibit enzyme activity, hinder metabolism and then lead to tissue asphyxiation and poisoning. Therefore Kuxingren must be processed before it can be used. The common processing methods include raw processing, steaming, and freezing. Different processing methods have been shown to affect the acute toxicity of Kuxingren. Acute LD_{50} values of amygdalin in processed Kuxingren and steamed Kuxingren are 10.77 and 14.88 g/kg in mice, respectively [9].

Toxicological data showed that the acute LD_{50} value of amygdalin via intravenous injection was 25 g/kg in mice, and that the values were 25 g/kg via intravenous injection and 8 g/kg via intraperitoneal injection in rats. The maximal tolerance dose of amygdalin was 3 g/kg in mice, rabbits and dogs via intravenous injection or intramuscular injection. Oral administration with amygdalin seemed to produce more toxicity than intravenous injection, mainly due to the production of hydrocyanic acid via microbial hydrolysis in gut. If intestinal microflora was suppressed, amygdalin at 300 mg/kg did not result in death in mice, but without the inhibition of intestinal microflora, the death rate could be 60 % [10].

Although there have been a number of studies on pharmacological activities and toxicities on Kuxingren, further investigations are still needed to fully evaluate its potential health benefits and safety. Caution must be exercised when taking Kuxingren for food or medication.

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Chapter 55
Prunus mume (Sieb.) Sieb. et Zucc. 乌梅 (Wumei, Japanese Apricot)

Jianhui Liu and Fei Yin

55.1 Botanical Identity

Prunus mume originated in the south of mainland China around the Yangtze River and was later introduced to Japan, Korea, Taiwan and Vietnam. It can be found in sparse forests, stream sides, forested slopes along trails and mountains, sometimes at altitudes up to 1700–3100 m, and regions of cultivation [1].

Prunus mume is an Asian tree species classified in the Armeniaca section of the genus *Prunus*. Chinese plum and Japanese apricot are its common names. This distinct tree species has a relationship with both the plum and apricot trees. Although generally referred to as a plum in English, it is more closely related to the apricot [2].

Prunus mume is a deciduous tree that starts to flower in mid-winter, typically around January until late February in East Asia. It can grow to 4–10 m tall. The flowers have a strong fragrant scent with a size of 2–2.5 cm in diameter. They have various colors such as white, pink, and red. After the petals fall shortly the leaves appear that are oval-shaped with a pointed tip, and are 4–8 cm long and 2.5–5 cm wide. The fruit ripens in early summer, around June and July in East Asia, and coincides with the rainy season of East Asia, the *meiyu* (梅雨, literally "plum rain"). The drupe is 2–3 cm in diameter with a groove running from the stalk to the tip. The skin turns yellow, sometimes with a red blush, as it ripens, and the flesh becomes yellow. The tree is cultivated for its fruit and flowers.

J. Liu (✉) · F. Yin
College of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, China
e-mail: jhliu@cqut.edu.cn

J. Liu
Chongqing Technology and Business University, Chongqing, China

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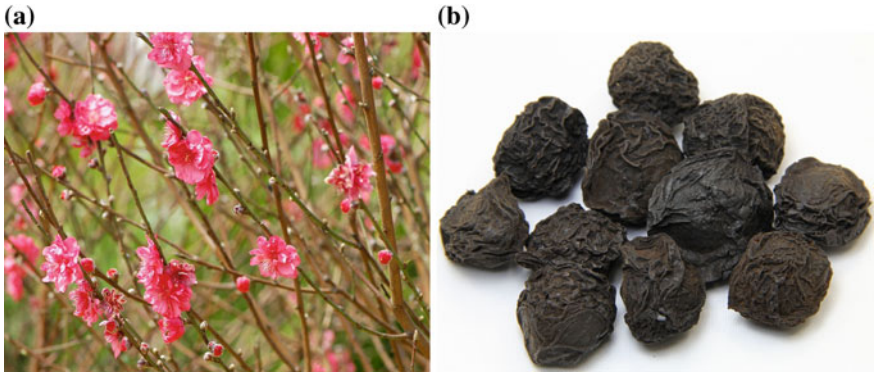


Fig. 55.1 Blossoming *Prunus mume* (**a**) and dried fruits used as crude drug (**b**)

The flower is known as the *meihua* (梅花) in Chinese, which came to be translated as "plum blossom" or sometimes as "flowering plum". The term "winter plum" may be used as well, specifically with regard to the depiction of the flower with its early blooming in Chinese painting (Fig. 55.1).

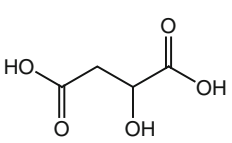
55.2 Chemical Constituents

55.2.1 Organic Acids

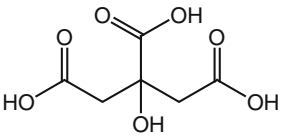
There are more than ten organic acids in *Prunus mume, such as* malic acid (1), citric acid (2), oxalic acid (3), glycolic acid (4), lactic acid (5), succinic acid (6), formic acid (7), acetic acid glacial (8) and propionic acid (9), etc. The major components of *Prunus mume* are citric acid and malic acid, which are used as standard compounds for evaluation of the quality of crude drug and relative pharmaceutical or natural health product preparations containing *Prunus mume* [3] (Fig. 55.2).

55.2.2 Terpenoid Compounds

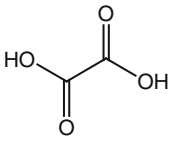
Terpenoids are an important class of bioactive components in *Prunus mume.* Stearate (10), arachidate (11), glycerylbehenate (12) and lignoceric acid methyl ester (13) have been isolated from it (Fig. 55.3).



Malic acid, 1



Citric acid, 2



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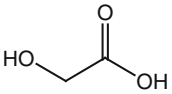

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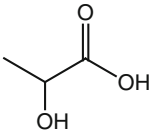
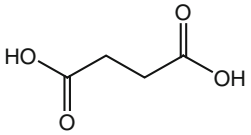
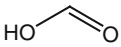


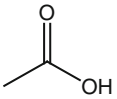
Lactic acid, 5



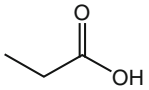
Succinic acid, 6



Formic acid, 7

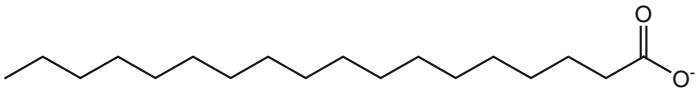


Acetic acid glacial, 8

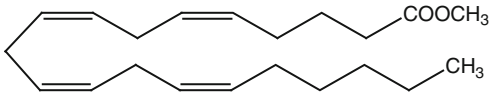


Propionic acid, 9

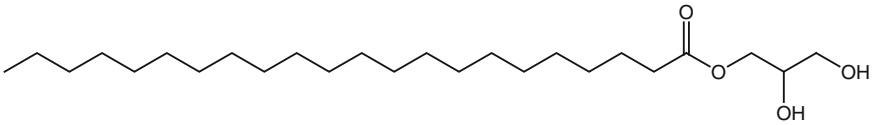
Fig. 55.2 The representative organic acids isolated from *Prunus mume*



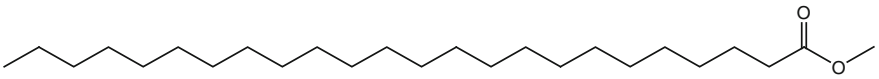
Stearate, 10



Methyl arachidate, 11



Glyceryl behenate, 12



Lignoceric acid methyl ester, 13

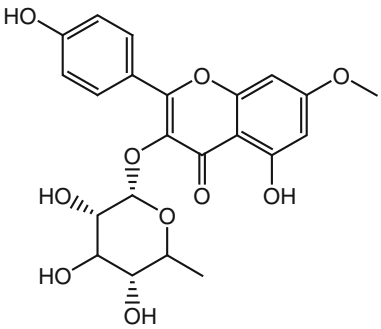
Fig. 55.3 The representative terpenoids isolated from *Prunus mume*

55.2.3 Flavonoids

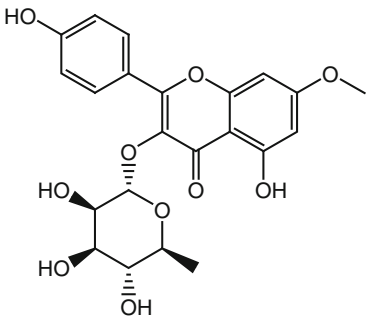
Some flavonoids have been isolated from *prunus mume*, which includes rhamnocitrin-3-O-rhamnoside (14), kaempferol-3-O-rhamnoside (15), rhamnetin-3-O-rhamnoside (16) and quercetin-3-rhamnoside (17) (Fig. 55.4).

55.2.4 Volatile Components

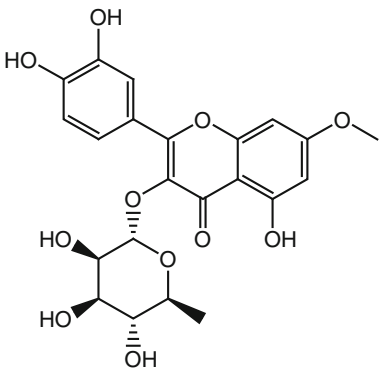
Volatile components are other class active compounds in *Prunus mume*. There are many compounds have been isolated and identified from it such as n-hexanal (18), trans-2-hexenal (19), n-hexanol (20), linalool (21), terpinen-4-ol (22), benzaldehyde (23), hexadecanoic acid (24), tetradecanoic acid (25), benzylalcohol (26) and some derivatives of 1-Naphthol (Fig. 55.5).



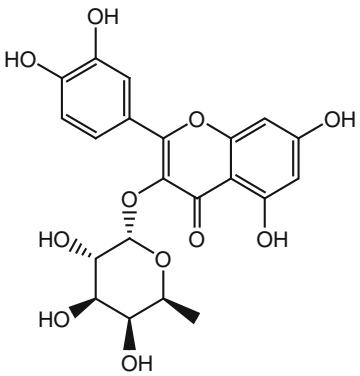
Rhamnocitrin-3-O-rhamnoside, 14



Kaempferol-3-O-rhamnoside, 15



Rhamnetin-3-O-rhamnoside, 16



Quercetin-3-rhamnoside, 17

Fig. 55.4 The representative flavonoids isolated from *Prunus mume*

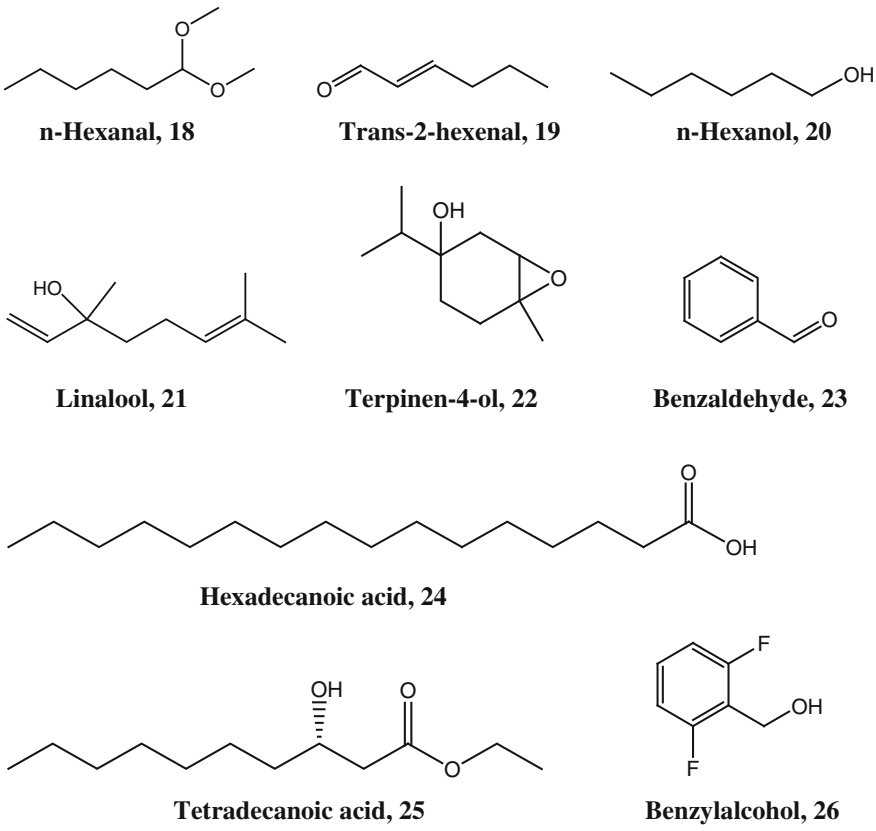


Fig. 55.5 The volatile components isolated from *Prunus mume*

55.3 Pharmacological Studies

55.3.1 Antibacterial Effects of Prunus mume

With a plaque reduction assay, it was showed that treatment of human influenza A viruses with the fruit-juice concentrate of Japanese plum (*Prunus mume* Sieb. et Zucc) had strong in vitro anti-influenza activity against human influenza A viruses before viral adsorption, but not after viral adsorption. And the 50 % inhibitory concentration (IC_{50}) values against A/PR/8/34 (H1N1) virus, A/Aichi/2/68 (H_3N_2) virus and A/Memphis/1/71 (H_3N_2) virus were 6.35 ± 0.17, 2.84 ± 1.98 and 0.53 ± 0.10 μg/ml, respectively. The plum-juice concentrate showed hemagglutination activity toward guinea pig erythrocytes. Its hemagglutination activity was inhibited by the monosaccharide N-acetylneuraminic acid and a sialoglycoprotein (fetuin), but not by the other tested monosaccharides including mannose, galactose, glucose and N-acetylglucosamine, suggesting the presence of a lectin-like molecule(s) in the Japanese plum-juice concentrate.

All these findings suggest that the fruit-juice concentrate of Japanese plum may prevent and reduce infection of human influenza A virus, possibly via inhibition of viral hemagglutinin attachment to host cell surfaces by its lectin-like activity [4]. Furthermore, *Prunus mume* extract showed antimicrobial effect on *S. mutants* biofilm on orthodontic bracket in vitro which may indicate its potential use as an oral antimicrobial agent for orthodontic patients [5].

55.3.2 Antitumor Activity of Prunus mume

MK615 is an extract from *Prunus mume*. At a neutral pH, it contains natural chemical substances such as triterpenoids that exert anti-neoplastic effects in several types of cancers. And malignant melanoma (MM) is characterized by rapid metastasis and a poor prognosis and an aggressive chemoresistant skin cancer. Matsushita et al. found that in patients with advanced MM, MK615 dramatically suppressed the in-transit metastasis of the disease. Pre- and post-treatment comparison of tumors showed that the apoptotic index was significantly increased by MK615. In vitro studies, MTT assay, flow cytometric cell cycle analysis and immunofluorescence microscopy revealed that MK615 could inhibit the growth of SK-MEL28 cells in a dose-dependent manner, increased the proportion of cells in sub-G1 phase and induced apoptosis. They further examined the expression of the receptor for advanced glycation end products (RAGE), which is a multi-ligand receptor that binds to a novel cytokine, high mobility group box protein 1 (HMGB1), as well as advanced glycation end products. There is evidence shows that RAGE/HMGB1 interaction enhances cell invasion in MM. Here, they indicated that MK615 inhibited the expression of RAGE in SK-MEL28 cells, and suppressed the release of HMGB1 by SK-MEL28 cells. All these findings suggest that MK615 may be a valuable tool for treating MM and other malignant tumors [6]. Moreover, MK615 has an anti-neoplastic effect against colon cancer cells. The effect may be exerted by induction of apoptosis and autophagy [7].

55.3.3 Anti-inflammatory Activity of Prunus mume

Maesil (*Prunus mume* Sieb. et Zucc.), is popularly used as a potential source of free radical scavengers and inhibitor of pro-inflammatory mediators in traditional Korean medical preparations as a remedy for skin disorders. Usually, the action of a probiotic fermented Maesil preparation on the development of atopic dermatitis (AD)-like skin lesions was determined with a NC/Nga mouse model, which was an initial step towards the development of a therapeutic feed supplement for use in dogs. Continuous ingestion of the experimental feed markedly inhibited the development of the AD-like skin lesions, because of the presence of a marked decrease in skin signs and reduced inflammation within the skin lesions. And the

anti-inflammatory efficacy was confirmed by significant decreases in eosinophil ratio and serum IgE concentration, and a reduction in the number of *Staphylococcus aureus* recovered from the ear. Furthermore, the relative mRNA expression levels of IL-4, interferon-gamma and tumor necrosis factor-alpha in the spleens of the experimental animals were also decreased and there was an increased serum concentration of IL-10 with a concurrent decrease in IL-4 concentration in comparison to a control group. Taken together, these results indicate that some component(s) of fermented Maesil have the ability to suppress the development of AD-like skin lesions, possibly by stimulation of IL-10. Beneficial effects of fermented Maesil may thus be expected in dogs with AD, although this and the nature of the active pathway remain to be clarified [8].

A large number of evidence shows that high mobility group box-1 protein (HMGB1), primarily from the nucleus, is released into the extracellular milieu either passively from necrotic cells or actively through secretion by monocytes/macrophages. And extracellular HMGB1 acts as a potent inflammatory agent by promoting the release of cytokines such as tumor necrosis factor (TNF)-alpha, has procoagulant activity, and is involved in death due to sepsis. Accordingly, HMGB1 is an appropriate therapeutic target for inflammation. An extract of *Prunus mume* strongly inhibited HMGB1 release from lipopolysaccharide (LPS)-stimulated macrophage-like RAW264.7 cells. Moreover, the inhibitory effect on HMGB1 release was potentiated by authentic oleanolic acid (OA), a naturally occurring triterpenoid. Similarly, the HMGB1 release inhibitor from *Prunus mume* extract was found to be OA. Regarding the mechanisms of the inhibition of HMGB1 release, the OA or *Prunus mume* extract was found to activate the transcription factor Nrf2, which binds to the antioxidative responsive element, and subsequently the hemeoxygenase (HO)-1 protein, was induced, indicating that the inhibition of HMGB1 release from LPS-stimulated RAW264.7 cells was mediated via the Nrf2/HO-1 system. These results suggested that natural sources of triterpenoids isolated from *Prunus mume* warrant further evaluation as 'rescue' therapeutics for sepsis and other potentially fatal systemic inflammatory disorders [9].

It was also reported that Japanese apricot had an inhibitory effect on Helicobacter pylori-related chronic gastritis [10], and (+)-syringaresinol from unripe Japanese apricot inhibited the motility of *Helicobacter pylori* [11].

55.3.4 Effect of Prunus mume *on Blood Fluidity*

The effects of food components on blood fluidity were studied by in vitro assay using a dedicated microchannel instrument for model capillaries. Chuda et al. found that the fruit-juice concentrate of the Japanese apricot (*Prunus mume* Sieb. et Zucc), a traditional Japanese food, markedly improved the fluidity of human blood. They identified that the active components are 1-[5-(2-formylfuryl)methyl] dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate (mumefural), and a related compound, 5-hydroxymethyl-2-furfural (HMF) [12].

55.3.5 *Effect of* Prunus mume *on Immune System*

Prunus mume has long been used as a traditional drug and healthy food in East Asian countries. It was showed that continuous ingestion of fermented *Prunus mume* with probiotics markedly increased the macrophage ratio in peripheral blood and the T lymphocyte ratio in the spleen. In addition, antibody production against formalin-killed *B. bronchiseptica* was also significantly increased in the mice fed fermented *Prunus mume* compared with the control group. The number of leukocytes was significantly higher in the bronchio-alveolar lavage obtained from the fermented *Prunus mume*-fed animals compared to it in the control group at day 3 (maximal peak time) after experimental *B. bronchiseptica* infection. Moreover, at 7 days post-infection, relative messenger RNA expression levels of tumor necrosis factor-alpha and interferon-gamma were significantly increased in splenocytes of mice fed fermented *Prunus mume* compared with those in the control group. Taken together, these findings suggest that feed containing fermented *Prunus mume* with probiotics enhances immune activity in mice, especially against *B. bronchiseptica*, via the potent stimulation of non-specific immune responses [13].

Furthermore, an oral administration of the ethanol extract of *Prunus mume* increased the interleukin (IL)-12p40 concentration in the serum and T-cell ratio in the spleen. In vitro studies revealed that the extract stimulated IL-12p70 production in peritoneal macrophages and natural killer activity. So, it is evident that the extract could enhance the immune function by stimulating innate immune cells [14].

55.3.6 *Anti-gout Effects of* Prunus mume

The fruit of the *Prunus mume* is used as a health food or medicinal material in traditional herb medicine for a long time in Eastern Asian countries. Yi et al. investigated the hypouricemic effect of the methanol extract from *Prunus mume* fruit (MPMF) in mice with potassium oxonate-induced hyperuremia. They demonstrated that hyperuricemic mice induced by potassium oxonate demonstrated an elevation in serum and liver uric acid levels (11.0 mg/dL and 0.52 mg/g tissue) and a reduction in urinary uric acid levels (49.9 mg/dL). Oral administration of 140 mg/kg MPMF for 7 days reversed the abnormalities in serum, liver and urinary uric acid levels (7.1 mg/dL, 0.37 mg/g tissue and 69.7 mg/dL, respectively). In addition, 70 and 140 mg/kg MPMF (3.1 and 2.9 nmol/min per mg protein) inhibited liver XO activity compared with hyperuricemic mice (3.9 nmol/min per mg protein). The results indicated that the beneficial hypouricaemic effect of MPMF may be mediated, at least in part, by inhibiting XO activity in the liver. This study suggests that *Prunus mume* and its extracts may have a considerable potential for development as an anti-gout agent for clinical application [15].

55.4 TCM Application and Dietary Usage

55.4.1 TCM Applications

Prunus mume is a common fruit in Asia and used in traditional Chinese medicine. It has long been used as a traditional drug and healthy food in East Asian countries. A recent study has indicated that *Prunus mume* extract is a potential candidate for developing an oral antimicrobial agent to control or prevent dental diseases, which was associated with several oral pathogenic bacteria [16]. Furthermore, *Prunus mume* extract may inhibit *Helicobacter pylori*, associated with gastritis and gastric ulcers [10, 11].

Experiments on endurance exercise training with rats suggested that *Prunus mume* extract enhanced the oxidative capacity of exercising skeletal muscle, and induced the muscle to prefer fatty acids for its fuel use rather than amino acids or carbohydrates, thus assisting endurance [17].

55.4.2 Dietary Usage [18]

The fruit of the tree is used in Chinese, Japanese and Korean cooking in juices, as a flavoring for alcohol, as a pickle and in sauces.

55.4.2.1 Juice

In mainland China and Taiwan, Suanmeitang (sour plum juice) is made from smoked plums, called Wumei. The *Prunus mume* juice is extracted by boiling smoked *Prunus mume* in water and sweetened with sugar to make Suanmeitang. It ranges from light pinkish-orange to purplish black in color and often has a smoky and slightly salty taste. It is traditionally flavored with sweet osmanthus flowers, and is enjoyed chilled, usually in summer. The juice produced in Japan and Korea, made from green plums, tastes sweet and tangy, and is considered a refreshing drink, also often enjoyed in the summer. In Korea, *Prunus mume* juice, which is marketed as a healthful tonic, is enjoying increasing popularity. It is commercially available in glass jars in sweetened, concentrated syrup form; it is reconstituted by stirring a small amount of syrup into a glass of water. The syrup may also be prepared at home by storing one part fresh plums in a container with one part sugar with no water.

55.4.2.2 Liquor

Plum liquor, also known as plum wine, is popular in Japan, Korea and China. Umeshu (sometimes translated as "plum wine") is a Japanese alcoholic drink made by steeping green plums in shōchū (clear liquor). It is sweet and smooth. A similar liquor in Korea, called maesilju, is marketed under various brand names, including Mae Hwa Su, Mae Chui Soon, and Seol Joong Mae. Both the Japanese and Korean varieties of plum liquor are available with whole plum fruits contained in the bottle.

In China, plum wine is called Meijiu. In Taiwan, a popular 1950s innovation over the Japanese-style plum wine is the Wumeijiu (smoked plum liquor), which is made by mixing *Prunus mume* liquor (méijǐu), *P. salicina* liquor (lǐjǐu), and oolong tea liquor.

55.4.2.3 Pickled and Preserved *Prunus mume*

In Chinese cuisine, *Prunus mume* pickled with vinegar and salt are called Suanmeizi (sour plum fruits), and have an intensely sour and salty flavor. They are generally made from unripe *Prunus mume* fruits. Huamei is Chinese preserved *Prunus mume* and refers to Chinese *Prunus mume* pickled in sugar, salt, and herbs. There are two general varieties: a dried variety, and a wet (pickled) variety.

Umeboshi are pickled and dried *Prunus mume* that are a Japanese specialty. Flavored with salt, they are quite salty and sour, and therefore eaten sparingly. They are often red in color when purple perilla leaves are used. *Prunus mume* used for making Umeboshi are harvested in late May or early June, while they are still green, and layered with salt. They are weighed down with a heavy stone (or some more modern implement) until late August. They are then dried in the sun on bamboo mats for several days. The flavonoid pigment in perilla leaves gives them their distinctive color and a richer flavor. Umeboshi are generally eaten with rice as part of a bento (boxed lunch), although they may also be used in makizushi (rolled sushi). Umeboshi are also used as a popular filling for rice balls wrapped in edible seaweed. Makizushi made with *Prunus mume* may be made with either Umeboshi or Bainiku (Umeboshi paste), often in conjunction with green perilla leaves. A byproduct of umeboshi production is umeboshi vinegar, a salty, sour condiment.

55.4.2.4 Sauce

A thick, sweet Chinese sauce called Meijiang or Meizijiang, usually translated as "plum sauce", is also made from *Prunus mume*, along with other ingredients such as sugar, vinegar, salt, ginger, chili, and garlic. Similar to duck sauce, it is used as a condiment for various Chinese dishes, including poultry dishes and egg rolls [19].

55.5 Clinical Evidences [20]

Prunus mume is a traditional Chinese medicine. Some biological activities of the fruit have been reported, for example, *Prunus mume* showed an inhibitory effect on *Helicobacter pylori*-related chronic gastritis, improvement on blood fluidity and inhibition on human influenza A virus infection, etc. In clinical, *Prunus mume* had been combined with Yinchen (Herb of *Artemisia scoparia*), Zhizi (fruit of *Gardenia jasminoides*), Chaihu (root of *Bupleurum chinense*), Zexie (tuber of *Alisma orientale*), Zhuling (sclerotium of *Polyporus umbellatus*), Zelan (herb of *Lycopus lucidus* var. *hirtus*), Yanhusuo (tuber of *Corydalis yanhusu*), Jiaosanxian (*Charred Triplet*), Chenpi (pericarp of *Citrus reticulata*), Chishao (root of *Paeonia lactiflora*) to treat chronichepatitis type B.

Prunus mume combined with Baishao (root of *Paeonia lactiflora*), Paojiang (processed rhizome of *Zingiber officinale*), Fangfeng (root of S*aposhnikovia divaricata*), Chenpi (pericarp of *Citrus reticulata*), Renshen (root of *Panax ginseng*), Zhigancao (processed root of *Glycyrrhiza uralensis*) had been decocted in water for oral dose to treat sensitive gastritis.

Prunus mume had also been used for the treatment of colorectal polyps, gallbladder polyps, polyp of vocal cord and nasal polyp in China.

Prumus mume, together with Ezhu (rhizome of *Curcuma phaeocaulis*), raw oysters, Tufuling (rhizome of *Smilax glabra*), Dihuang (root of *Rehmannia glutinosa*) had been decocted in water to treat psoriasis.

Prumus mume, together with Longgu (fossil fragments), Zhifuzi (processed daughter root of *Aconitum carmichaelii*), Xixin (root of *Asarum heterotropoides*), Rougui (bark of *Cinnamomum cassia*) had been decocted in water for oral dose to treat neurasthenia.

55.6 Safety Evaluation and Toxicity Issue

The ethanol extract of *Prunus mume* (EPM) from branches (with leaves) of *Prunus mume* containing a lot of polyphenol compounds could be used as a functional ingredient for antioxidant and antiobesity therapy. An EPM was prepared and evaluated for oral acute and subacute toxicity in Sprague-Dawley rats, while its mutagenic potential was assessed by a reverse mutation test using Salmonella typhimurium, by a bone marrow cell micronucleus test using ICR mice, and by a sperm abnormality test using ICR mice. The results showed no acute lethal effects at the maximal tested EPM dose of 20 g/kg in either rats or mice, suggesting that EPM can be regarded as virtually nontoxic. Administration at levels of 0.84, 1.67, and 3.33 g/kg to rats for 30 days did not induce any significant hematological, clinical, chemical, or histopathological changes. And no mutagenicity evidence was detected in any of the 3 mutagenic tests. The level of "no observed adverse effect" (NOAEL) for EPM was above 3.33 g/kg for the subacute toxicity study [21].

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Chapter 56
Rosa davurica Pall 刺玫果
(Cimeiguo, Dahurian Rose Fruit)

Min Fu and Yanze Liu

56.1 Botanical Identity

Dahurian rose fruit, called Cimeiguo in Chinese, is the fruit of *Rosa davurica Pall*. It belongs to the Rosaceae family. *R. davurica* is a deciduous wild rose growing to 1.5 m, which mainly grows in sunny places along forest edges, grassy hills, sea sides, and glades at altitudes from 400 to 2500 m. It is common in the provinces of Hebei, Heilongjiang, Jilin, Liaoning, Inner Mongolia, and Shanxi in China, and also in Korea and Siberia. The branches vary from purple to gray-brown and are densely reinforced. The unpaired pinnate leaves are fibrous, 4–10 cm long and consist of 7–9 leaflets with serrated edges. Fragrant pink flowers bloom from June to July, individually or in small bunches. The roses are fivefold, hermaphroditic, with a diameter of 3–4 cm. The fruits ripen from August to September, appearing bright red with elliptical rose hips with an average size of 15 mm.

The fruit, whether raw or cooked, has a sweet flavor but the flesh is fairly dry [1]. It contains about 2.8 % vitamin C by dry weight [2]. The dry fruit is about 13 mm in diameter, with a thin layer of flesh surrounding its seeds, which serve as a good source of vitamin E. It can be ground and mixed with flour or added to other foods as a supplement (Fig. 56.1).

M. Fu
McGill University, University Street, 3640, Montreal, QC H3A 2B2, Canada

Y. Liu (✉)
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, China
e-mail: yzliu@implad.ac.cn

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Fig. 56.1 Flowering plant (**a**) and dried fruits (**b**) of Dahurian rose

56.2 Chemical Constituents

56.2.1 Main Phytochemicals

Chemical constituents of *R. davurica* are flavonoids and tetracyclic triterpenes from the fruits and hydrolysable tannins from the roots [3–5]. These include tiliroside (**1**), casuarictin (**2**), agrimoniin (**3**), laevigatin B (**4**), davuriciin M/1, D/1, D/2, T/1, oleanolic acid (**5**), ursolic acid (**6**), leucoanthocyanidin, anthocyanindin and catechin, ethyl beta-fructopyranoside and methyl 3-O-beta-glucopyranosyl-gallate. Hydrolysable tannins include 1,2,3,6-tetra-O-galloyl-β-D-glucose, 1,2,4,6-tetra-O-galloyl-β-D-glucose, 1,2,3,4,6-penta-O-galloyl-β-D-glucose (5GG, **7**). New constitutes were later isolated and identified as ethyl beta-fructopyranoside and methyl 3-O-beta-glucopyranosyl-gallate [6].

56.2.2 Other Phytochemicals

The rest of the chemical composition of the Dahurian rose includes organic acids, sugars, pectin, vitamin C, carotenoid, mineral and trace elements calcium, magnesium and fluoride, and proteins (Fig. 56.2).

56.3 Pharmacological Studies

56.3.1 Antiaging Effects

Rosa davurica Pall powder can improve the superoxide dismutase (SOD) activity in cultured human lymphocytes and in sheep erythrocyte. When tested in rat serum (added with 1 % powder), the maximum and average lifespan of Drosophila was

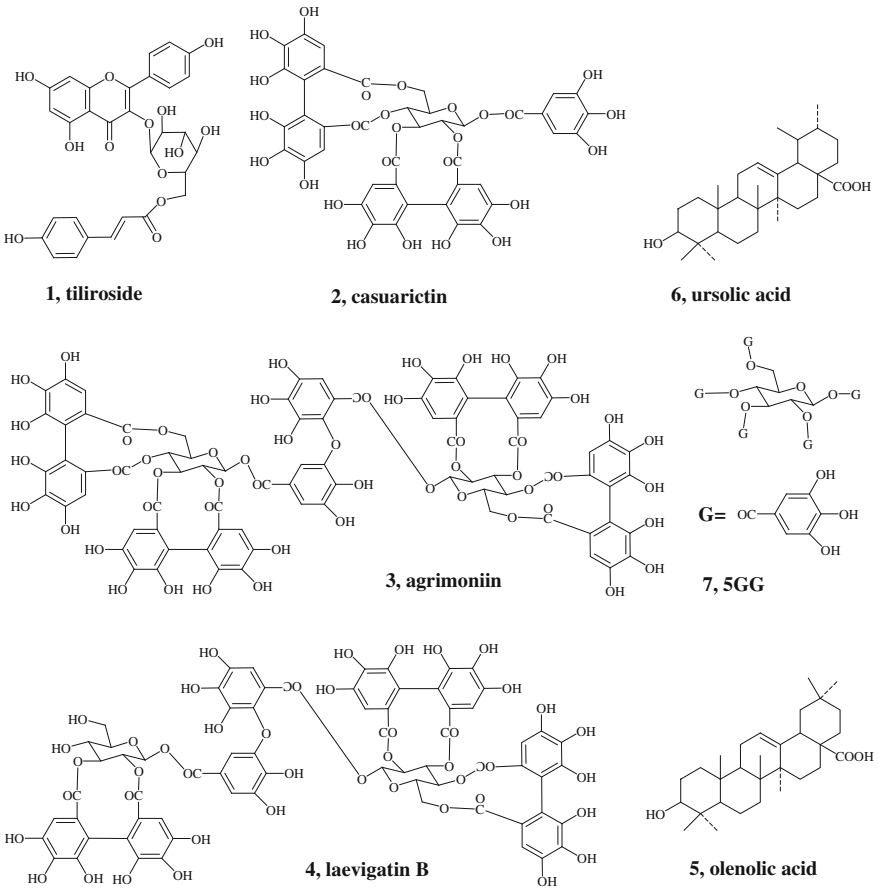

Fig. 56.2 Structures of major compounds isolated from *Rosa davurica* Pall

significantly prolonged and the lipid peroxide (LPO) content in the serum decreased [7]. The sleep, appetite, energy, and physical strength was improved with Dahurian rose fruit extract treatment. Dahurian rose fruit can also improve intelligence, especially problem-solving and memory abilities, along with improving the extrapyramidal symptom significantly [8].

56.3.2 Anti-cancer Effects and Anti-inflammatory Effects

Rosa davurica Pall has traditionally been used to treat inflammatory diseases and tumors. The leaves of *R. davurica* possess anti-angiogenic and related anti-inflammatory and anti-nociceptive qualities, which can provide some therapeutic support for its traditional use [9]. Ethanol extract of Dahurian rose fruit has also

been proven to block the synthesis of dimethylnitrosamine (DMN), which is particularly toxic to the liver. In addition, by enhancing the free radical scavenging ability of the immune system, it can resist the urethane-induced lung adenomas when tested on mice. When tested on cancer mice, the effects of the ethanol extract of Dahurian rose fruit on the activity of superoxide dismutases (SOD) and glutathione peroxidase (GSH-Px) suggested that it can potentially be used as an agent of tumor chemotherapy and a radiotherapy agent [10]. Other experiments showed that Dahurian rose fruit induces the tumor-bearing mice's T lymphocyte subsets, increases T cell number, and T/H/Ts ratio, while decreasing T inhibition (T/s) cell number, proving its positive role on humoral immunity [11].

56.3.3 Effect on Cardiovascular System

Injection of 1 ml Dahurian rose fruit alcohol extract could induce the relaxation of rat aortic strips, lower blood-pressure, reduce cerebral and coronary vascular resistance, and increase coronary blood flow [12]. When given to rabbits, it inhibits free atrial contraction, slows the heart rate, and inhibits the posterior pituitary hormone, and induces myocardial ischemia during S-T period. It also has effect on the inhibition of rabbit platelet gathering and thrombosis via its effective flavone compounds. In mice it showed inhibition of mouse normobaric hypoxia and isoproterenol induced hypoxia effects [13].

56.3.4 Hepatoprotective Effect

Dahurian rose fruit can reduce liver damage induced by carbon tetrachloride, ethanol, and nitrite rubber. It can also decrease the alteration of human serum alanine aminotransferase (ALT) and turbidity abnormalities, reduce and eliminate the degeneration and necrosis of liver cells, reduce inflammation and fibrosis, and improve the hepatoprotective effect of oleanolic acid [14]. Dahurian rose fruit could decrease the contents of malondialdehyde (MDA) of liver and red blood cells. Administration of this extraction successively for six days can augment the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) [15]. *Rosa davurica* Pall fruit can also significantly prevent lipid peroxidation [16].

56.3.5 Anti-fatigue and Anti-hypoxia Effect

A peritoneal injection of 0.5 ml of Dahurian rose fruit extract in mice showed that the hypoxia tolerance survival time was significantly higher than that in the control group [7]. In the behavioral despair test, the swimming time was significantly higher than that of the control group [17].

56.3.6 Other Effects

Compound *Rosa davurica* formula showed anti-diabetic effects in the streptozotocin-induced diabetic rats, which is a composition of *Alnus hirsuta*, *Rosa davurica*, *Acanthopanax senticosus*, and *Panax ginseng* [18].

56.4 TCM Applications and Dietary Usage

56.4.1 Traditional Chinese Treatment

Rosa davurica has been used in traditional Chinese medicine for the treatment of dyspepsia, gastroenterologia, and menoxenia with a long history. It is also being used to treat astringing lung, indigestion, anorexia, abdomen distending pain, diarrhea, menstruation, dysmenorrhea, atherosclerosis, and tuberculosis cough.

56.4.2 TCM Application

1. Orally taken decoction, 6–10 g.
2. 3 g of Dahurian rose fruit, 2 g of tea, serve with boiling water to treat irregular menstruation, vaginal discharge, diarrhea, mastitis, and swelling due to poison.
3. 3–5 g of processed buds in boiling water for 5 min, sugar or honey can be added, or mixed with brew tea together, which can be used for ration of qi and blood, liver stagnation, anti-lipid diet, skin beauty and so on. Especially useful for menstrual pain and irregular menstruation.
4. In addition to the extraction of rose oil, the stem, buds, and roots can be also used as medicine. The fruit is rich in vitamins, and can be used for natural beverages and food. Roses can be used for rose wine, rose dew, and rose sauce. It is also widely used in cosmetics and beauty care products.
5. Folk usage: 100 g of roses added to about 500 g of water, boiled for 20 min, filtered flower residue, and then add 500–1000 g of brown sugar, boiled to a paste, which can replenish blood and qi, and nourish the face and body. For long-term use, put in the refrigerator.

56.5 Side Effects and Toxicity

The toxicity test showed that in the mouse intravenous injection of water and alcohol, plus extracts of *R. davurica* fruit, the LD_{50} are 4–5 and 4.3–5.8 g/kg, respectively. For mouse intravenous injection of flavones from Dahurian rose fruit,

the LD_{50} is 872–1048 mg/kg. The subacute toxicity test showed no toxicity reaction to heart, liver, kidney, spleen, stomach, or bladder.

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Chapter 57
Rosa laevigata Michx. 金樱子 (Jinyingzi, Cherokee Rose)

Xiaozhe Zhang

57.1 Botanical Identity

Rosa laevigata Michx, or the Cherokee rose in English, is an evergreen climbing shrub, belonging to the Rosaceae family [1]. The plant can grow up to 5 m in height. *R. laevigata* Michx is normally distrubted at an altitude of 200–1600 m, prefering places like sunny mountains, fields, and riverbanks. It is found most ofen in parts of southern China like Jiangxi, Jiangsu, Guangdong, Guangxi, Zhejiang, Anhui, and Hunan provinces. Its stems have barb-like prickles and bristle and it has a pinnately compound leaf with petioles and rachis that also have prickles and bristles. The stipules are lanceolate, caducous and are separated by petiole. The leaflets are leathery, glabrous, shiny, elliptic-ovate or lanceolate-ovate, and are commonly 2.5–7 cm long, and 1.5–4.5 cm wide. The leaflets have an acute or acuminate apex, rounded base, and denticulate margin. Its flowers solitarily grow on the top of lateral branches. The Cherokee rose's pedicel and calyx are densely covered with setae, while the fruits are developed from the receptacle fake fruit, which has obovate shape with a diameter of 2.5–4 cm length and 1–1.5 cm width. The pericarp has a thickness of about 1.5–2 mm, and appears from redish-yellow to reddish brown in colouring. The inner surface has a yellow, dense consistency and contains the majority of its small achenes.

Rosa laevigata Michx has long been used as herbal medicine for the treatment of a variety diseases. Traditionally, the raw material of this herb came from scavenging in the wild. It is processed into dry fruits (the crude drug, called Jingyingzi in Chinese), tea or wine for clinical usage or dietary supplement. With the increasing commercial demand for this herb, cultured plants have become an important source of supply [2]. The flowering plant (a) of *R. laevigata* Michx and commercial Jinyingzi as a crude drug (b) are shown in Fig. 57.1.

X. Zhang (✉)
Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China
e-mail: xiaozhe.zhang@unifr.ch

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Fig. 57.1 Flowering plant (**a**) and crude drug (**b**) of *R. laevigata* Michx

57.2 Chemical Constituents

Tannins and related polyphenols are abundent in the fruits of *R. laevigata Michx*. Flavonoids, triterpenes, and polysaccharides are also the major classes of bioactive compounds found in *R. laevigata Michx*.

57.2.1 Tannins and Related Polyphenols

Hydrolysable tannins and related polyphenols have been extensively investigated in the fruits of *R. laevigata Michx*. In total, more than 30 kinds of compounds, such as sanguiin H-4 [3], casuarictin [3], potentillin [3], agrimoniin [3], and laevigatin A-G [4], have been identified. Figure 57.2 shows the structures of representative tannins from the fruits of *R. laevigata Michx*.

57.2.2 Flavonoids

The pulp of *R. laevigata Michx* contains high levels of flavonoids. The total number reached to near 6.5 % when *R. laevigata Michx* was extracted using microwave techniques [5], while the content of total flavonoids reached around 15.4 % of the fruits when extracted using 70 % ethanol [6]. Despite the difference caused by the extraction methods, these studies clearly demonstate the high abundance of flavonoids in *R. laevigata Michx*.

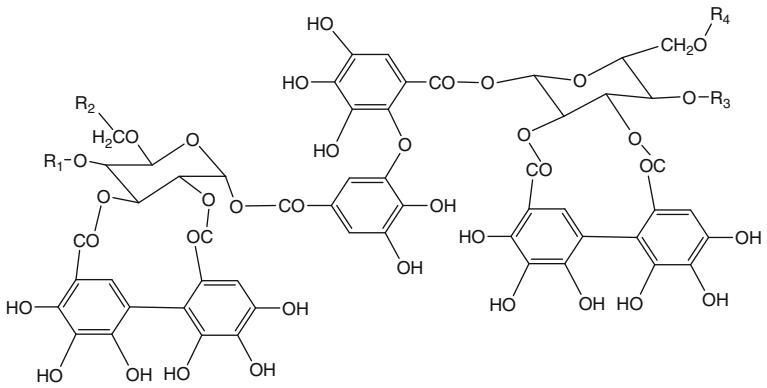

Fig. 57.2 Structures of representative tannins from the fruits of *R. laevigata Michx*. *Agrimoniin* R_1, R_3 = (S)-HHDP (hexahydroxydiphenyl); R_2, R_4 = H; *Laevigatin B* R_1, R_2, R_4 = H, R_3 = HHDP; *Laevigatin E* R_1, R_2, R_3, R_4 = H

57.2.3 Triterpenoids

A diversity of triterpenoids and their derivates have been identified from *R. laevigata Michx*. These compounds are classified into three classes: oleanane, ursane, and lupa. They include but are not limited to: ursolic acid, pomolic acid, oleanolic acid, maslinic acid, 2α,3α-dihydroxyurs-12-en-28-oic acid, euscaphic acid, 2α,3β,19α-trihydroxyurs-12-en-28-oic acid, 2α,3α,23-trihydroxyurs-12-en-28-oic acid, 2α,3β,23-trihydroxyurs-12,18-dien-28-oic acid, 2α,19α-dihydroxy-3-oxo-urs-12-en-28-oic acid, 2α,3β,19γ,23-tetrahydroxyurs-12-en-28-oic acid, 19α-hydroxyasiatic acid, tormentic acid-28-O-β-D-glucopyranoside, 19α-hydroxyasiatic acid-28-O-β-D-glucopyranoside, 2α,3α-dihydroxyolean-12-en-28-oic acid, 2α,3α,23-trihydroxyolean-12-en-28-oic acid, 2α,3β-dihydroxylup-20(29)-en-28-oic acid, 2α,3β,23-trihydroxylup-20(29)-en-28-oic acid, 2α,3β,23-trihydroxy-19-oxo-18, 19-seco-12, 17-dien-28-norursane, 2α,3β,23-trihydroxy-12, 17-dien-28-norursane, 2α,3α,23-trihydroxy-19-oxo-18, 19-seco-urs-11, 13(18)-dien-28-oic acid, 3β-[(α-L-arabinopyranosyl)oxy]-20β-hydroxyursan-28-oic acid δ-lactone, 2α,3β-dihydroxyolean-13(18)-en-28-oic acid, 2α,3α,19α,23-tetrahydroxyolean-12-en-28-oic acid [7–12].

57.2.4 Polysaccharides

R. laevigata contains abundant quantities of polysaccharides, which are mainly composed of glucose, mannose, galactose, rhamnose, arabinose, and xylose [13]. So far five polysaccharides [13, 14] with the molecular weights of 8000–23,000 Da have been isolated.

57.2.5 Other Compounds

Other bioactive compounds such as steroidal compounds, phenylpropanoids, and lactones were found in *R. laevigata Michx*. In addition, *R. laevigata Michx* contains abundant vitamins, amino acids, inorganic salts, and trace elements, which can enhance human hematopoietic function and a variety of enzyme activity, and can also prevent cell aging [15].

57.3 Pharmacological Studies

As a class of bioactive ingredients in *R. laevigata Michx,* polysaccharides are able to improve and restore immune function, encourage anti-stress, anti-tumor, anti-aging, anti-ischemic, and other biological activities [15]. Flavonoids possess hypoglycemic, lipid-lowering, anti-arrhythmic, and anti-oxidation effects. Flavonoids from *R. laevigata* showed a strong antioxidant capacity. Triterpenoids and their derivatives can lower blood cholesterol, triglycerides, lipoprotein, and can inhibit platelet aggregation, help blood circulation, eliminate thrombosis, increase metabolism and permit the body to achieve a balanced and healthy condition.

57.4 TCM Applications and Dietary Usage

57.4.1 TCM Applications

Jinyingzi is considered in TCM as a “sour and pucker” herb that can treat improper emission raised from some organs. It has been used in clinics for tuning kidney functions and preventing spermatorrhea. It can also treat sustained diarrhea caused by spleen deficiency, cough caused by lung deficiency, as well as spontaneous nightly sweat. To strengthen such effects, Jinyingzi is commonly used in combination with other herbs in TCM.

57.4.2 Dietary Usages

Jinyingzi is a valuable dietary botanical material because of its bioactive functions and low associated risks. It has been processed into different style products, such as wine and juice. The following dietary forms can be even made at home.

57.4.2.1 Wine

Jinyingzi can be used to prepare wine. As direct fermentation could generate methanol due to abundant pectin, Jinyingzi alone is not used to prepare wine. Alternatively, Jinyingzi is used to prepare fruit wine. It is also used to produce tonic wine with other Chinese herbs to treat various diseases.

57.4.2.2 Juice

Jinyingzi is rich in sugar, citric acid, malic acid, saponins, tannins, resins, mineral elements, sugar, vitamin C, zinc, and selenium. This property renders Jinyingzi as an attractive material for juices with high energy and nutrition. It alone or combined with other fruits such as kiwi is good material for preparation of tonic juice.

57.4.2.3 Natural Colorant

Brown pigment extracted from Jinyingzi is sweet, odorless, and water-soluble material. The pigment exhibits good resistance to heat, light, oxidation and reduction. The color of its aqueous solution tenders yellow in weak acidic conditions and reddish brown in weak basic conditions. As natural colorant, pigment extracted from Jinyingzi is suited for color wine or acidic beverages.

57.5 Clinical Evidence

Clinical evidence showed that Jinyingzi is efficient for treatment of diarrhea [16, 17]. In a clinical trial, Jinyingzi in combination with Acera was used to treat chronic intractable diarrhea [17]. Patients were randomly divided into observation groups that received Jingyingzi-Acera extracts, and a control group to consolidate their intestines. The treatment took 7 days. The results showed that the total effective rate of Jingyingzi-Acera extracts was 94.00 %, higher than the effective rate of 68.00 % observed in the control group. This study indicated that Jinyingzi was worthy of clinical application for its treatment of diarrhea. In addition to treat diarrhea, Jingyingzi, used alone or combined with other herbs, also showed positive effect in the treatment of diverse disorders such as urinary frequency, uterine prolapse, and spleen discomfort [18].

57.6 Safety Evaluation and Toxicity Data

In a previous study on the mutagenic effects, it was proven that the Jinyingzi in doses of 1.25, 2.5, 5.0, and 10.0 k/kg had neither influence on bone marrow micronucleus nor sperm abnormality, nor influence on the induction of mouse germ cells (UDS) [19]. In acute and sub-acute testes, its polyhydroxy pigments caused slower growth in body mass, an increase in the number of white cells and a decrease in the number of red blood cells. However, serum glutamic pyruvic transaminase (SGPT), serum uric acid, and other non-protein nitrogen (NPN) content had no significant changse [20]. Other organs, such as heart, liver, kidney, spleen, intestine, and gland showed no lesions. The sub-acute toxicity investigation indicated that total flavonoids were safe even when the dose reached to 500 mg/kg. Taken together, the toxicity studies showed that *R. laevigata Michx* is a non-toxic and safe Chinese herb.

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Chapter 58
Rubus chingii 覆盆子 (Fupenzi, Immature Raspberry Fruit)

Tongxiang Liu, Shengyu Hua and Zongwei Wang

58.1 Botanical Identity

Fupenzi (Fructus Rubi) is the dried fruit of the perennial woody plant *Rubus chingii* Hu., which belongs to the family of Rosaceae. It was first listed in Mingyi Bielu (Miscellaneous Records of Famous physicians) as the material of traditional Chinese medicine (TCM). In Shennong's Herbal Classic (Shennong Bencao Jing), it was named Fupen, which is based on its function of nourishing kidney and improving the function of urine control. Hence, the name Fupen in which Fu means covering and Pen means bed pan. The main producing region of this plant is southeast China which includes places such as Zhejiang and Fujian provinces. [1, 2]. The fruit is harvested in the early summer when the fruit color changes from green to yellow. It is dipped into boiling water or steamed slightly, and then dried before being stored in either a dry container or a cool storehouse. The fruiting plant and dry material as a crude drug is shown in Fig. 58.1.

Rubus chingii is a lianoid shrub which is typically 1.5–3 m tall. Branchlets are green when young becoming reddish brown with age. The plant is cylindrical, slender, and glabrous, with sparse prickles 5–6 mm and a glaucous bloom. Leaves are simple with petioles that are green and measuring 2–4 cm. The leaves are slightly pubescent or glabrous with 5–6 mm sparse prickles. There is inflorescences terminal on short branchlets. Pedicels are 2–4 cm and usually glabrous. Flowers are 2.5–5 cm in diameter. The aggregate fruits are composed of many drupelets.

T. Liu
Institute of Chinese Minority Traditional Medicine, Minzu University of China, Beijing 100081, China

S. Hua
Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China

Z. Wang (✉)
Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
e-mail: zwang0@mgh.harvard.edu

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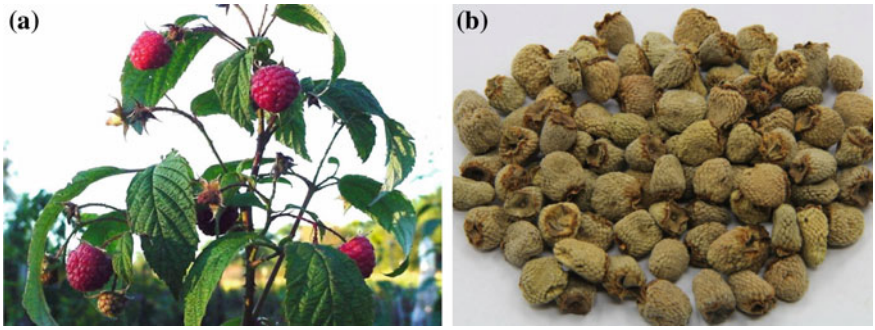


Fig. 58.1 The fruiting plant (**a**) and dry material as crude drug (**b**) of Fupenzi

The fruits are conical or flat conical in shape. Their measurements range from 0.6–1.3 cm in height and 0.5–1.2 cm in diameter. The surface is yellow-green or light brown, with obtuse top and a center-recessed base. Persistent calyx is tan in color and with fruit stem mark below. Drupelets are easy to peel off. Each drupelet is half-moon-shaped, with densely fuzz covered back, clearly textured flanks, and ridged abdomen. The dry fruit is lightweight, hard, and has a light acerb taste.

58.2 Chemical Constituents

The major bioactive compounds of *R. chingii* include diterpenes, triterpenes, triterpene acids, phenolics and flavonoids, as shown in Fig. 58.2. Also, it has steroids, alkaloids, β-sitosterol, and Fupenzic acid in its makeup. In addition, Fupenzi contains organic acids, sugar, and vitamin C [3, 4].

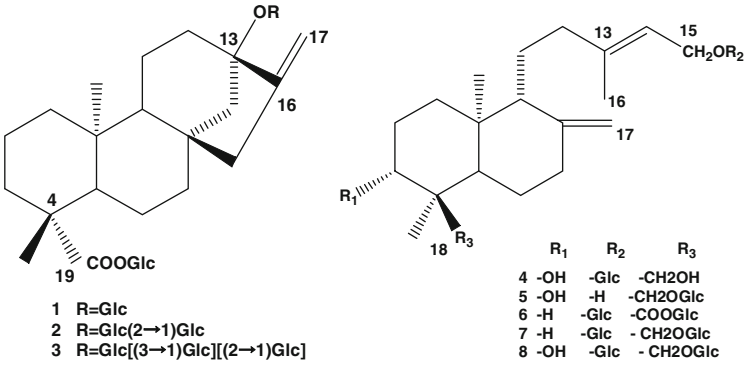


Fig. 58.2 Diterpene glycoside from leaves of Chinese *R. chingii*

58.2.1 Diterpenes

Five ent-labdane type diterpene glucosides F1, F2, F3, F4 and F5 (compound **4**–**8**), were isolated from the leaf of Japanese *R. chingii* [5].

58.2.2 Triterpenoids

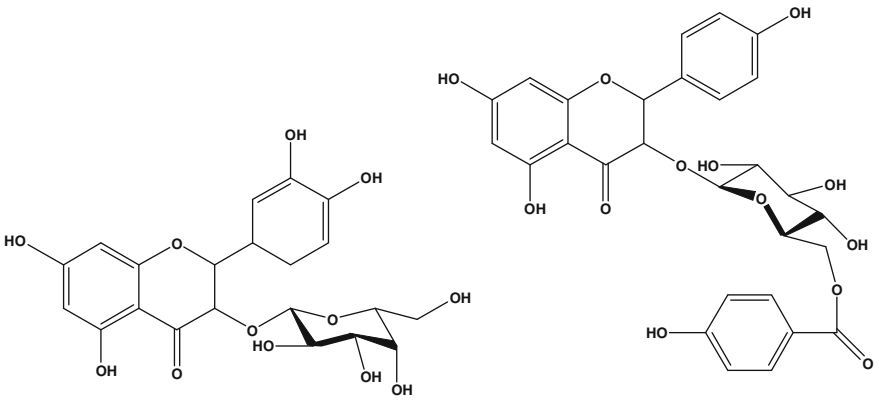
Fourteen triterpenoids have been isolated from the fruits and leaves of *R. chingii* [6, 7].

58.2.3 Flavonoids

Sixteen flavonoids have been isolated from the fruits and leaves of *R. chingii* [8–10]. Hyperoside (quercetin-3-O-galactoside) and tiliroside, two flavonoids, might be developed to provide a firm basis for the quality control of Fupenzi [11] (Fig. 58.3).

58.2.4 Steroids

Steroids isolated from *R. chingii* include β-sitosterol [12], daucosterol [13], beans-4-ene-3β, 6a-diol [14], stigmast-5-en-3-ol, and oleate [15].



Hyperoside **Tiliroside**

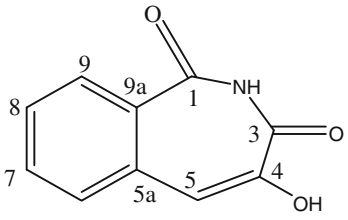
Fig. 58.3 Representative flavonoids isolated from Fupenzi. Hyperoside; Tiliroside

58.2.5 Alkaloids

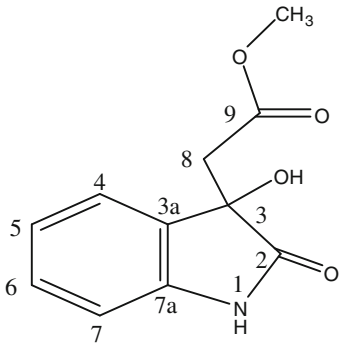
Eight quinoline, isoquinoline, and indole alkaloids have been separated from *R. chingii*. They are as follows: 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid, methyl 1-oxo-1,2-dihydroisoquinoline-4-carboxylate, 1-oxo-1,2-dihydroisoquinoline- 4-carboxylic acid, 2-hydroxyquinoline-4-carboxylic acid, rubusine, methyl (3-hydroxy-2-oxo-2,3-dihydroindol-3-yl) acetate, methyldioxindole-3 acetate, and 2-oxo-1,2-dihydroquinoline-4-carboxylic acid [10]. Rubusine is a new alkaloid compound which was discovered recently (Fig. 58.4).

58.2.6 Organic Acids

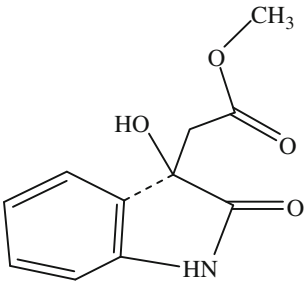
Organic acids isolated from *R. chingii* include the following: oleanic acid, ursolic acid, maslinic acid, alpha-hydroxyursolic acid, arjunic acid, stearic acid, and lacceroic acid [3] (Fig. 58.5).



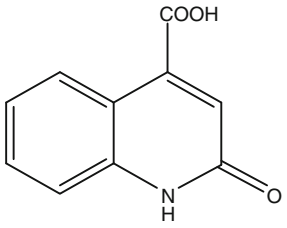
Rubusine



Methyl acetate



Methyldioxindole-3- acetate



2-oxo-1,2-dihydroquinoline-4-carboxylic acid

Fig. 58.4 Alkaloids have been separated from *R. chingii*

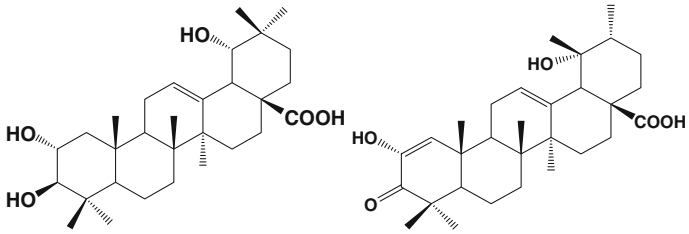


Fig. 58.5 Organic acids separated from *R. chingii*

58.3 Pharmacological Studies

Studies have demonstrated that Fupenzi has multiple pharmacological activities, which include antioxidant, anti-inflammatory, and improving cognitive impairment. Yau et al. [16] reported that the aqueous extract of *R. chingii* protects cultured primary hepatocytes from oxidative stress induced by *t*-butyl peroxide (*t*-BHP), attenuates cytotoxicity of other oxidants, and significantly improves the cell viability. Furthermore, Tian [17] and Wu et al. [18] reported that crude extract glycoprotein of Fupenzi has the significant antioxidant function.

Ethanolic extract fractions from dried *R. chingii* fruits, such as ethyl acetate and n-butanol have demonstrated strong free radical scavenging activity with the IC_{50} values 17.9, 3.4 and 4.0 μg/mL respectively. All the major compounds of Fupenzi, which are Methyl acetate, vanillic acid, kaempferol, and tiliroside have further shown the potent activity of free radical scavenging. Free radical scavenging might be used as a natural antioxidant to improve the quality, stability, and safety of cosmetic, food, and medication [5, 10]. In addition, Tiliroside was reported as ameliorating obesity-induced metabolic disorders via activating adiponectin signal, followed by enhancement of fatty acid oxidation in liver and skeletal muscle in obese-diabetic mice [19].

The study on Wuziyanzong Pills, the representative compound preparation of Fupenzi, displayed a significant improvement of cognitive impairment induced by $A\beta_{25\text{-}55,}$ via adjusting the activity of acetylcholine [20]. In an in vitro test, this preparation was also found to increase the activity of superoxide dismutase and catalase, improve the cell viability, and reduce the release of lactate dehydrogenase and malondialdehyde. The aforementioned data suggested that Fupenzi has the potential protective effect from Alzheimer's disease (AD) [21, 22]. Moreover, Lee et al. [23] reported that Fupenzi inhibit the activity of matrix metalloproteinase (MMP-1) and the secretion of interleukin-8 (IL-8) stimulated by tumor necrosis factor (TNF-α), so it could be potentially used to treat the disease of skin inflammation.

58.4 TCM Applications and Dietary Usage

58.4.1 TCM Applications

Fupenzi is sweet and sour in flavor, warm in nature, and acts mainly on the liver and kidney. Its functions include strengthening the kidney to preserve the vital energy, consolidating essence, reducing urination, and nourishing the liver and kidney to promote visual acuity [24]. Fupenzi is frequently used to treat impotence, premature ejaculation, seminal emission, spermatorrhea, enuresis, frequent urination, vaginal discharge of women, blurred vision, and poliosis [25–27].

Fupenzi acts mainly on meridians of liver and kidney to nourish kidney *Yang,* but it does not act on the kidney *Yin*. To treat impotence and seminal emission due to kidney deficiency, it can be smashed into powder and applied alone. For seminal emission, spermatorrhea, impotence and insterility due to kidney deficiency, Fupenzi can also be used together with kidney tonics and essence-securing herbs, such as Shayuanzi (*Astragalus complanatus*), Shanzhuyu (*Cornus officinalis*), and Qianshi (*Euryale ferox*). To treat impotence with kidney *Yang* deficiency, herbs that tonify the kidney *Yang*, such as Bajitian (*Morinda officinalis*), Roucongrong (*Cistanche deserticola*), and Tusizi (*Cuscuta chinensis*) can be used together with Fupenzi.

Fupenzi has the function of securing essence and reducing urination and is used to treat enuresis and frequent urination. For the condition of enuresis in which there is frequent urination due to kidney deficiency and insecurity of bladder, Fupenzi is usually combined with herbs functionalized as tonifying kidney and reducing urination, such as Sangpiaoxiao (*Tenodera sinensis*), Yizhiren (*Alpinia oxyphylla*), and Buguzhi (*Psoralea corylifolia*). In addition, Fupenzi improves vision via tonifying liver and kidney to treat poor vision due to the deficiency of liver and kidney. It can be applied on a long-term basis either alone or combined with other herbs that tonify the liver and kidney, such as Shudihuang (Prepared Dihuang, *Rehmannia glutinosa*), Nvzhenzi (*Ligustrum lucidum*), Gouqizi (*Lycium barbarum*), Sangshenzi (*Morus alba*), and Tusizi (*Cuscuta chinensis*).

58.4.2 Dietary Usage

58.4.2.1 Treating of Impotence

Fupenzi can be soaked in wine, dried and ground into a powder. Taking 3–10 g of this powder daily with wine could prevent impotence (Binhu Jijian Fang).

58.4.2.2 Treating of Frequent Urination

Urinary retention and incomplete void of bladder is caused by bladder cold and bladder deficency. 150 g of Fupenzi can be soaked in wine and fried, then mixed

with Mutong (*Clematis armandi* or *C. montana*, 45 g) and Gancao (*Glycyrrhiza uralensis* or *G. inflata* or *G. glabra*, 15 g), then ground into powder. Taking 15 g of this powder every morning could be effective on impaired bladder void (Bencao Huiyan).

58.4.2.3 Treating of Enuresis in Pediatric

30 g of Fupenzi can be boiled with 2 bowls of water and ended when one bowl of soup is left. 60–90 g of lean pork could be cooked in the soup on slow fire. Drinking soup and eating meat once per day for 2–3 days could be benificial for enuresis in children.

58.4.2.4 Treating of Diabetic Insipindus and Urinary Incontinence

9 g of Fupenzi can be decocted with 6 g of Shanyao (*Dioscorea opposita*), 6 g of Yizhiren (*Alpinia oxyphylla*), 6 g of Wumei (*Prunus mume*), and 4.5 g of honey-soaked Gancao (*Glycyrrhiza uralensis* or *G. inflata* or *G. glabra*) for the treatement of diabetes insipindus and urinary incontinence in elder patients.

58.5 Clinical Evidences

Fupenzi is usually used in compound preparations to warm-up kindey, promote kidney *Yang*, control nocturnal emission, and to treat insufficient consolidation due to a kidney deficiency. It is used in relieving the symptoms of involuntary discharge of semen, corresponding frequent urination, involuntary ejaculation, and vaginal discharge of women. To treat male infertility, for example, Fupenzi can be used with Cheqianzi (*Plantago asiatica* or *P. depressa*), Gouqizi (*Lycium barbarum*), Wuweizi (*Schisandra chinensis* or *S. sphenanthera*), Tusizi (*C. chinensis*), Nvzhenzi (*L. lucidum*), Buguzhi (*P. corylifolia*), Huangqi (*A. membranaceus*), Fuzi (*Aconitum carmichaeli*), Bajitian (*M. officinalis*) in decoction. The effective rate was achieved to be 93.5 % in 31 cases of clinical trial [28].

58.6 Safety Evaluation and Toxicity Data

Tang et al. [29] reported that the leaves of Fupenzi were non-toxic to mice via oral administrating and the genotoxicity test was negative. There weren't any symptoms of poisoning and death in Wistar rats after oral gavage of Fupenzi for 90 days.

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Chapter 59
Schisandra chinensis 五味子 (Wuweizi, Chinese Magnoliavine)

Jing-jing Zhu

59.1 Botanical Identity

Schisandra chinensis is a plant native to northeast Asia that is cultivated in South Korea and China. The fruit of *S. chinensis* has been used in traditional medicine, in beverages, tea, wine, and cosmetics [1, 2]. It has been used as an important component in various prescriptions in East Asia [3–6]. Its traditional effects are astringency of sweating, seminal emission, diarrhea and tranquillizing of the mind.

S. chinensis is a vine about 30 feet high in a season. The new leaves surrounding the blossoms are variegated and the leaves along the stem are solid green, and slightly heart shaped. The white blooms are lightly fragrant. The blooms of *S. chinensis* are followed by red edible berries on the female plants. The Chinese name for the fruit is Wuweizi, which means "five flavored seed," because the fruit is reputed to be sweet, sour, bitter, pungent and salty. It likes to grow in moist soil, rich with organic matter, with its roots in the shade. It was reputed to relieve digestive distress and to increase energy. In the garden, it is featured as an ornamental rather than an edible (Fig. 59.1).

59.2 Chemical Constituents

Phytochemical investigations have resulted in the isolation and identification of many compounds such as lignans, polysaccharides, essential oils and anthocyans. Among them, the lignans with a dibenzocyclooctadiene skeleton are the major bioactive compounds in *S. chinensis*.

J. Zhu (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, 100700 Beijing, China
e-mail: zhujj15@163.com

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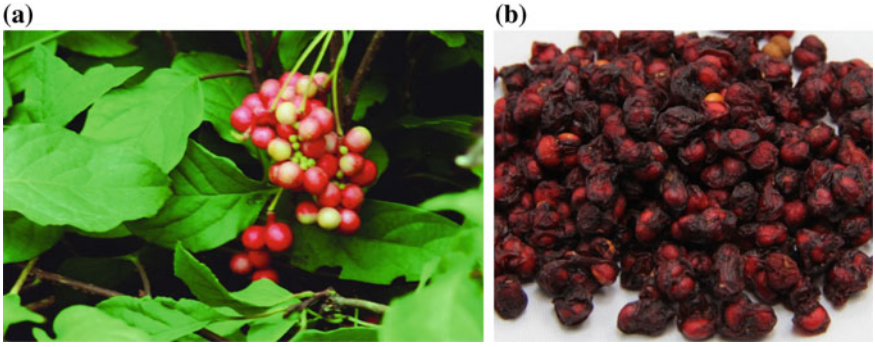

Fig. 59.1 The fruiting plant (**a**) and crude drug (**b**) of Wuweizi

59.2.1 Lignans

Lignans are the main components isolated from extracts of *S. chinensis*. So far, about 30 lignans have been found. They included schizandrin (1), schisantherin A (2), deoxyschizandrin (3) [7], schisandrol A [8], gomisin J (4), schisandrol B, angeloylgomisin H, gomisin G, schisantherin B, deoxyschisandrin, γ-schisandrin, schisandrin B, schisandrin C [9], gomisin N [10–12], gomisin C, gomisin D, gomisin A [13], pre-schisanartanin and schindilactones A-C [14] etc. (Fig. 59.2).

59.2.2 Others

S. chinensis also contains nortriterpenoids [14–17], polysaccharide (SCP-IIa) [18], anthocyan, cyanidin [2]. Essential oils mainly include ylangene, beta-himachalene and alpha-bergamotene [19] etc.

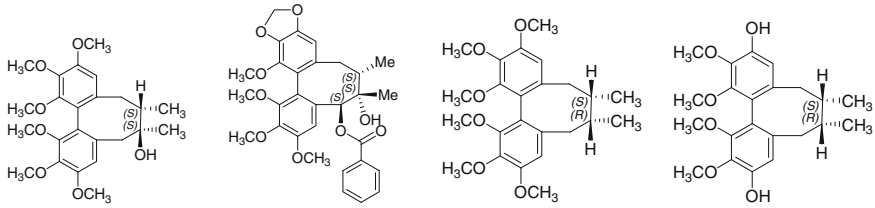

Fig. 59.2 Chemical structures of lignans isolated from *S. chinensis*

59.3 Pharmacological Studies

Pharmacological studies showed that Wuweizi had good biological activities, including antihepatotoxic, anti-cancer, antioxidant, anti-inflammatory, platelet activating factor antagonistic and central nervous system protecting activities etc. Wuweizi has been found to prevent liver damage and stimulate liver repair and normal liver function. In addition, Wuweizi aids in digestion and regulating gastric acid release [20]. It also stimulates the central nervous system. Wuweizi has been shown to quicken reflexes, control anger, and relieve headaches, insomnia, dizziness, and palpitations. Other reports have mentioned that Wuweizi can increase cognitive and memory functions. Wuweizi may be useful in reversing depression, particularly when it is due to exhaustion. Wuweizi is also a registered medicine for vision problems, since it appears to prevent eye fatigue and increase visual acuity [20–25].

59.4 TCM Applications and Dietary Usage

The fruit of *S. chinensis* is used as an ingredient in traditional medicine in East Asia. It is also consumed as tea and wine in which it displays a pinkish-red color with beneficial physiological activity. It has a long-standing history of medicinal use as a tonic, a sedative, an anti-tussive, and an anti-aging drug.

59.4.1 TCM Applications

In Traditional Chinese Medicine, Wuweizi is used to astringe, replenish Qi, promote production of body fluid, tonify the Kidney, and induce sedation [26]. It is prescribed with Yingsuke (fruit pericarp of *Papaver somniferum*) constituting Wuweizi pill for treatment of Lung deficiency and chronic cough. For Spleen and Kidney Yang deficiency and dawn diarrhea, it is commonly used with Buguzhi (fruit of *Psoralea corylifolia*), Wuzhuyu (fruit of *Euodia rutaecarpa*) and Roudoukou (kernel of *Myristica fragrans*), such as Sishen pill.

Numerous clinical trials have demonstrated the efficiency of Wuweizi in the following conditions: asthenia, neuralgic and psychiatric (neurosis, psychogenic depression, astheno-depressive states, schizophrenia and alcoholism) disorders, in impaired visual function, hypotension and cardiotonic disorders, in epidemic waves of influenza, in chronic sinusitis, otitis, neuritis and otosclerosis, in pneumonia, radioprotection of the fetoplacental system of pregnant women, allergic dermatitis, acute gastrointestinal diseases, gastric hyper- and hypo-secretion, chronic gastritis, stomach and duodenal ulcers, wound healing and trophic ulcers [20].

59.4.2 Dietary Uses

As previously stated, Wuweizi is consumed as tea and wine resulting in beneficial physiological activity [2]. Wuweizi herbal supplements are used as adaptogenic and ergogenic aids in sport [27].

59.4.2.1 Wuweizi

Wuweizi offers support for a wide range of health conditions which are known to have a positive effect on the sympathetic and parasympathetic nervous system, as well asprovide relief from chronic fatigue, stress, and physical and mental exhaustion. Wuweizi has acalming effect on the body and acts as a mild sedative, whereby helping those who taking prescription tranquilizers to decrease their dependency on synthetic drugs. Wuweizi is a great source of comfort for individuals who experience irritability, night sweats, insomnia, nightmares, and palpitations.

59.4.2.2 Wuweizi Tea

Wuweizi tea is made from the small red schisandra berries. It is a very flavorful option, comprising all the elements of flavor: bitter, sour, sweet, salty and spicy. This tea is a very popular option in China and Korea. As well, it can be found in America in many specialty stores which carry Asian products. Schisandra tea has a wide range of health benefits. It is reported to be benefit of nearly every system in the body. Schisandra tea acts as a mood stabilizer which may make it effective as a treatment for mild depression. It has sedative properties which can help the tea drinker to relax as well. Schisandra tea also can improve the mental functions.

59.5 Clinical Evidences

As a clinical therapeutic medicine, Wuweizi is mostly used in combination with other herbal medicines. Shengmai powder (SMP), a TCM formulation, is composed of Renshen (root of *Panax ginseng*), Maidong (root of *Ophiopogon japonicas*) and Wuweizi (fruit of *Schisandra chinensis*) for treating cardiac disorders, inhibiting cerebral oxidative damage [28].

59.6 Quality Evaluation and Assurance

Lignans are the main components isolated from extracts of *S. chinensis* and their content varies depending on where *S. chinensis* was collected. Several methods were used for control of the quality of *S. chinensis*. HPLC-UV method was developed for the simultaneous quantification of the eleven major characteristic lignans in *S. chinensis* and for control the quality of *S. chinensis* from different sources [9]. Electrospray ionization ion trap multiple-stage tandem mass spectrometry (ESI-MS^n) was used to evaluate *S. chinensis* of similar species (fruits of *Schisandra chinensis* (Turcz.) Baill. and fruits of *Schisandra sphenanthera* Rehd. et Wils.) and different growth characteristics (color, shape, etc.) [29]. Thin layer chromatography-Direct analysis in real time-Mass (TLC-DART-MS) was used to determine *S. chinensis* [30].

59.7 Safety Evaluation and Toxicity Data

The alcoholic extract of *S. chinensis* is reported to be virtually non-toxic to mice and dogs, whilst toxic effects of the ethereal oil and the fatty oil derived from Schizandra seeds could only be observed when very high dose levels were administered orally to these experimental animals.

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Chapter 60
Sesamum indicum L. 黑芝麻 (Heizhima, Black Sesame)

Haixia Li and Chunbo Lu

60.1 Botanical Identity

Heizhima, an annual herb in the family of Pedaliaceae, was widely cultured for thousands of years as one of the most important oilseed crops and plays an important role in the ancient system of medicine. The medicinal part are the seeds with black coats and therefore is called black sesame. Although the color of the seed coat varies from white to various shades of brown, red, olive, gray, and black—up to 12 colors due to landrace [1], only the seed with black coats has been thought to be the best. The sesame oil can be made by all colour sesame including black. The genus *Sesamum* contains 24 taxa, including six subspecies and one variety. *S. indicum* L. is the legal source recorded in The Pharmacoepia of People's Republic of China. *Sesamum indicum* L., a name that remains in common usage, has as synonym *Sesamum orientale* L. and is commonly known as sesame, beni-seed or Huma. As the typical botanical traits, sesame grows to the height of between 0.6–1.50 m with a growing period of 100–120 days. The plants are unbranched or have few branches. The stems may be round or square in cross section; they are usually erect, pubescent, and woody. The first true leaves are usually small and full, then they increase in size, with the fourth or fifth leaves being the largest; they are flat and sometimes tri-lobed. The flowers are geniculate, and are pigmented with colors ranging from white to pink, violet, red, and maroon—up to nine colors. The colors that are more common are a white color with purple or yellow halo. The calyx is small, five-parted, and the corolla is tubular, campanulate, five-lobed. The capsules that are borne in the leaf axils can vary in length from ca. 2–7 cm. The seeds are attached to the placentas in rows. Sesame seeds are oval and small, with 1000 weight usually varying between 2 and 4 g. The seed coat is thin and smooth to rough (partially or more) [2].

H. Li (✉) · C. Lu
School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450002, China
e-mail: lihx1024@zzu.edu.cn

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In the *Sesamum* species of 24 taxa, only one species *S. indicum* is cultivated. Thus, a cultured one is the only source of supply of Heizhima. The seed is harvested in fall. Due to indeterminate growth habits leading to asynchronous capsule ripening, the plants carry the flower buds at the apex, while the flowers, young capsules, and mature capsules are carried toward the base. Any harvest date is thus a compromise, aiming to maximize the proportion of non-shattering mature capsules and to minimize the proportion of shattering ones. For obtaining the seeds, the plants are cut above the ground or uprooted, then bundled and stacked upright to dry. The capsules dehisce due to the bundles drying. At this time, the bundles are inverted over a smooth surface (cloth or polyethylene sheets, hardened floor), beaten, and shaken to ascertain that all the seeds are released. Then the seeds are collected, dried further, cleaned, stored, and marketed. All of these procedures must be carried out carefully to avoid the lost of shattering because of the very small seeds. Further processing methods are performed according to edible or medicinal purposes, such as baked Heizhima, squeezed or aqueous extraction after grinded Heizhima for oil (Fig. 60.1).

60.2 Chemical Constituents

Hezhima contains many types of bioactive compounds. Lignans, oil (about 55 %), tocopherol, and protein (about 20 %) are the main components. In addition, resveratrol, flavonoids, ethyl protocatechuate, lecithin, quinones [3–5], phytosterols which is consisted of major β-sitosterol (>80 % of total phytosterols), campesterol (about 10 %), and stigmasterol (<5 %) [6], and polysaccharides have also been detected.

Fig. 60.1 Flowering plant (**a**), Heizhima (*black sesame*, **b**), and Huangzhima (*yellow sesame*, **c**) of *Sesamum indicum* L.

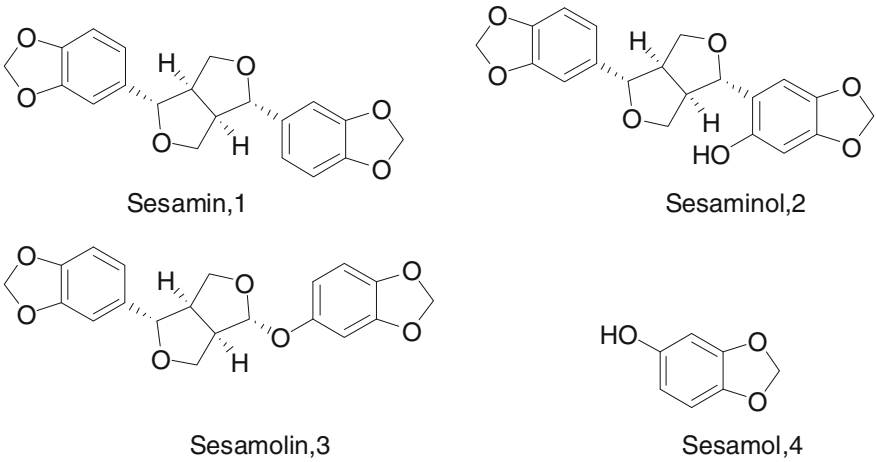

Fig. 60.2 Representative lignans and a degradation product (**4**) isolated from Heizhima

60.2.1 Lignans

Heizhima is a rich source of furfuran lignans with a wide range of potential biological activities, its content can be high up to 2.5 % [5]. Sesamin (**1**), sesaminol (**2**), sesamolin (**3**), and sesamol (**4**) which is a degradation product of sesamolin in the roasted sesame (shown in Fig. 60.2), are characteristic components and used as the index for evaluating the activity of crude drug. And fifty cultivars of sesame from different geographic regions of the world showed no differences in sesamin and sesamolin content.

60.2.2 Oil and Tocopherol

Heizhima contains unique oil, which is very easily digested and is stable to oxidative stress. For these reasons, it is useful and healthy for consumption [6]. The oil is rich in the predominance of γ-tocopherol, up to 98 %, over the other isomers of vitamin E, such as α-tocopherol. And, the fatty acid composition of oil is very desirable, with about 80–85 % of unsaturated acids. The ranges of fatty acid percentages of the total lipids were oleic acid (18:1) 32.7–53.9 % and linoleic acid (18:2) 29.9–45.6 %. The polyunsaturated fatty acids, linolenic, occurred in small amounts [1].

60.3 Pharmacological Studies

Heizhima, which is considered as an extremely beneficial medicine, has inherent power to cure many diseases and maintain health. These include diseases related to the digestive organs, urinary organs, cardiovascular system, eyes, cancer, infections, ageing, alzheimer, weight gain control and promoting hair growth, etc. These effects may help to its use in popular medicine [4]. Modern pharmacological studies have indicated that the health benefits of this enigmatic seeds include anti-cancer, anti-oxidation, anti-hypersensitivity, anti-fungal, renal function enhancement, lowering cholesterol and lipid metabolism regulation, antiatherosclerotic, anti-hypertension, antiinflammatory, antiphotooxidative, immunoregulatory, smoothing of the skin, promoting hair growth, hypoglycemic, enzyme regulation, and vitamin E enhancer activities [7]. Sesame—containing a good source of copper, manganese, and calcium, is effective in reducing pain, osteoporosis and swelling in rheumatoid arthritis.

Sesame oil and its lignan sesamol have been proved to be potent anti-inflammatory agents [8]. Sesame oil, which is rich in linoleic and oleic acids, γ-tocopherol, phytosterols and high content of fat-soluble lignans (sesamin and sesamolin), also has a phytoestrogen activity [9]. Sesame lignans also showed other useful functions such as acceleration of alcohol decomposition in the liver [9, 10]. Recently, alkylpyrazines, such as 2,3,5-trimethyl pyrazine, known as the main characteristic components of the deep-roasted sesame oil flavor, showed very strong antithrombosis activities comparable to that of the standard specimen, aspirin [9]. Sesame oil has been reported to ease joint pains when used as an ointment. The cholesterol-lowering properties of phytosterols of sesame were demonstrated. In addition, sesame oil has been used as a synergist for pyrethrum insecticides.

The lignans (including lipid-soluble lignans and water-soluble lignan glucosides) and tocopherols identified as the major antioxidants responsible for the resistant oxidative deterioration of sesame seeds, showed the same antioxidant bioactivities in vivo. One of the potential antioxidants were lignan glucosides because they are hydrolyzed into antioxidative lignans in the body [11]. Moreover, sesame lignan can inhibit the degradation of vitamin E; thus antioxidant activity in vivo was enhanced by mutual interactions of sesame lignan and vitamin E, and has the antiaging effect. The antioxidant function produced by these antioxidant components is one of mechanisms of many other activities, such as protective effects against liver injury, neuroprotective, anticarcinogenic and cardiovascular protective effects [12]. And, the protective effect of sesamol on γ-radiation was partly related to its antioxidant activity [13]. Animal studies showed that the dietary sesamin efficiently suppressed the hypertension, and sesamin metabolites exerted potent radical scavenging activity and provoked vasorelaxation in vitro [14]. The peptide prepared from sesame, another active principle, showed angiotensin-converting enzyme inhibitory and antihypertensive activities [15]. In addition, the lipid lowering function of sesame lignans, including sesamin, can be extended to various effects on fatty acid metabolism, such as lowering fatty acid concentration in liver and serum due to acceleration of fatty acid oxidation, suppression of fatty acid

synthesis and inhibition of triacylglycerol secretion in the liver, increasing formation of ketone body, and the controlling influence on the ratio of n − 6/n − 3 polyunsaturated fatty acids under excess intake of either n − 6 or n − 3 fatty acids in the diet. Furthermore, sesame lignans combined with tocopherol further lowered the cholesterol concentration in serum, due to the inhibition of absorption from the intestine and suppression of synthesis in the liver. Taken together, Heizhima and its active components may be a potent natural agent with both therapeutic applications and use in preventing human illness.

60.4 TCM Applications and Dietary, Cosmetic Usage

60.4.1 TCM Applications

As a well-known herb with many functions for maintaining good health, Heizhima has been traditionally used in the treatment of various diseases for centuries in almost all parts of the world. According to TCM theory, Heizhima exerts its masses of activities through promoting vital essence and blood genernation, reinforcing the liver and kidney replenishing, smoothing the intestine, and relieving the constipation. It is always used by alone in the treatment of hemorrhoids, dysentery, constipation, cough, amenorrhea, dysmenorrheal, ulcers, and baldness [16]. Sesame is also used as external poultice, lactagogue, diuretic, tonic, and demulcent, or used for massage and health treatments of the body [17]. In TCM application, sesame oil is a very good carrier for medicines and help the drug to pass through the barriers of skin.

60.4.2 Dietary Usages

60.4.2.1 Heizhima as Food

There are many reasons why people use Heizhima; the main ones being that it contains much high oil (about 50 %), which is very stable against oxidative degradation, and superior nutritional value containing about 20 % protein plus various minor nutrients. The good flavor generated by roasting Heizhima is also a highly desirable characteristic. Heizhima is used either decorticated or whole in making sweets such as sesame seed bars, candy bars, and halva, or in baked foods for condiments such as bread, biscuits, and crackers. Traditionally, tahini, the sesame paste that is widely used in foods in many countries, is prepared by grinding lightly roasted seeds using stone millstones. Heizhima mash and paste made by grinding seed in a conical ceramic mortar- are widely utilized as seasoning for salads, cooked rice, boiled meat, and other foods [9]. Lightly Roasted Heizhima may be used as a topping on cooked rice, or mixed with common salt after broken into pieces to make Zhimayan. Sesame-tofu (goma-dofu) prepared from mashed Heizhima seed

and a starch such as arrowroot starch, is a popular food in some countries of Asia. The embryo of the sesame seeds are used to make sesame butter-like that is called Tehineh (a popular food in the Middle East), Ogerie in Sierra Leone West Africa, used in bakeries, confectionaries, formulation of baby food, and sesame oil [1, 6, 9].

Like most oilseeds, sesame also contains anti-nutritional factors of both trypsin and chymotrypsin inhibitors which interfere with process, digestion and lower the digestibility of sesame proteins. However, heating, the most commonly used treatment, destroys their inhibitory. Thus, roasted sesame is used more than raw sesame due to its good flavor and more nutrition.

60.4.2.2 Heizhima Oils [6]

Heizhima has long been cherished for its culinary uses of oil in many countries. The oil is unique because it contains the "good" fat (monounsaturated fat), which is very easily digested and high in a variety of helpful antioxidants that protect the human being from the damaging effects of free radicals. For these reasons they are useful and healthy for consumption. In addition, the antioxidative activity which is much higher than other edible oils prevents rancidity and gives it a long shelf-life. Mixing small amounts of sesame oil in other oil-containing products (e.g., peanut butter) prolongs their shelf-life. Typically, the high-grade edible and prized oils are obtained by the method of water replacing extraction which employs water to replace oil after milling roasted sesame using stone millstones. Extraction by mechanical pressing is the industrialized method. It is believed that water extraction is better than squeeze extraction in flavor, mouthfeel and nutritive value. Sesame oil can be used by adding to soups, or stuffing with meat or chive and vermicelli to enhance flavor and appetite. Also, sesame oil can be mixture with egg and salt to make steamed egg custard, or adding boiled water in the mixture of egg, sesame oil and sugar make egg soup.

60.4.2.3 Heizhima Used in Functional Foods and Nutraceuticals

Reported activities of sesame lignans, mainly sesamin, sesamolin, sesaminol, and sesaminol glucosides, include modulation of fatty acid metabolites, inhibition of cholesterol absorption and biosynthesis, antioxidant and vitamin E-sparing effects, hypotensive effects, improvement of liver functions in connection with alcohol metabolism, and anti-aging effects. These beneficial activities resulted in the uses of its lignans in functional foods of health promotion [5].

60.4.3 Cosmetic Uses

It has been known that lignan glycosides in germinating sesame seeds have anti-oxidative effects, thus used as raw material in anti-aging cosmetics [18]. And,

sesame oil functions as a cleansing agent, emulsifying agent, and a nonaqueous viscosity increasing agent, and used in lotions, oils, powders, and creams of baby products, bath products, eye makeup, hair care products, makeup, nail care products, oral hygiene products, personal hygiene products, shaving products and skin care products, etc. The concentrations of sesame oil used are ranging from 0.0001 to 73 % [3].

60.5 Clinical Evidences

As a versatile medicine, sesame including its mainly active constituents of lignans and oil, are widely used in clinically for various diseases. Clinical report showed that the ingestion of sesame oil can exert beneficial effects on serum lipids and improve antioxidant capacity in hypercholesterolemic patients. And, the beneficial effects of diet with sesame disappeared when patients returned to their regular diets [19]. Sesame lignans and single compound sesamin or sesamolin all showed anticancer, antioxidant, antihypertensive effect in patient with breast cancer or hypertension, respectively. For sesame oil, it not only exhibited synergistic effect with glibenclamide in patients with type 2 diabetes mellitus [20], but also was a safe and effective adjunct to the standard treatment of partial adhesive small bowel obstruction (SBO) because the intervention with sesame oil added result in significantly fewer patients required surgical intervention, less SBO resolution time and a shorter hospital stay in cases of partial adhesive SBO [21]. Therefore, sesame or its mainly active constituents provide a safe and effective option for the drug combination.

60.6 Safety Evaluation and Toxicity Data

Except for allergies, few clinical reports of sesame on the toxicity or side effects are available that could be ascribed to the use of Heizhima [6]. Based on the available data, only a single case of death due to an allergic reaction to sesame has been reported [22]. Clinically, the significant numbers of sesame allergy patients usually presented in two major forms [23]: (1) Immediate hypersensitivity, often expressed as systemic anaphylaxis, and (2) Delayed hypersensitivity to lignin-like compounds in sesame oil clinically expressed as contact allergic dermatitis. In addition, a case presentation described a 48-year-old man who had experienced subcutaneous nodules nine months after self-injection of sesame seed oil into the pectoral area for muscle augmentation [24].

Although sesame can induce allergy in patients with atopic dermatitis, particularly in children, this allergy is approximated to one-half of that of persistent cow's milk allergy. And, the process can reduce the immediate hypersensitivity triggered by protein and oil components of sesame [23]. Moreover, elimination of sesame

from the diet is not justified, and may even increase the risk for developing sesame food allergy [22]. In addition, the ingredients of sesame used in cosmetics are neither skin irritants, sensitizers, and teratogens, nor carcinogens at exposures that would result from cosmetic use, they are safe in the present practices of use and concentration as described in the safety assessment and may be applied to or may come in contact with skin, eyes, hair, nails, and mucous membranes [3].

As narrated above, sesame is definitely a safe herbal medicine often used for the great potential in the treatment and prevention of chronic diseases. And, the combination of functional ingredients and rich nutritional composition of sesame makes it very unique and a very good functional food for the children as well as for the aged. For individuals who are not allergic, it remains a first choice for nutrition and health maintaining purpose.

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Chapter 61
Sterculia lychnophora Hance 胖大海 (Pangdahai, Malva Nut Tree)

Chun Li

61.1 Botanical Identity

Pangdahai is a traditional Chinese herb, specified by the ripe seeds of *Sterculia lychnophora* Hance in the Chinese pharmacopoeia [1]. It is one of the third varieties listed as both edible and medicinal resources as published by the Ministry of Health of China. Pangdahai is mainly produced in the tropical region of Southeast Asia, such as Vietnam, Thailand, Cambodia, Laos, India and Malaysia. The largest output is in Laos, but the Vietnam producer is regarded as the best. China, however, is not the country of origin for production of Pangdahai. It was not until the 1970s that Chinese scientists introduced and cultivated *Sterculia lychnophora* from Cambodia and *Sterculia wallich* from Thailand in China. As a result, only in the Hainan province and Xishuangbanna of the Yunnan province that the trees grew well and blossomed, but the seeds were harvested only in Xishuangbanna [2]. However, the seeds harvested in Xishuangbanna were not enough to provide for the Chinese market. So, Pangdahai in China was mainly imported from Southeast Asia until now.

Sterculia Lychnophora Hance is a tall wild deciduous arbor of the Sterculia Family growing in the drier regions. Its traditional medicinal component is the seed. The small brown-skinned seeds are harvested when the fruit ripens and cracks during the dry season in annual March and April. They are then dried in the sun for use. The seed tapers toward each end, and is 2–3 cm long and 1.0–1.5 cm in diameter. Apex is obtuse-rounded, and the base is somewhat acute and oblique, bearing a pale and rounded hilum. The eternally brown or dark brown seed is somewhat lustrous, with irregular wrinkles. The seed swells to a spongy-like state until it is 4–6 times of its original volume when treated with water. Notice that

C. Li (✉)
China Academy of Chinese Medical Sciences, Institute of Chinese Materia Medica, Beijing 100700, China
e-mail: yujiaolong1977@aliyun.com

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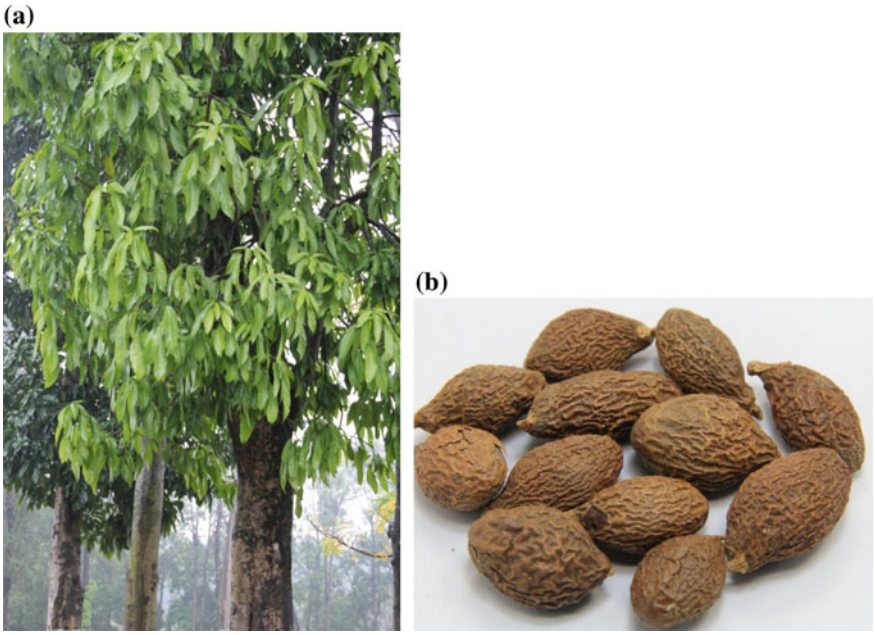

Fig. 61.1 The plant (**a**) and crude drug (**b**) of Pangdahai

essentially, the medicinal material must be prevented from moisture and worms. The shapes of *Sterculia lychnophora* Hance tree and seeds are shown in Fig. 61.1.

61.2 Chemical Constituents

Chemical composition analysis revealed that Pangdahai imported from Vietnam contained 12.36 % crude protein, 5.89 % crude fat, 53.23 % carbohydrate and 29.45 % reducing sugar [3]. Specifically, Pangdahai also contained polysaccharides, lipids, alkaloids, flavonoids, trace elements and so on.

61.2.1 Polysaccharides

Polysaccharide is one of the important components of Pangdahai. The content of polysaccharide in Pangdahai varies from 7.61 to 12.55 %, from different producing areas [4]. There were a neutral polysaccharide (NSP) and an acidic polysaccharide (ASP) isolated from Pangdahai. The chemical composition analysis results showed NSP contained large amounts of glucose and a small quantity of galactose, and

xylose, while ASP consisted of 40.13 % of galacturonic acid, as well as rhamnose, arabinose, galactose and a small amount of xylose and glucose [5].

61.2.2 Lipids

Lipids only constituted 5.5 % (range 4.0–6.0 %) of Pangdahai and were mainly located in the internal seed capsule [6]. In terms of lipids in Pangdahai, fatty acids were most studied. It is reported that the ethanol extract of Pangdahai by GC-MS analysis contained twenty-one kinds of fatty acids and five kinds of non-fatty acids [7]. The fatty acids mainly included linoleic acid (37.96 % of total ethanol extract), palmitic acid (24.77 %), oleic acid (19.77 %) and stearic acid (5.01 %), and the unsaturated fatty acids including oleic acid, linoleic acid, palmitoleic acid, 10-nonadecyenoic acid and 8-nonyne acid occupied 60.43 % of the total fatty acids.

61.2.3 Trace Elements

The trace elements in Pangdahai mainly included calcium, potassium, magnesium, phosphorus, sulfur manganese, phosphorus, zinc, etc. [8].

61.2.4 Alkaloids, Cerebrosides, Flavonoids, and Other Organic Compounds

In addition, Pangdahai contained four alkaloids: sterculinine I (**1**), sterculinine II (**2**), uracil (**3**), adenosine (**4**); four cerebrosides: soya-cerebroside I (**5**), soya-cerebroside II (**6**), 1-O-β-D-glucopyranosyl-(2S,3R,4*E*,8*Z*)-2-[(2-hydroxyl-icosanoyl) amido]-4,8-octa- decadiene-1,3-diol (**7**), 1-O-β-D-glucopyranosyl-(2S,3R,4*E*,8*Z*)-2-[(2-hydroxyl-octadecanoyl) amido]-4,8-octadecadiene-1,3-diol (**8**); three flavanoids: kaempferol-3-O-β-D-glucoside (**9**), isorhamnetin-3-O-β-D-rutinoside (**10**), kaempferol-3-O-β-D-rutinoside (**11**); two sterols: β-sitosterol (**12**) and daucosterol (**13**); two organic acids: succinic acid (**14**) and 2,4-dihydroxy benzoic acid (**15**); as well as three sugars: sucrose (**16**), D-galactose (**17**) and L-rhamose (**18**) [6, 9, 10]. The structures of the characteristic compounds from Pangdahai are shown in Fig. 61.2.

61.3 Pharmacological Studies

Modern pharmacological studies have showed that extracts and individual compounds isolated from Pangdahai had a wide variety of biological effects; including promoting excretion, reducing blood pressure, inhibiting the formation of calcium

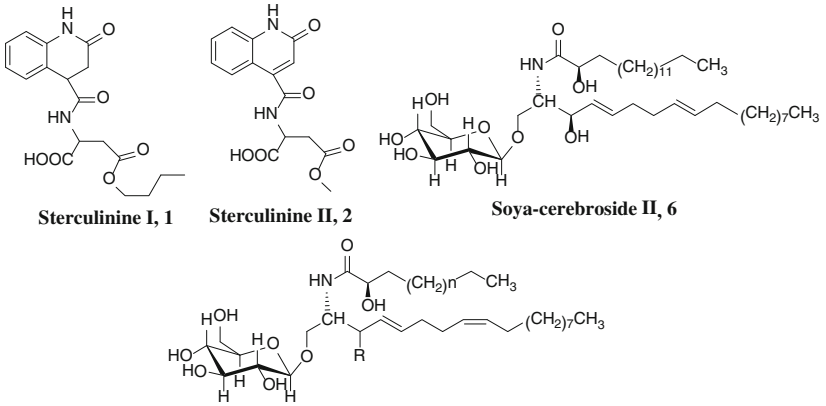

Fig. 61.2 Representative compounds from Pangdahai

oxalate crystal, anti-inflammatory, antihypertensive, antibacterial and weight-loss and so on.

61.3.1 Laxative Effect

Experiment analysis of Pangdahai water infusion by oral administration, muscle and intravenous injection of dopey dog found that the three methods could promote the peristalsis of intestines, with the effect of Pangdahai kernel water infusion was the strongest [11]. Infusion with a ratio of Pangdahai kernel to water 1:400,000 could make the peristalsis of the off-body rabbit intestines increase, but the effect could be antagonized by atropine [11].

61.3.2 Anti-inflammatory Activity

Pangdahai could obviously inhibit the mice ear edema induced by 2 % croton oil, and the bioactive components were polysaccharides [12]. However, both oral administration and partial external use of polysaccharides could not play a remarkable anti-inflammatory role, and only by celiac injection was the bioactivity of polysaccharides obvious. In another in vivo study, W-SPA and W-SPN, two polysaccharides isolated from Pangdahai, exhibited significant inhibitory effect on

the ear edema in mice, and their inhibition rates were 26.29 % and 3.21 %, respectively [3]. A model of hyperplasia of granuloma tissue in rats estimated further chronic anti-inflammatory activity of W-SPA, and the inhibition rate was 28.38 % equivalent to 82 % effect of aspirin, which showed 34.38 % of inhibition rate [3].

61.3.3 Antihypertensive Effect

The 25 % aqueous solution of Pangdahai dry powder, which was obtained from the defatted seed kernels, significantly decreased the systolic blood pressure of cats and dogs, no matter by oral administration or by muscle injection [13]. This anti-hypertensive effect continued for 3–4 h in cats, but only 30 min for dogs. Furthermore, if dogs kept oral administration at a daily dose of 2–3 g/kg for 10–15 days, there occurred toxicosis even death. So, it was deduced that the anti-hypertensive effect of Pangdahai was related to the central nervous system.

61.3.4 Inhibiting the Calcium Oxalate Crystal Formation

Zhang et al. [14] reported by the experimental study in vivo and vitro that water extract of Pangdahai which contained 693.1 mg/L of glycosaminoglycans (GAGs) could inhibit the calcium oxalate crystallization. The extract in vitro could reduce the crystal growth index from 48.2 to 25.8 %. In vivo it could inhibit the growth and aggregation of calcium oxalate crystal in rat kidney, and the content of monohydrate calcium oxalate crystal decreased from 5.26 mg to 1.51 mg/g dry kidney. A 24-hour urine sample of healthy persons and Ca-oxalate-stone patients after oral administration of Pangdahai extract made no difference in urine volume, pH of urine, calcium, uric acid, oxalic acid and GAGs. The content of GAGs in Ca-oxalate-stone patients' urine increased from 29.27 to 35.94 mg/24 h. Further study showed the mechanism lied in the water extract of Pangdahai could concentration-dependently prohibit the transformation of calcium oxalate dehydrate (COD) to calcium oxalate monohydrate (COM), and COM was thermodynamically the most stable isomer and 70 % of Ca-oxalate-stone existed as COM [15].

61.3.5 Antibacteria Effect

The water extract of Pangdahai effectively inhibited *Escherichia coli* and *Dysentery bacillus*, and at the same concentration, the inhibition strength was similar to that of furazolidone [16].

61.3.6 Weight-Losing Effect

The ethanol extract of Pangdahai could inhibit fatty acid synthetase (FAS) activity and the appetite of the rats [17]. SPF-grade adult male Wistar rats were fed with high-fat diet, at the same time the ethanol extract from Pangdahai 10, 30 and 100 mg/kg were administered by oral gavage once daily respectively, which lasted for 45 days. As a result, the body weight, adipose, food intake and the hepatic FAS activity were significantly decreased in the Pangdahai extract 100 mg/kg intervention group ($P < 0.05$) compared with the model-control group.

61.3.7 Other Effect

Immunobiological activity assay showed that SSL, a water-soluble polysaccharide from Pangdahai, could increase the ConA-induced lymphocytes proliferation in vitro [18].

61.4 TCM Application and Dietary Usage

61.4.1 TCM Applications

Pangdahai was first recorded in the Bencao Gangmu Shiyi, a supplement to compendium of materia medica written by Xuemin Zhao in the Qing Dynasty (1765). According to TCM theory, Pangdahai is sweet in flavor, cold in nature and light in property, and it is related to the lung and large intestine. Moreover, it has the following functions of clearing heat from the Lung, relieving sore throat, treating constipation by relaxing the bowels and clearing away toxic substances.

So, firstly Pangdahai is often used alone or combination with other heat-clearing and detoxifying herbal medicines to treat sore throat, especially useful in treating hoarseness and loss of voice. The commonly combined drugs includes Gancao (root and rhizome of *Glycyrrhiza uralensis*), Chantui (slough of *Cryptotympana pustulata*), Huangqi (root of *Astragalus membranaceus*), Dangshen (root of *Codonopsis pilosula*) and Maidong (root of *Ophiopogon japonicus*), ect. Secondly, Pangdahai is used for treating cough induced by Lung Heat and Lung Dryness, but this effect is not significant, so it is usually combinated with Huangqi (root of *Astragalus membranaceus*), Yuxingcao (herb of *Houttuynia cordata*) and Lugen (rhizome of *Phragmites communis*) to treat cough induced by Lung Heat and Tianhuafen (root of *Trichosanthes kirilowii*), Maidong (root of *Ophiopogon japonicus*) and Pipaye (leaf of *Eriobotrya japonica*) for cough caused by Lung Dryness. Thirdly, Pangdahai is also used to treat constipation and slow fecal transit, but its purgingforce is not strong, only suitable for mild, and usually used together with other cathartics.

61.4.2 Dietary Usages

Pangdahai can be used as food, except the traditional medicine. Now in the Chinese market there are many health products made from Pangdahai, such as Pangdahai herbal tea, various Pangdahai buccal tablets, thick soup of Pangdahai and Pangdahai lozenge with health function of refreshing, cooling and moistening throat, eliminating halitosis, etc. In food industry, Pangdahai can be used to make the cans, desserts and various kinds of drinks. But, Pangdahai tea is the most commonly used and convenient way in ordinary life. The tea is made and used as follows: 2–4 pieces of Pangdahai, soaked by boiling water, and the solution is drunk as ordinary tea as needed. The tea can be used as a supplementary therapy for hoarseness by Lung Heat, sore throat, cough and constipation. As required, moderate amount of honey is added into the solution for exerting laxative effect.

61.5 Clinical Evidences

In a clinical setting, Pangdahai is used alone or combination with other medicines for treating hoarseness, cough, sore throat, constipation, headache and red eyes. It was reported that Pangdahai tea was used to treat 100 cases of acute tonsillitis, and the results showed that 68 cases were recovered, 22 cases showed actural reversal and 14 cases were invalid [19]. The tea was made and used as follows: 4–8 pieces of Pangdahai were put into a bowl, adequte amount of boiling water was added, coverd and soaked for half an hour, the infusion was drunk as ordinary tea every four hours for 2–3 days. In another clinical investigation, Pangdahai Qingliang Runhou Soak was used to treat chronic pharyngitis and amoxicillin was used as the positive drug. As a result, whether the significant efficiency or total effectiveness, Pangdahai Qingliang Runhou Soak was better (20.5 and 69.6 %) than amoxicillin (11.4 and 34.3 %) [20]. Pangdahai Qingliang Runhou Soak is mainly composed of Pangdahai (seed of *Sterculia lychnophora*), Muhudie (seed of *Orozylum indicum*), Juhua (flower of *Chrysanthemum morifolium*) and pear, etc.

61.6 Safety Evaluations and Toxicity Issues

Modern pharmacological studies have proved Pangdahai is not suitable for long-term use. Since it can promote intestinal peristalsis and has mild laxative effect, it is not suitable for people of inferior gastrointestinal functions to use a long time. Pangdahai also has anti-hypertensive effect, so there is hypotension risk for the person of normal or low blood pressure after a long-term use.

Therefore, although Pangdahai is one of both edible and medicinal resources in China, it is not suitable for some people of special physical fitness and long-term

use as a healthy drink. In general, the feasible strategy of using Pangdahai should be as following: if it works, continue to take it until recovery; but if it does not work, stop immediately and see a doctor.

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Chapter 62
Terminalia chebula Retz. 诃子 (Hezi, Chebulic Myrobalan)

Chunnian He

62.1 Botanical Identity

Terminalia chebula Retz., a perennial tree belonging to the family Combretaceae and is found throughout Southeast Asia, South Asia and Southern China, especially in deciduous forests and areas of light rainfall., It is a medium-sized deciduous tree with a height of up to 30 m, with wide spreading branches and a broad roundish crown. It grows in an altitude of 1500–2000 m in mostly clay as well as shady soils. The leaves are elliptic rhombus, with an acute tip, cordate at the base, and glabrous above with a yellowish pubescence below. The flowers are monoecious, monotonous white to yellow, with a strong unlikable odor, born in terminal prickle or short panicles. The fruit are glabrous, ellipsoids ovoid drupes, yellow to orange brown in colour, enclosesing a single angle stone.

The dried ripen fruits of *Terminalia chebula* Retz. are used as traditional Chinese herbal medicine with the name of Hezi in Chinese and Chebulic Myrobalan in English. Hezi was first described as a medicine by the name "*helile*" (transliteration from Arabic) in *Essentinals of the Golden Cabinet* (*Jin Gui Yao Lue*). It is officially recorded in the Chinese Pharmacoepia (2010) as one of the official botanical origins of the Chinese medicinal Hezi (Chebulae Fructus). There are three types of Hezi, which are actually they are different stages of maturity of fruits: (a) small Myrobalan, the immature fruit; (b) yellow Myrobalan, after development of seed, the maturing stage of the fruit; (c) large Myrobalan, the fully matured fruit. When the unripe young fruit is steamed and sun-dried and is used as medicine, it is traditionally knowed as Zangqingguo (Tibetan *Canarium album*), but is also known as Xiqingguo (Western *Canarium album*) [1]. Figure 62.1 shows the fruiting tree and fully ripe fruit of *Terminalia chebula* Retz.

C. He (✉)
Chinese Academy of Medical Science, Institute of Medicinal Plant Development, Beijing 100193, China
e-mail: cnhe@implad.ac.cn

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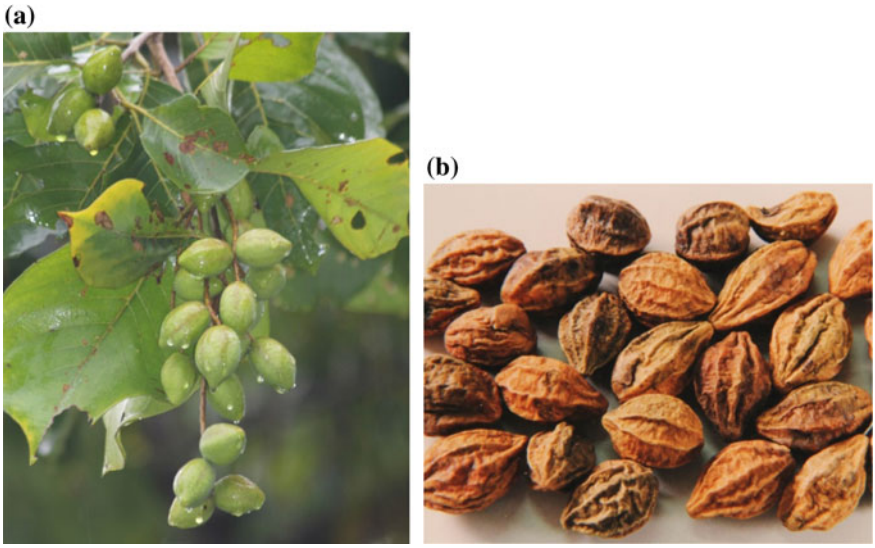

Fig. 62.1 Fruiting tree (**a**) and dried nuts (**b**) of *Terminalia chebula* Retz

The genus *Terminalia* consists of 250 species and is widely distributed in tropical areas of the world. About 8 species can be found in China, mainly distributed in Guangdong, Guangxi, Sichuan, Yunnan, Tibet, and Taiwan. About four species and one variety in this genus are used as herbal medicines. *T. chebula*is is mainly distributed in western and southwestern Yunnan, and is cultivated in Guangdong and Guangxi provinces. It is also distributed in Vietnam, Laos, Cambodia, Thailand, Myanmar, Malaysia, Nepal, and India.

The medicinal material is mainly produced in the Lincang District and Dehong Dai-Jingpo Autonomous Prefecture, Yunnan, China. Futhermore, Hezi is also considered as the "king of medicines" by Tibetans and second-to-none by Ayurvedic apothecaries, and is also held in high regard by other folk medicinal practitioners.

62.2 Chemical Constituents

The fruits of *T. chebula* contain several types of phytochemicals like hydrolysable tannins, flavonoids, sterols, and amino acids etc.

62.2.1 Tannins

The fruits of *T. chebula* is fairly rich in hydrolysable tannins (approximately 32 % tannin content). the tannin content of *T. chebula* largely depends on its geographic location [2]. A group of researchers have found 14 components of hydrolysable

tannins and related phenolic acids, such as chebulinic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose, 1,6-di-*O*-galloyl-D-glucose, casuarinin, 3,4,6-tri-*O*-glloyl-D-glucose, terchebulin, ellagic acid, and gallic acid from the fruits of *T. chebula* [3]. The major components of tannin are chebulic acid (**1**), chebulinic acid (**2**), chebulagic acid (**3**), gallic acid (**4**), corilagin (**5**) and ellagic acid (**6**). Figure 62.2 showed the structures of some specific hydrolysable tannins and related phenolic acids from Hezi.

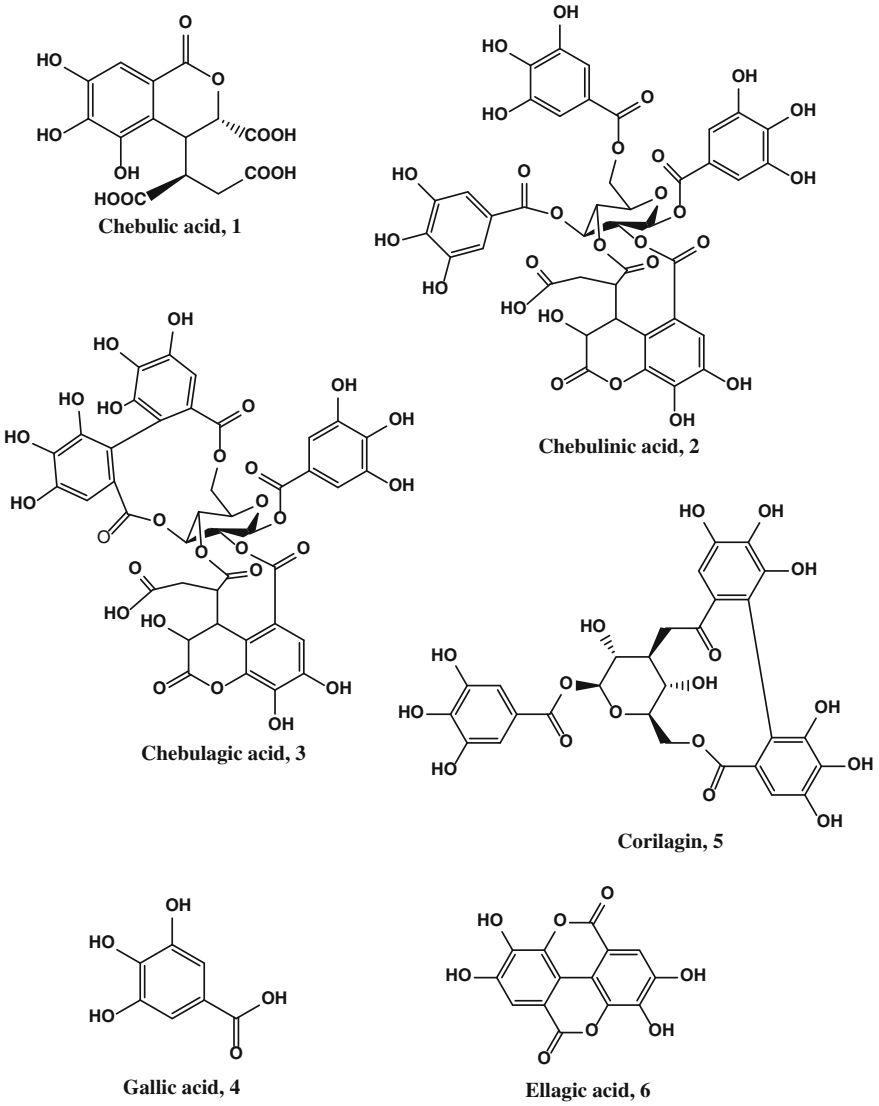

Fig. 62.2 Representative hydrolysable tannins and related phenolic acids isolated from Hezi

62.2.2 Triterpenes

Triterpenoid glycosides such as chebulosides I (7) and II (8), arjunin (9), arjunglucoside (10), 2α-hydroxyursolic acid, terminoic acid and 2α-hydroxymicromiric acid have also been reported [4].

62.2.3 Others

Other constituents include phenolics such as galloyl glucose, terflavin A, maslinic acid. Besides, fructose, amino acids, succinic acid, betasitosterol, resin, and purgative principles of anthraquinone are also present [5]. Flavonols and their glycosides, triterpenoids, coumarin conjugated with gallic acids called chebulin as well as other phenolic compounds were also isolated [6]. Twelve fatty acids were isolated from *T. chebula*, of which palmitic acid, linoleic acid, and oleic acid were main constituents [7].

62.3 Pharmacological Studies

Traditionally, Hezi is used to treat a huge variety of health problems. It is one of the most important medicinal plants used as medicines of TCM, Ayurveda, Siddha, Unani, and homeopathy because it has number of pharmacological properties. Modern studies have revealed [8] that Hezi is the source of a variety of biologically active phytochemicals such as tannins, chebulic acid, chebulinic acid, chebulagic acid, gallic acid, corilagin, ellagic acid, and other related compounds which are responsible for antimicrobial, antioxidant, antiviral, antihyperglycemic, anticancer, anticonvulsant, antimutagenic, cardiotonic and protective effects on various vital organs such as nerves, heart, kidney, and liver

T. chebula possesses high antioxidant activity and phenolics which were found to be responsible for this activity [9]. A mixture of chebulic acid (CA) and its minor isomer, neochebulic acid with a ratio of 2:1 isolated from ethanolic extract of *T. chebula* fruits showed strong hepatoprotective activity [10]. *T. chebula* exhibited antibacterial activity against a number of both Gram-positive and Gram-negative human pathogenic bacteria [11]. Ethanedioic acid and ellagic acid isolated from butanol fractions of *T. chebula* fruit extract had strong antibacterial activity against intestinal bacteria [12]. Gallic acid (GA) and CA were isolated from the extract of the fruit of *T. chebula* as the active principal that blocked the cytotoxic Tlyphocyte-mediated cytotoxicity. Granule exocytosis in response to anti-CD3 stimulation was also blocked by GA and CA at the equivalent concentrations [13]. A group of researchers have reported the inhibitory action on cancer cell growth by the phenolics of *T. chebula* Retz fruit and found that chebulinic acid, tannic acid and ellagic acid were the most growth inhibitory phenolics of *T. chebula* [14].

62.4 TCM Applications and Dietary Usage

62.4.1 TCM Applications [1]

Terminalia chebula, a common astringent drug, is a popular traditional medicine not only used in China, but also in other countries of Asia and Africa. It is used in traditional medicine due to the wide spectrum of pharmacological activities associated with the biologically active chemicals present in this plant. In China, the drug is one of the main remedies against a sore throat and cough, ulcers, dysentery, and against long duration diarrhea connected with a prolapsed rectum. Hezi could be used in a single form in folk medicine, or in combination with other herbs based on TCM theory. In Tibetan medicine and Mongolian medicine, it is mostly used in the form of prescription medication, such as the Shibawei Hezi pill, Renshen Hezi pill, Ershiwuwei Shanhu pill, Shibawei Hezi Liniao pill, Hezi Wuwei capsule, etc. Tibetan medicine generally uses *Terminalia* with cloves, nutmeg, and sheep bones to treat palpitations, chest discomfort, and madness disease.

62.4.2 Dietary Usages

The fruits of *Terminalia chebula* are highly nutritious for human health as they contain various vitamins, minerals, and proteins. They are an excellent source of vitamin C. These fruits are also rich in several minerals including selenium, potassium, manganese, iron, and copper. As edible fruits, Hezi is used for various purposes: fresh Hezi fruits are added to salad, they are sometimes pickled in brine or boiled in sugar syrup to be used in food preserves. These fruits are also used for making Black Salt which is used in many dishes. Black Salt is also one of the main ingredients of the popular spice blend called Chaat Masala. Moreover, the following dietary forms also can be easily made.

62.4.2.1 Hezi Teas

Herbal tea made of Hezi alone or mixed with other herbs is the most common way to use Hezi. Triphala tea is a traditional Ayurvedic herbal formulation consisting of three fruits native to the Indian subcontinent: Amalaki (*Emblica officinalis*), Bibhitaki (*Terminalia belerica*), and Haritaki (*T. chebula*). Triphala is prepared by grinding it into a fine powder or further processing it into tablets. Triphala is recommended and used more often than any other Ayurvedic herbal formulation and is most commonly known for its use as a gentle bowel tonic, helpful in digestion, and supporting regular bowel movements. Tiphala tea is a dietary supplement that alleviates constipation, promotes weight loss, and lowers cholesterol.

Hezi Gancao Tea composed of Hezi (9 g), Gancao (Glycyrrhizae Radix, 3 g), appropriate white sugar and *Camellia* tea. This tea has the effect of clearing lungs, relieving sore throat and folding of the lung *Qi*.

Hezi can also be used to make cool tea and fruit juice in southern and south-western China.

62.4.2.2 Hezi Wine

Hezi itself or combined with other herbs can be used to prepare herbal wine for irregular menstruation and coronary diseases. In the Tengchong county of Yunnan, China, Hezi was used for wine brewing in folk medicine, which referred to as Hezi fruit wine, and was also known as the lover tears from a beautiful legend story.

62.4.2.3 Hezi Used in Medicated Foods

Hezi can be used to make porridge with water chestnuts, semen coicis, and appropriate rice for auxiliary treatment of esophageal cancer. Hezi meat can be used to make preserved fruit, candied fruit, and dried fruit with salt and sugar, etc.

62.5 Clinical Evidences

As a therapeutic medicine and medicated food, Hezi is called the "King of Medicine" in Tibet and always listed at the top of the list of "Ayurvedic Materia Medica" because of its extraordinary power of healing.

Oral rinsing with extract of Hezi was found to significantly reduce both total bacterial counts and streptococcal counts in saliva samples. The protective effect lasted for about 3 h after rinsing, demonstrating a potential role of Hezi in the prevention of dental caries [15].

A short term clinical trials have been carried out on patients with simple constipation. Hezi increases the stools and has got property of evacuating the bowel completely [16].

Some other drugs containing Hezi as one of the components have been subjected to clinical trials regarding their effects on constipation, mental and physical disability, allergic rhinitis, and mental stress. In all the cases the drugs containing Hezi showed good effects in the treated groups when compared to their normal control patients [17].

62.6 Safety Evaluation and Toxicity Data

From the literature it has been noted that the aqueous, ethanol, and ethyl acetate extracts of Hezi fruits demonstrated no cellular toxicity on sheep erythrocytes as well as acute oral toxic effects on rats at recommended and higher doses [18]. The aqueous alcoholic extract of Hezi fruits demonstrated cytochrome P-450 inhibition potential in rats [19]. Hezi by itself had no genotoxic effect both in VITOTOX test and Ames assay [20]. Rather, Hezi fruit could reduce the lead and aluminium induced genotoxicity [21]. The hydrolysable tannins obtained from Hezi fruits also showed antimutagenic activity against direct-acting mutagens like sodium azide and 4-nitro-O-phenylene diamine. These findings indicated that Hezi is a safe substance to be used as drug normally.

Hezi fruits do not need to be completely avoided during pregnancy for their laxative properties. But one should always consult an expert before consuming them in any form during pregnancy as they may cause various complications. It is advisable to discontinue using these fruits in case of any adverse effects. In addition, Hezi may cause the following side effects: It sometimes lowers the blood sugar levels, this fruit causes some adverse reaction in people with diabetes and hypoglycemia, and some people may also develop allergic reactions to it.

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Chapter 63
Vigna umbellata (Thunb.) Ohwi et Ohashi or *Vigna angularis* (Willd.) Ohwi et Ohashi 赤小豆 (Chixiaodou, Rice Bean)

Yingfang Wei, Jie Yan, Fei Long and Guanghua Lu

63.1 Botanical Identity

As a kind of small grain, with high protein, low fat, rich nutrition and delicious taste, rice bean is one of the main edible beans in China. Because of its rosy seed coat and rich starch in seeds, it is also named as 'Red bean' or 'Adzuki bean'. The cultivation procedure and application techniques of rice bean are extensively documented in the ancient Chinese agricultural book Qimin Yaoshu (533–544 AD), in which it indicates that rice bean plantation has at least 1500 years of history in China.

As a commonly used Chinese traditional medicine, rice bean is first recorded in the Classic of the Materia Medica (Shennong Bencao Jing), which is the earliest Chinese pharmacy monograph published in 2000 years ago. The seeds of *Vigna umbellata*(Thunb.) Ohwi et Ohashi and *Vigna angularis* (Willd.) Ohwi et Ohashi are the major and legal sources of rice bean recorded in the Pharmacopoeia of People's Republic of China [1] and some historical books of Chinese herbal works. However, according to the Compendium of Materia Medica (Bencao Gangmu 1596 AD), their qualities are recorded to be slightly different, e.g. rice bean harvested from the plant of *V. umbellata* is superior to that of *V. angularis*. Nowadays, rice bean mainly comes from the plant of *V. angularis* due to its higher output of seeds and widely distributed planting area. Both of the two species of plants belong to the same genus *Vigna*, and therefore hold similar plant morphology. They are annual herbaceous plants. Pinnate compound leaves are composed of 3 lobules, which are lanceolate or ovate-lanceolate, entire or 3 slightly lobed with 3 basal veins. Axillary raceme has 2–3 yellow papilionaceous flowers. Pods are linear or cylindrical, pendulous, in which contain 6–10 seeds, often red [2]. The difference between the two species of plants lies in the stems, i.e. the former (*V. umbellata*) is slender and up to 1 m height, whilst

Y. Wei · J. Yan · F. Long · G. Lu (✉)
School of Pharmacy, Chengdu University of Traditional Chinese Medicine,
611137 Chengdu, China
e-mail: luguanghua@hotmail.com

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the latter (*V. angularis*) is erect herb with the height between 30–90 cm, and the whole plant covered sparsely hairy. Moreover, the seeds of *V. umbellata* with purplish-red, long elliptic and hilum sag differ from those of *V. angularis* with dark brown-red, short cylindrical and hilum not raised (Fig. 63.1).

Generally, rice bean is harvested in autumn. When the pods are fully matured before cracking, the whole plant is pulled up, dried in the sun and beaten to make seeds out. Then, the seeds are removed from the impurities and then dried completely. The clean and dried beans should be stored in dry and ventilated place, and should be protected from insects and mildews.

Rice bean has a widespread cultivation throughout China. The plant of *V. umbellata* is widely planted in south China, such as Guizhou, Sichuan, Guangxi, Hunan provinces, etc. While *V. angularis* is mainly produced in northeast, north and southwest of China, e.g. Heilongjiang, Shanxi, Henan, Anhui, Sichuan province, etc. Currently, China is a major exporter in rice beans with the largest export volume throughout the world.

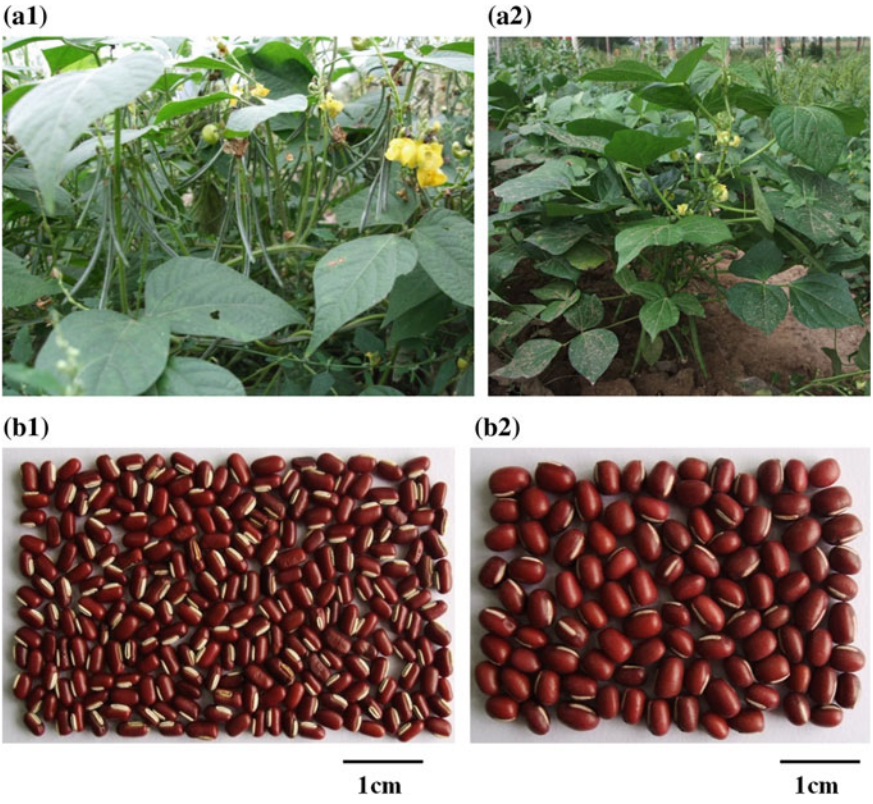


Fig. 63.1 The plant (**a1**, **a2**) and seed (**b1**, **b2**) of Rice bean. **a1** *Vigna umbellata* (Thunb.) Ohwi et Ohashi, **a2** *V. angularis* (Willd.) Ohwi et Ohashi, **b1** *V. umbellata* (Thunb.) Ohwi et Ohashi, **b2** *V. angularis* (Willd.) Ohwi et Ohashi

63.2 Chemical Constituents

Triterpenoid saponins, polyphenols and flavonoids are major classes of bioactive compounds found in rice bean.

63.2.1 Triterpenoid Saponins

The amount of total saponins is in the range of 0.3–0.7 % in rice bean [3]. Some compounds belonging to triterpenoid saponin have been isolated from this herb, e.g. azukisaponins I, II, III, IV, V and VI, sophoradiol, soyasapogenol b, gypsogenic acid, etc. [4] (Fig. 63.2). They are the bioactive components with anti-inflammation, antivirus, hepatoprotection, etc.

63.2.2 Polyphenols

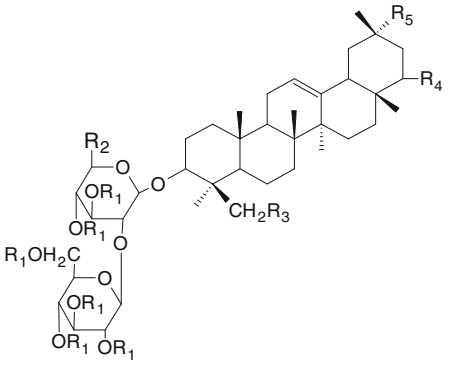
Polyphenol is another class of bioactive component found in rice bean, such as proanthocyanidins, catechin, epicatechin, etc. [5]. This class of compounds shows the actions of radical scavenging and antioxidant [6], which is useful for people's healthcare.

63.2.3 Flavonoids

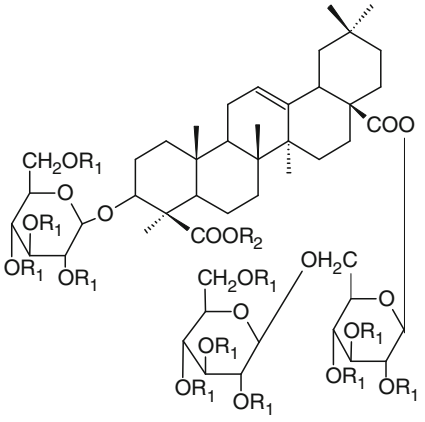
Many compounds of flavonoids have been extracted and isolated from rice beans, e.g. myricetinrutinoside, myricetin, quercetin, rutin, procyanidin, etc. [5]. They are the main chemical constituents in the natural pigment existing in the seeds coat.

63.2.4 Nutrients

Rice bean is considered as a legume with rich nutrition. It contains abundant protein, amino acid (rich lysine), fat, dietary fiber, carbohydrate, vitamins, minerals and other nutrients [7]. Albumins and globulins are the major composition of proteins. Meanwhile, the main components of lipid are phospholipids and triglycerides. In addition, the fatty acid profile revealed the high percentage of unsaturated fatty, i.e. linoleic and linolenic acid. All these components are nutritionally desirable in the diet.



		R_1	R_2	R_3	R_4	R_5
	1	**H**	**COOH**	**H**	**OH**	**Me**
azukisaponins I	**1a**	**H**	**COOMe**	**H**	**OH**	**Me**
	1b	**Me**	**COOMe**	**H**	**OMe**	**Me**
	2	**H**	**COOH**	**OH**	**OH**	**Me**
azukisaponins II	**2a**	**H**	**COOMe**	**OH**	**OH**	**Me**
	2b	**Me**	**COOMe**	**OMe**	**OMe**	**Me**
	3	**H**	**COOH**	**OH**	**H**	**COOH**
azukisaponins III	**3b**	**Me**	**COOMe**	**OMe**	**H**	**COOMe**
	3c	**Me**	**CH_2OH**	**OMe**	**H**	**COOMe**



azukisaponins IV, 4, R_1=R_2=H

Fig. 63.2 Structures of azukisaponins I, II, III and IV isolated from rice bean

63.3 Pharmacological Studies

As a kind of diuretic [8], rice bean is commonly used in traditional Chinese medicine and is good for mitigating the edema caused by the heart, liver or kidney problems. Due to its richness in flavonoids and polyphenols, rice beans may be an important source of dietary antioxidants and healthy weight-loss products, which have been supported by the results of pharmacological studies to contain the following bioactivities, such as scavenging oxygen free radicals, reducing the elevated blood pressure, suppressing the postprandial blood glucose level, suppressing the serum cholesterol levels, lowering serum triglyceride concentrations, etc. [5, 9–11]. Furthermore, research works also show that the extract of rice bean possesses hepato-protection, anti-inflammation, anti-cancer, enhancing immunity, contraception, inhibition of trypsin activity and estrogenic effects [12, 13].

63.4 TCM Applications and Dietary Usage

63.4.1 TCM Applications

Rice bean is a well-known folk medicine and is widely used in China, Japan and Korea. It owns the action to induce diuresis, counteract toxicity and promote the drainage of pus [1]. As a traditional Chinese herbal medicine, rice bean shows the therapeutic efficacy on the treatment of edema, particularly edema of the legs, jaundice with dark urine, acute rheumatic arthritis, boils, sores, abscess and appendicitis by internal or external taking.

Internal taking most act as compatibility with other herbs based on theory of traditional Chinese medicine or as dietetic therapy in purpose of adjuvant function. One of the commonly proved recipes is Mahuang Lianqiao Chixiaodou decoction. It shows significant effects on hepatobiliary diseases, i.e. chronic hepatitis [14], acute icteric hepatitis and cirrhosis ascites, and on nephropathy, such as acute or chronic nephritis, proteinuria and nephrotic syndrome with pleural effusion [15–17]. In addition, this decoction is also used in all kinds of edema, allergic dermatosis [18], lower limbs dermal vasculitis, anal-intestinal diseases and so on. For external use, appropriate quantity of rice bean is ground into powder and mixed with water to reduce exudation and remove swelling. It is clinically used in the treatment of acute parotitis, boil sores, varicella, acute lymphadenitis, herpes zoster, strain with stasis blood, beriberi, etc.

63.4.2 Dietary Usage

Rice bean is on the top of all cereals resulting in its well-known in China, Japan, Korea and other countries. In the ancient books, rice bean is described as a mystery

food to have the function on driving ghost out and avoiding pestilence, which implies its therapeutic and preventing efficacy. Due to the homology characteristic of medicine and food, rice bean is not only the indispensable food in people's daily life, but also exerts the health-maintaining actions on dispelling summer heat, resolving dampness, moisturizing the intestines to relax the bowels, reducing blood-lipid and body weight, promoting lactation and so on. Hence, rice bean is usually used in many kinds of delicious and healthy foods, such as soup, gruel, staple food, dessert and pastry. The following dietary forms can be easily made at home.

63.4.2.1 Rice Beans and Crucian Crap Decoction

This is a common kind of soup in the south of China. Rice bean (about 90 g) is washed to clean, soaked in water for over a night. Crucian crap (or carp) is washed and removed internal organs, or put into pan with some edible oil to fry for a moment. Then put soaked rice beans and fried crucian crap together into casserole with water, boil until rice beans are soft and fully cooked. Fenge (root of *Pueraria thomsonii*) and Chenpi (pericarp of *Citrus reticulata*) can be added in soup and cooked simultaneously. This decoction holds the function of invigorating spleen, eliminating dampness, diuresis and detumescence.

63.4.2.2 Rice Beans and Coix Seed Gruel

The same quantities of rice beans and Yiyiren (*Coix lacryma-jobi* var. *ma-yuen*) are washed to clean, soaked over a night, boiled with water on strong fire, and then cooked on slow fire for about 60 min till rice beans look like sand-blowing and coix seed exploding. The soup of gruel seems as clear instead of dense, and is also spiced and smooth. This gruel owns the function of resolving dampness and removing swelling, moisturizing the intestines to relax the bowels, invigorating heart and tranquillizing mind, invigorating spleen and supplementing *Qi*. This gruel is suitable to have in summer, in particular for the people whose body is under heavy moisture, such as obesity subjects, postpartum women and edema disease patient. While cooking, do not add rice in it because rice grows in water resulting in wet and sticky characteristic.

63.4.2.3 Rice Beans Paste

After washed and cleaned, put rice bean into water and soak for over 2 h, add some water, boil until they become soft and the water is almost dried up. And then crush and stir the rice beans by wood shovel mixing with an appropriate amount of crystal sugar and salad oil and further stir them to be a paste. The rice bean paste can be eaten directly or used as dessert filling.

63.4.2.4 Rice Bean Decoction

Rice bean is washed to clean, soaked over a night, boiled with water till exploding and the soup looks clear. This decoction can be a drink as tea, which exerts the function of reducing weight and promoting cosmetology.

63.4.2.5 Japanese Adzuki Bean Rice

Adzuki bean rice is the most representative food made by adzuki bean (rice bean) in Japan. Rice bean is washed and cleaned, added some water and boiled to half cooked, and cooled down. Then, long glutinous rice is washed, drained and mixed with rice bean solution for 1 h. This mixture is steamed to be fully cooked. Before eaten, some salt and black sesame seeds are sprinkled. What is interesting is that the red color of rice bean and the white color of rice happen to be the colors used in wedding in Japanese culture. So, red bean rice is considered as a lucky food in Japan.

In addition, there are many other kinds of dietary ways. For instance rice bean sprouts, steamed bun stuffed with red bean paste, red bean rice, rice bean pudding, rice bean ice cream, etc. As a kind of precious grain, rice bean foods are delicious, soft, sweet-smelling, and also useful for healthcare.

63.5 Clinical Evidences

In western countries, rice bean is considered as a kind of nutritious food. As a traditional medicine, rice bean is widely used in traditional Chinese medicine. There are hundreds of related reports published on the clinical effects of single or compound, and internal or external taking of rice bean for dozens of diseases [14–18]. The most typical compounds containing rice bean are Mahuang Lianqiao Chixiaodou Decoction. For example, a clinical study was conducted on 121 patients with allergic dermatosis. The results showed the therapeutic effect of Mahuang Lianqiao Chixiaodou Decoction was better than that of terfenadine [18]. A clinical observation about 91 patients with chronic nephritis also showed that supplementing Mahuang Lianqiao Chixiaodou Decoction was able to improve significantly patient's clinical symptoms and reduce urine protein [16]. Mahuang Lianqiao Chixiaodou Decoction was administrated on 90 patients with chronic hepatitis. It was found that this decoction could assist related western medicine and improve treatment effect [14].

Besides the clinical prescription, there are some Chinese patent medicine preparations containing rice beans, such as Toubiao Huichun Pill containing Fangfeng (root of *Saposhnikovia divaricata*), Shandougen (root of *Sophora tonkinensis*), Chuanxiong (rhizome of *Ligusticum chuanxiong*), Chixiaodou (seed of *Vigna umbellata*), etc.

and Liushenqu which contains Laliao (herb of *Polygonum pubescens*), Qinghao (herb of *Artemisia annua*), Cang'erzi (fruit of *Xanthium sibiricum*), Chixiaodou (seed of *Vigna umbellata*), etc.

63.6 Safety Evaluation and Toxicity Data

In recent years, rice bean is widely used to reduce weight, promote cosmetology, clear summer heat and dampness. Few clinical reports on the toxicity or side effects are available to relate the use of rice bean. However, one paper report that two pregnant women prematurely birth resulting from the excessive and chronical eating of rice bean [19]. Meanwhile, the same group of authors also reports that rice bean may short the term of pregnant rabbit processes and the stages of labor [20]. It indicates that rice bean should be cautiously used for pregnant women in case of overdose. The usual dose of rice bean is 9–30 g/day.

Besides, there are no other adverse reactions and toxicity reported. In general, rice bean is a safe food and medicine.

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Chapter 64
Ziziphus jujuba Mill. 大枣
(Dazao, Common Jujube)

Panbo Qiu and Mingsan Miao

64.1 Botanical Identity

Dazao, is the ripe fruit of *Ziziphus jujuba* Mill. from Rhamnaceae. As a common edible fruit with medicinal properties, Dazao has over 300 varieties, with the Xinzheng Dazao being one of the best in China. Its health benefits and traditional uses have been well documented in literature and recognized in the Chinese Pharmacopoeia [1].

Ziziphus jujuba is a deciduous tree or shrub that mainly grows in central or northern China. The leaves are intergrowth with serrate, leaf shapes are ovate or ovate-lanceolate, oblong drupe, fruit stones pointed at both ends. It flowers in May to June, and it bears its fruit in September.

The fruit can be eaten as it is fresh, or as a dried and brightly coloured red fruit, which is more common in the market (Fig. 64.1).

64.2 Chemical Constituents

Jujube is rich in carbohydrates, organic acids, saponins, alkaloids and vitamins, etc.

P. Qiu · M. Miao (✉)
Science and Technology Department, Henan University of Traditional Chinese Medicine, Zhengzhou 450008 Henan, China
e-mail: miaomingsan@163.com

P. Qiu
e-mail: qiupanbo@163.com

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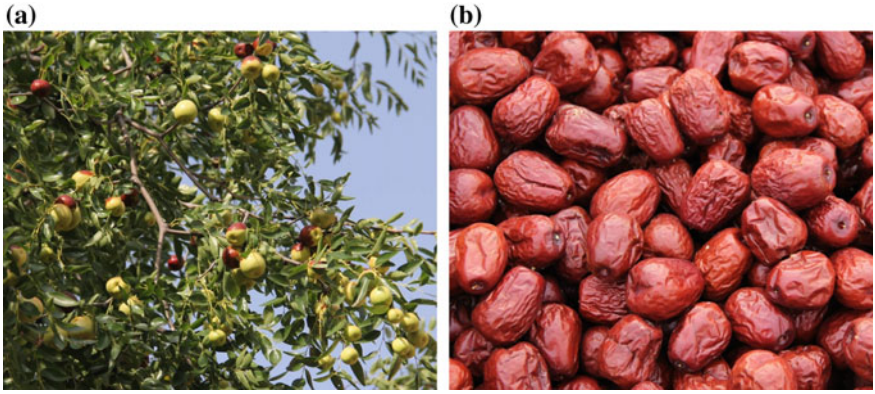


Fig. 64.1 Fruiting tree (**a**) and dried fruit (**b**) of Dazao

64.2.1 Carbohydrates

Dazao contains relatively higher level of sugars in comparison with other fruits, and the majority of which is reducing sugar. The major monosaccharides are rhamnose, xylose, mannose, arabinose, glucose and galactose [2].

64.2.2 Organic Acids

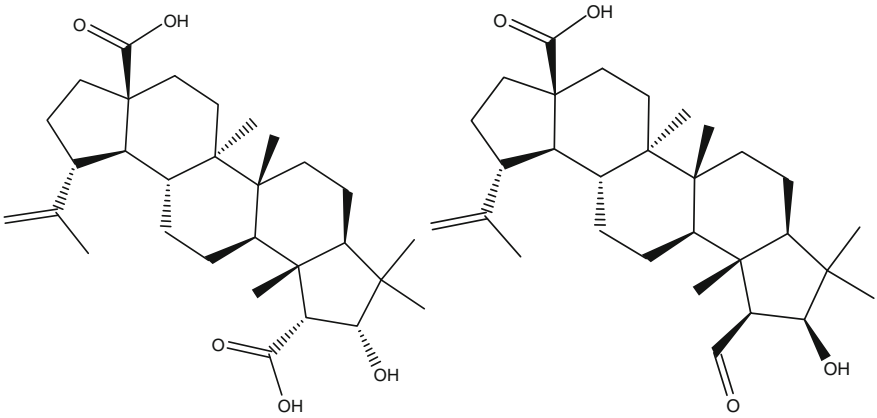
The tendency of jujube fruit organic acids content is high throughout flowering, and falling after fruit rapidly, as jujube fruit matures. Organic acids have been isolated and identified from jujube are citric acid, malic acid, tartaric acid, and succinic acid [3].

64.2.3 Saponins and Triterpenoids

Saponins from jujube plant are mainly found in the leaves, while the red jujube contains triterpenoids, of which most belong to the pentacyclic triterpenes, including ceanothic acid (0.0063–0.4135 mg/g) and zizyberanalic acid (0.0064–2.2386 mg/g) [4], as shown in Fig. 64.2 (1 and 2).

64.2.4 Alkaloids

Alkaloids in jujube are mainly grouped into two classes, the cyclopeptides and isoquinolines. Nearly 100 cyclic peptide alkaloids in larger quantities have now



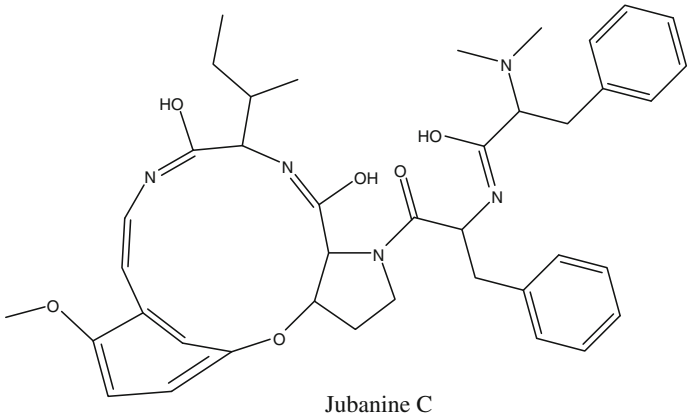
Ceanothic acid, 1 Zizyberanalic acid, 2

Fig. 64.2 Triterpenes from jujube

been isolated, such as jubanine C (Fig. 64.3). Based on the backbone structure it can be divided into three types, type I, II, and III varying in ring size. Isoquinoline alkaloids reported includes tepharine, N-nornuciforine and asimilobine [5, 6].

64.2.5 Vitamins

Jujube fruit was reported rich in vitamins A, B, and C. Its vitamin C content is higher than that in grape and apple, as the top few among various fruits and vegetables, and is thus called "natural vitamin pill". The analysis results of 13



Jubanine C

Fig. 64.3 Representative cyclopeptide alkaloids from jujube

jujube fruit varieties showed that it contained vitamin C 4.36–18.2 mg, vitamin A 8.06–27.7 IU (international units), vitamin E 2.66–6.77 IU, vitamin B1 0.11–0.39 mg, and vitamin B2 0.26–0.56 mg per 100 g [7].

64.2.6 Other Substances

Cyclic adenosine monophosphate (cAMP) was found to be the highest in all plant and animal material measured. In addition, steroids, proteins, and 36 trace elements have also been reported in jujube.

64.3 Pharmacological Studies

Dazao has a number of biological and pharmacological activities, mainly manifests in cardiovascular, central nervous, and immune systems.

64.3.1 Effect on Cardiovascular System

The cyclic adenosine monophosphate in jujube has effects of enhancing myocardial contractility, dilating coronary blood vessels, improving myocardial nutrition, and inhibiting platelet aggregation. Jujube juice had been shown to significantly improve blood lipid levels of hyperlipidemia mice caused by fat diet, with gavage of 10.5 ml testing juice daily, for eight weeks [8, 9].

64.3.2 Effect on Central Nervous System

Jujube has sedative and hypnotic and step-down effect to the central nervous system. Ganmai Dazao decoction, which is composed of Dazao (fruit of *Ziziphus jujuba*), Gancao (root of *Glycyrrhiza uralensis*), wheat (fruit), showed significant improvement of behavioral characteristics of unpredictable chronic mild stress depression rat model. The monoamine neurotransmitter activity or content in brain were also improved, implying its potential benefit for depression [10].

64.3.3 Effect on the Immune System

Jujube polysaccharides (at doses of 400, 200 mg/kg, 7 days) were found to significantly improve the peritoneal macrophage phagocytic rate and phagocytosis

index of immune suppressed mice, and markedly promote the formation of hemolysin and hemolysis plaque of the mice [11]. In addition, diets supplemented with 1000–1500 mg/kg jujube polysaccharides significantly increased the average daily food intake, immune organ index and the content of serum IgA, IgM and IgG in chickens [12].

64.3.4 Antitumor Activity

Triterpene compounds isolated from jujube have certain inhibitory effect on rat gastric adenocarcinoma and sarcoma. Jujube showed significant inhibitory effect on mice lung tumor cell proliferation and colony formation ability. Cancer patients, due to radiotherapy and chemotherapy, have manifestations of dizziness, pale lips, colds, fever and other symptoms, jujube was suggested to reduce or inhibit these adverse symptoms [13].

64.3.5 Antioxidant Capacity

Using DPPH radical scavenging assay and the total reducing capacity model to determine antioxidant activity of 20 jujube varieties, the results showed that jujube extracts all showed good antioxidant capacity [14, 15].

64.3.6 Others

In addition to the bioactivities described above, anti-fatigue, anti-allergy effects have also been reported for jujube decoction or its extracts.

64.4 TCM Applications and Dietary Usage

64.4.1 TCM Applications

Dazao has sweet and warm properties according to TCM theory. It tonifies Qi and digestion function, nourishes the blood and tranquilization, and eases and melodizes effects of other herbs in a formula. Dazao is applicable to fatigue, weakness, dizziness due to Qi and blood deficiencies.

64.4.2 Dietary Uses

Dietary uses of jujube are mainly in the forms of decoction or porridge. It is also used with other food or herbs for maintaining health or as dietary therapies. For example, a spleen-tonic cake comprises Baizhu (rhizome of *Atractylodes macrocephala*) 125 g, Ganjiang (dried rhizome of *Zingiber officinale*) 63 g, Jineijin (membrane of chicken gizzard) 63 g, Zaorou (jujube pulp) 250 g. The four items are crushed, cooked, mashed, and made into tortillas, as a health snack, tonifying spleen function and thus easing stomach discomfort, diarrhea and other digestion problems.

64.5 Clinical Evidences

The dietary and therapeutic effects of Ganmai Dazao porridge on perimenopausal insomnia was studied by following up 30 subjects after two months of treatment. The results showed that most of the subjects responded positively, particularly for mild insomnia (total effective rate 93.33%) [16].

Jujube may also be used for constipation. In a clinical observational study involving 120 patients with senile habitual constipation, treatment with a decoction of sweet potato 300 g and jujube 50 g concentrated to 300 ml, with honey 25 g, twice a day (morning and evening) for a month, it was found that all the subjects in treatment group showed full relief from constipation. The jujube decoction was found to be more effective than that of compound aloe capsule used in the control group [17].

64.6 Safety Evaluation and Toxicity Issues

No report was found on jujube for its adverse reaction.

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Chapter 65
Ziziphus jujuba var. *spinosa* 酸枣仁 (Suanzaoren)

Panbo Qiu and Mingsan Miao

65.1 Botanical Identity

Zizyphus jujuba var. *spinosa*, is a perennial woody plant (Rhamnaceae) that mainly grows in northern China. It is a thorny shrub, 1–4 m tall with leaves simple or alternate, oval. The flowers are small, umbrella-like, with dark green calyx. The drupe is small, and reddish brown in color when it is ripe, globose or oblong, 0.7–1.5 cm long, sour, and both ends of kernel are blunt. It is closely related to other sweet *jujube* species, *Ziziphus jujuba*. The medicinal part is the seed, or kernel, thus also called *jujube* kernel. It is prepared from the ripe fruit by removing the pulp and crushing the stone. This *jujube* kernel is listed in Chinese Pharmacopoeia [1], recognizing its importance in TCM.

The medicinal part of *jujube* kernel is shown in Fig. 65.1.

65.2 Chemical Components

Jujube kernels contain flavonoid glycoside, triterpenoids, saponins, and organic acids, among which triterpenoid saponins being the main bioactive components.

P. Qiu · M. Miao (✉)
Science and Technology Department, Henan University of Traditional Chinese Medicine, Zhengzhou 450008, Henan, China
e-mail: miaomingsan@163.com

P. Qiu
e-mail: qiupanbo@163.com

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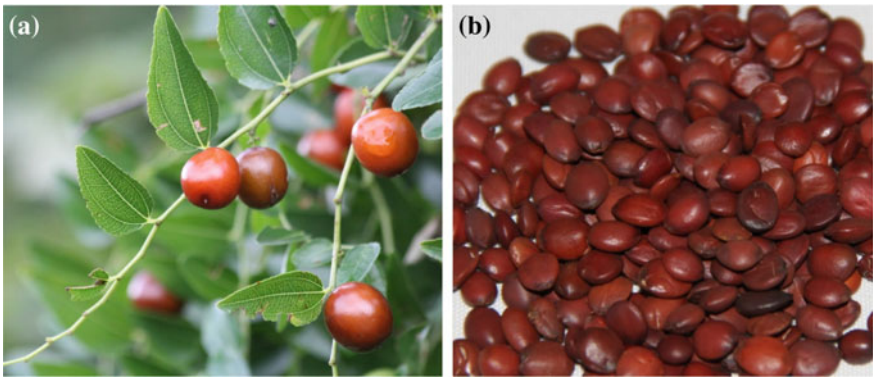
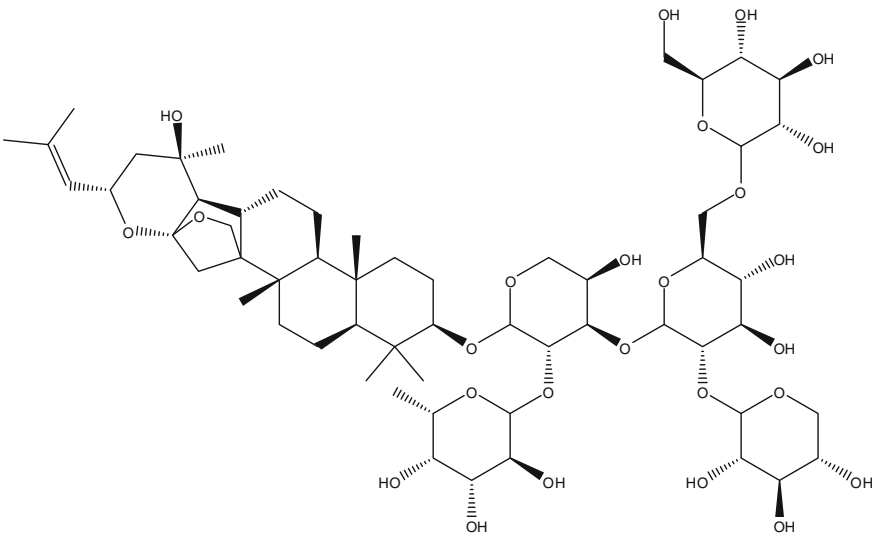


Fig. 65.1 Fruiting plant (**a**) and medicinal kernel (**b**) of *Zizyphus jujuba* var. *spinosa*

65.2.1 Triterpenoid Saponins

These include betulinic acid, betuine, jujuboside A, A1, B, B1, C, and acetyljujubosides B, proto-jujubosides A, B, B1. Jujuboside A (Fig. 65.2) is always used as the marker compounds for quality control of seed of *Zizyphus jujube* var. *spinosa*, in both qualitative and quantitative tests. Jujuboside D and H have also been discovered in recent years [2–4].



Jujuboside A

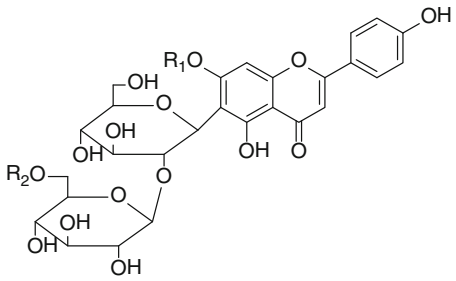
Fig. 65.2 Representative triterpenoid saponin from *jujube* kernel

65.2.2 Flavonoids

Flavonoids isolated and identified from seed of *Zizyphus jujuba* var. *spinosa* all belong to flavone-C-glucosides, include 6‴-sinapoylspinosin (1), 6‴-feruloylspinosin (2), 6‴-p-coumaroylspinsin (3), 6‴-p-hydroxybenzoylspinosin (4) etc. (Fig. 65.3) [5].

65.2.3 Others

Sour *jujube* kernels also contain large amounts of lipids (12 fatty acids), 17 amino acids, and minerals [6].



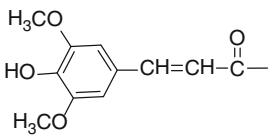
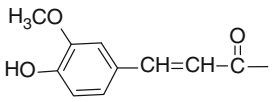
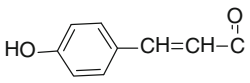
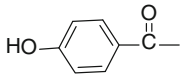
	R1	R2
6‴-sinapoylspinosin, 1	CH_3	
6‴-feruloylspinosin, 2	CH_3	
6‴-*p*-coumaroylspinsin, 3	CH_3	
6‴-*p*-hydroxybenzoylspinosin, 4	CH_3	

Fig. 65.3 Chemical structures of representative flavonoids of *Zizyphus jujuba* var. *spinosa* seed

65.3 Pharmacological Studies

65.3.1 On the Central Nervous System

Suanzaoren has been shown to have a sedative hypnotic effect in mice, rats, guinea pigs, cats, dogs and rabbits. The water extract was revealed to reduce the coordinated movement and convulsions and death rates in mice. *Jujube* kernel decoction also prolongs sleep time and decreases strychnine fatality rate in mice. Jujubosides, the flavonoids in the kernel were found to have sedative and hypnotic effects [7]. Decoction of Suanzaoren can reduce chlorophenylalanine rat brain glial dorsal raphe nucleus and the activation of microglia, and improve the degree of nerve cell damage [8].

65.3.2 For Cardiovascular Nervous System

Total saponins of *jujube* kernel lower blood lipids and regulate blood lipid protein to inhibit the development of atherosclerosis. Intraperitoneal injection of total saponins was shown to significantly reduce the normal rat serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), and markedly increase in high-density lipoprotein cholesterol (HDL-C) and the second component high-density lipoprotein cholesterol (HDL2 C) [7].

65.3.3 Immune Enhancement

Ethanol extract of *jujube* seed was revealed to improve the lymphocyte transformation in mice, while its polysaccharides showed humoral and cellular immune stimulatory effects [7].

65.3.4 Others

Studies also indicated that *jujube* kernel decoction has obvious analgesic cooling resistance to hypoxia. The alcohol extract of *jujube* kernel has a step-down against myocardial ischemia, and the aqueous extract of *jujube* kernel improves the survival rate scald in mice.

65.4 TCM Applications and Dietary Usage

65.4.1 TCM Applications

Jujube kernel is used in TCM for insomnia, and claimed to be the "oriental sleep fruit". According to TCM theory, it is often used with other herbs for achieving synergistic effect or overall balance.

Commercial TCM products of *jujube* kernel are mainly oral preparations (granule, capsule, or liquid), used for the treatment of insomnia, improving sleep quality, relieving headache, dizziness, fatigue, anxiety, depression, memory loss, weakness and treating other symptoms [8].

65.4.2 Dietary Usage

Jujube kernel is usually used to make decoction and porridge in dietary therapy.

Jujube kernel porridge has a long history of use for insomnia. It is made with *jujube* kernel (10 g), Dihuang (root of *Rehmannia glutinosa*, 15 g), and rice (100 g).

Jujube kernel and ginseng powder is also used for helping with sleep. It consists of *jujube* kernel (20 g), Renshen (root of *Panax ginseng*, 12 g), and Fuling (sclerotia of *Poria cocos*, 30 g).

65.5 Clinical Evidences

Preparations of *jujube* kernel are mainly used for treatment of insomnia. In a trial involving 30 cases of patients with insomnia, *jujube* kernel flavonoids extract was given 1.04 g each time, three times a day, for 14 consecutive days. The total effective rate was shown to be 93.33 %, *jujube* kernel was found to significantly improve the symptoms of insomnia, different degree of recovery sleep [9]. Also, in a study of 140 cases using *jujube* kernel granule for senile insomnia, 8 g granule was taken each time, three times a day for 30 days. The effect was found to be better than that of diazepam [10].

65.6 Safety Evaluation and Toxicity Issues

No adverse or side effect on clinical use of *jujube* kernel has been reported. In animal studies, both intravenous and intragastric administration of *jujube* kernel alcohol extract, showed no significant toxicity. Mouse tail vein injection of different

doses of alcohol extract of *jujube* kernel, for 14 days, with extract concentration of 17 g/mL, dosed at 20 g/kg, the LD_{50} was measured to be 27.5 g/kg, and no organ pathology observed. After 14 days of treatment, the surviving mice gained an average of 20.4 % body weight. In a gavage feeding experiment, mice were treated with alcohol extract of *jujube* kernel (340 g/kg, equivalent to 326 times of the adult human dose), the continuous observation of 14 day, all mice survived with no apparent toxicity, and the average body weight of mice increased by 17.2 % [11].

In summary, the ethanol extract of *jujube* kernel was shown to have good safety profile. However, for long-term use in the treatment of insomnia, a doctor should be consulted.

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Part IV
Aerial Part, Stem, Stem Bark, and Leaf Materials

Chapter 66
Aloe barbadensis Miller 芦荟 (Luhui, Aloe vera)

Muxin Gong and Xuran Lu

66.1 Botanical Identity

Luhui, called "aloe" in English, is a perennial evergreen herb. It belongs to the Lily family, and since ancient times has been referred to as an "Emergency Doctor", "Panacea" and "Natural Beautician". There are between 360 and 500 species of aloes worldwide [1, 2], but only a few are useful in medicine, and only 5 species can be eaten. The aloes used most for medicine, beauty, and health care are *Aloe barbadensis* Miller, *A. arborescens* Miller, *A. ferox* Miller, *A. vera* var. *chinesis*, and *A. saponaria*.

A. barbadensis Miller is the most popular species used in the food, pharmaceutical, and cosmetic industries, and legally the most mass produced source of aloe recorded in the Pharmacopoeia of the People's Republic of China [3]. The species is native to southern Africa, but is now mainly produced on Curaçao Island and Barbados Island of the West Indies in Central America, where it is called "Barbados Aloe". The fleshy leaves grow up to 0.5 m long in a rosette. They have a short stem, and grow 8–10 cm across at the base, tapering to a point with saw-like teeth along the margins of the leaves. In young plants, the leaves are a vivid green colour with irregular whitish spots on both sides. As the rosettes mature, the leaves have fewer spots, and fully matured leaves are a spotless grey-green colour (Fig. 66.1a). The inflorescence is a dense raceme with a 30–50 cm long peduncle, growing from the

M. Gong (✉) · X. Lu
School of Traditional Chinese Medicine, Capital Medical University, Beijing, China
e-mail: gongmuxin@126.com

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centre of the rosette. The flowers are nutant with a tubular yellow perianth [4] (Fig. 66.1b). Japan, South Korea, Taiwan, and Hainan all have a large area of commercial culture, mainly used for extraction of aloe juice.

Each aloe leaf consists of three layers:

(1) An inner transparent gel that contains 99 % water and the other 1 % made of glucomannans, amino acids, vitamins, sterols and lipids.
(2) The middle layer is made of latex, the bitter yellow sap which contains anthraquinones and glycosides.
(3) The thick outer layer called a rind and works as a protective barrier. It also synthesizes carbohydrates and proteins. Inside the rind are vascular bundles, which are responsible for transportation of substances such as water (xylem) and starch (phloem) [5]. Luhui is the dry concentrate of the middle layer of latex in Chinese Materia Medica [3] (Fig. 66.1c).

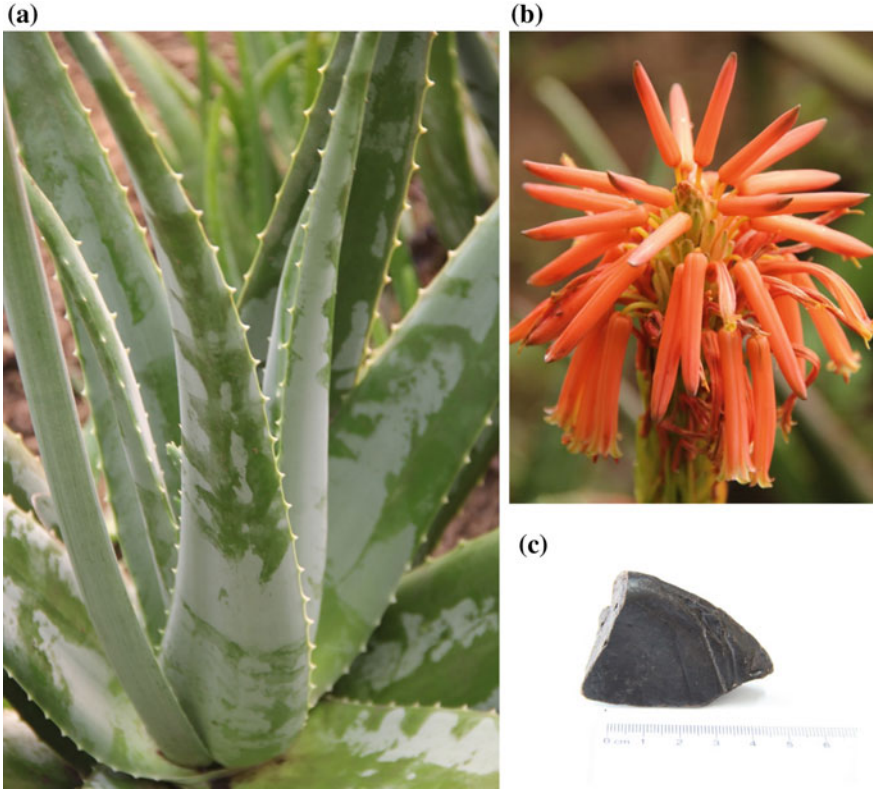


Fig. 66.1 The leaves (**a**), flowers (**b**), and crude drug (**c**) of Luhui

66.2 Chemical Constituents

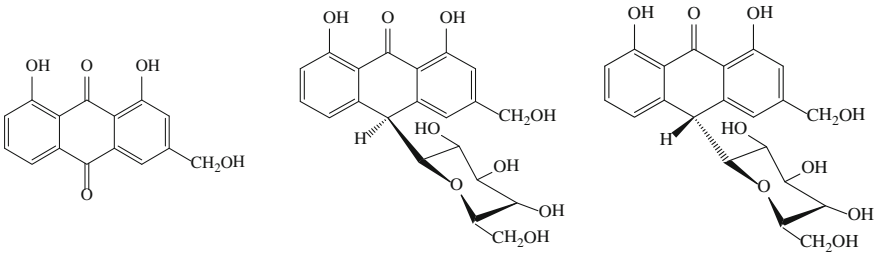
Aloe vera contains many potentially active constituents including: anthraquinones, saccharides, vitamins, enzymes, minerals, lignin, saponins, salicylic acids and amino acids.

66.2.1 Anthraquinones

The anthraquinones in Luhui are mainly aloe-emodin (**1**), anthranol, barbaloin (aloin A (**2**) and aloin B (**3**)), isobarbaloin, emodin, cinnamic acid esters [6] and their glycosides (Fig. 66.2). They are phenolic compounds traditionally known as laxatives. Aloin and emodin possess analgesic, antibacterial and antiviral effects [5].

66.2.2 Saccharides

Luihui provides monosaccharides such as glucose and fructose, and polysaccharides such as glucomannans and polymannose. They are derived from the mucilage layer of aloe leaves and are known as mucopolysaccharides. Mannose-6-phosphate is the most important monosaccharide, and glucomannans are the most common polysaccharides. Acemannan, alprogen and C-glucosyl chromone isolated from *Aloe vera* gel play important roles [5]. With regards to the skin, acemannan appears to be a superb emollient with very important moisturizing capabilities [1].



Aloe-emodin, 1 **Aloin A, 2** **Aloin B, 3**

Fig. 66.2 Representative anthraquinones isolated from Luhui

66.2.3 Vitamins

Aloe vera contains vitamins A, C and E, all of which are antioxidants to neutralize any free radicals. It also contains vitamin B_{12}, folic acid, and choline [5].

66.2.4 Enzymes

Aloe vera contains several enzymes: aliiase, alkaline phosphatase, amylase, bradykinase, carboxypeptidase, catalase, cellulase, lipase, and peroxidase. Bradykinase helps to reduce excessive inflammation when applied to the skin topically, while others help the body break down of sugars and fats [5].

66.2.5 Minerals

Aloe vera provides calcium, chromium, copper, selenium, magnesium, manganese, potassium, sodium and zinc. They are essential for the normal working of various enzyme systems in different metabolic pathways and a few are antioxidants [5].

Besides these, there are amino acids, organic acids, hormones and flavonoids and other components in Luhui.

66.3 Pharmacological Studies

Aloe vera gel has therapeutic properties such as immunomodulatory, anti-inflammatory, wound healing, anti-viral, antitumor, anti-aging and anti-oxidative effects [6].

66.3.1 Immunomodulatory Effects

A number of studies have indicated immunomodulating activity of polysaccharides in *Aloe vera* gel. These tests suggest that the effects occur via activation of macrophage cells to generate nitric oxide, secrete cytokines, and express cell surface markers; however, some other immunomodulation effects were shown to be linked to glycoproteins, namely lectins.

66.3.2 Anti-inflammatory Effects

Inflammation is the body's reaction to injury and is characterized by swelling, pain, redness, heat, and loss of function. This natural response can delay healing, but it may also be detrimental to suppress inflammation before its purpose is accomplished. The anti-inflammatory activity of mannose 6-phosphate is believed to resemble the effects observed for acetylated mannan in aloe gel. Aloe gel reduces inflammation via promotion of prostaglandin synthesis, as well as through increased infiltration of leucocytes, but is less effective against inflammation caused by allergic reactions.

66.3.3 Wound Healing Effects

Aloe gel can improve wound healing after topical and systemic administration according to several studies. The stability of the active ingredients after harvesting is vital to the proper function of *Aloe vera*. The enhanced wound healing effect and cell proliferation of a 5.5 kDa glycoprotein fraction was confirmed in hairless mice.

66.3.4 Antitumor and Antiviral Activities

Aloe anthraquinones can directly inhibit various strains of viruses, including cytomegalovirus. The acetylated glucomannan, acetylated acemannan, and aloesin can improve immunity and inhibit the growth of abnormal cells and neutralize exotoxins, making the body capable of fighting cancer. In addition, aloeutin can increase human natural killer cells (NK), and improve the ability of the body to kill cancer cells [6].

66.3.5 Anti-aging and Anti-oxidative Activities

Animal experimentation showed that aloe polysaccharides have positive effects in scavenging oxygen-free radicals and delaying the body's aging. By significantly enhancing the proliferation and regeneration-ability of cells, the body's cell count did not decrease and aging was slowed. The mucoprotein is another important component being supplied to the muscle and gastrointestinal mucosa, which makes the organism flexible and limits aging along with enhancing resistance to bacteria and virus invasion. Secondly, superoxide dismutase, peroxidase, vitamin C, vitamin E, β-carotenoid contained in *Aloe vera* can cleanse the body of free radicals and significantly enhance the regeneration of cell to delay body aging [6].

66.4 TCM Applications and Detary Usage

66.4.1 TCM Applications

The Chinese medicine Luihui is the dry concentrate of leaves juice from *Aloe barbadensis* Miller, often called "Old Aloe". It comes in irregularly shaped blocks of various sizes. The surface is reddish brown or dark brown and dull. It is light weight, not easily broken, and has rough sections. It has high hygroscopicity, with a unique smell and a very bitter taste [3]. In traditional use, it has the function of draining persperation, purgation, clearing away heat from liver, remedying infantile malnutrition and expelling parasites. It can also be used to treat constipation caused by heat, headache with hepatitis, seizures in children brought on by fright, heat in indigestion, parasites accumulation, and tinea caused by dampness.

66.4.1.1 Danggui Longhui Pill

Danggui Longhui Pill is a traditional Chinese medicine preparation recorded in the Pharmacopoeia of the People's Republic of China. It is used for treating dysphoria, dizziness, tinnitus, hypochondriac pain, and constipation [3]. It is composed of Danggui (root of *Angelica sinensis*, 100 g), Longdan (root and rhizome of *Gentiana manshurica*, 100 g), Luhui (50 g), Qingdai (natural indigo made from leaf and stem of *Baphicacanthus cusia*, 50 g), Zhizi (fruit of *Gardenia jasminoides*, 100 g), Huanglian (rhizome of *Coptis chinensis*, 100 g), Huangqin (root of *Scutellaria baicalensis*, 100 g), Huangbai (bark of *Phellodendron chinese*, 100 g), Dahuang (root and rhizome of *Rheum palmatum*, 5 g), Muxiang (root of *Aucklandia lappa*, 25 g), Shexiang (musk, 5 g). The above medicinal materials are ground into powder and prepared into liquid pills. Danggui Longhui Pill can be taken at a dose of up to 6 g twice daily.

66.4.1.2 Luhui Junzi Powder

Luhui Junzi Powder is a mixture of Luihui and Shijunzi (fruit of *Quisqualis indica*) with a weight proportion of 1:1. It could be used for treating indigestion of child by taking 3 g with rice soup twice a day [7].

66.4.2 Dietary Usages

To eat aloe as a vegetable, it is necessary to choose leaves more than 1 centimetre in thickness, with a weight from 0.5 to 1 kg. The leaves should have lots of mesophyll, be glossy, clean, less prickly, and with few white flecks. When processing, make

sure to wash the dirt off the surface, wipe off the spines of both sides, and remove the leaf epidermis (including anthraquinones and bitters, which may contain toxins), take out the mesophyll, boil and drain the water. After this, it can be eaten directly or used as cooking material. For aloe with more mucus, first sprinkle moderate amounts of corn flour and mix well. After a few minutes' standing, rinse clean.

No more than 15 g per day for an adult, and the dosage should be reduced for the elderly and children. Aloe can be made into scrambled eggs (aloe 10 g, per egg), aloe salad, aloe stewed pork ribs, aloe baked fish head, aloe fillets, aloe fried beef and other dishes as well as aloe pastry, aloe fried rice, aloe sandwiches, aloe dumplings and noodles, aloe porridge and other staple foods [8].

The aloe mesophyll as raw material can also be used to make aloe chocolate, aloe yogurt, aloe tea, aloe wine, aloe juice, aloe preserved fruit and other food.

66.4.2.1 Luhui Danggui Drink

Herbal drinks made of Luhui always contain other herbs besides Luhui. One of these is Luhui Danggui Drink. It is composed of Luhui (20 g), Juemingzi (seed of *Cassis obtusifolia*, 20 g), Danggui (root of *Angelica sinensis*, 15 g) and tea. All of the ingredients should be boiled gently for 20–30 min, then soaked for 20 min. The uses for Luhui Danggui Drink are relaxing the bowels, invigorating the circulation, and lowering blood lipids.

66.4.2.2 Luhui Pork Chop Soup

The soup is made of fresh leaves of Luhui (3–4 pieces), pork chop (300 g), dried skipjack pieces (10 g), some salt, and water. Make some slices on the clean leaves of Luhui and mash them, then put them into a pot with the rest of the ingredients. It can be eaten after the pork chop is well done [9].

66.5 Clinical Evidence

After the approval of the drug administration, Luhui is available as a raw material for the production of medicinal capsules, medicinal granules, injections, tablets and other drugs, with applications of internal medicine, surgery, gynecology, pediatrics, dermatology and otorhinolaryngology. It has unique curative effects for many chronic diseases such as disease of the intestines and stomach, hypertension, heart disease, diabetes, liver disease, constipation, stomatitis and other symptoms. It also has beneficial effects on infections, injuries, skin complaints, pain, inflammation and other ailments [10]. One hundred patients suffering from constipation were treated with Compound Luhui Capsules, which were comprised of Luhui (6 g),

Qingdai (natural indigo, 6 g), Hupo (amber, 6 g), Zhusha (cinnabar, 3 g). After treating for a month, the total effective rate was 94 % with 71 cases cured, 23 cases getting better and 6 invalid [11].

66.6 Safety Evaluation and Toxicity Data

Modern toxicology study finds that aloe extracts of water and methanol can lead to gene mutation of bacteria and mammalian cells in vitro. The clinical symptoms consist of abdominal pain, diarrhea, vomiting, pelvic congestion, even nephritis after eating aloe products. There have been many reports on the study of effects on kidneys, such as aggravating renal disease, presenting nephritis, proteinuria, hematuria, renal dysfunction. Clinical observation finds that constipation patients with long-term use of aloe products easily lead to melanosiscoli, and precancerosis of colonic carcinoma, mainly due to the effect of the anthraquinone of *Aloe vera* (aloin) [12].

Aloin mainly exists in the internal surface the leaf skin of aloe, and it is an important active substance of many functions. Because aloin can be oxidized into aloe-emodin, and aloe-emodin is similar to rheum-emodin in structure (containing a known mutagen named 1, 8-dihydroxy anthraquinone), it may present a risk of cancer and renal injury. In general, the Pharmacopoeia of China prescribes a daily dosage of dry aloe products worth 3–9 g; the content of aloin is 15–25 %, while 0.3–1 % is in the plant leaves and leaf-skin powder, and 0.005 % in aloe juice [12].

One study showed that the commercial stabilized aloe gel consumed as a beverage was not genotoxic or toxic in vivo [13].

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Chapter 67
Cinnamomum cassia Presl. 肉桂 (Rougui, Cassia Bark Tree)

Tingting Feng, Xiongli Liu, Bing Lin and Ying Zhou

67.1 Botanical Identity

Rougui is the dried bark of *Cinnamomum cassia* Presl. belonging to the Laurel family, Lauraceae [1, 2]. According to the Pharmacopeia of People's Republic of China [3], Rougui is harvested usually in autumn and then dried in the shade. *Cinnamomum cassia*, one of the most important trees in the subtropical evergreen broadleaf forest, is widely distributed in the south of China along the Yangtze River valley, and is also found in Korea, Japan and Vietnam [4]. It has been widely planted in cities throughout southern China because of its high landscaping value and resistance to disease and pollution [5]. Guangxi and Guangdong provinces are the main producers and account for more than 95 % of Chinese production of Rougui.

Cinnamomum Cassia Presl. is an evergreen tree and grows to the height of between 12 and 17 m. The bark is a gray brown colour, has a sweet smell and can be up to 13 mm thick. Young branches are quadrangular with a gray yellow fuzz. Leaves grow in an alternate or nearly opposite pattern. They are shiny green, coriaceous in texture, long elliptic to nearly lanceolate in shape (apex shortly pointed, base cuneate) and grow ternately from base. The flowers are white, axillary panicles containing: three layers of six tepals, nine fertile stamens, and a base of inner filament with two glands and an oval ovary. The berries are purple black,

T. Feng · X. Liu · B. Lin · Y. Zhou (✉)
College of Pharmacy, Guizhou University, Guiyang 550025, Guizhou, China
e-mail: yingzhou71@126.com

T. Feng · X. Liu · B. Lin · Y. Zhou
Guizhou Engineering Center for Innovative Traditional Chinese Medicine and Ethnic Medicine, Guiyang 550025, Guizhou, China

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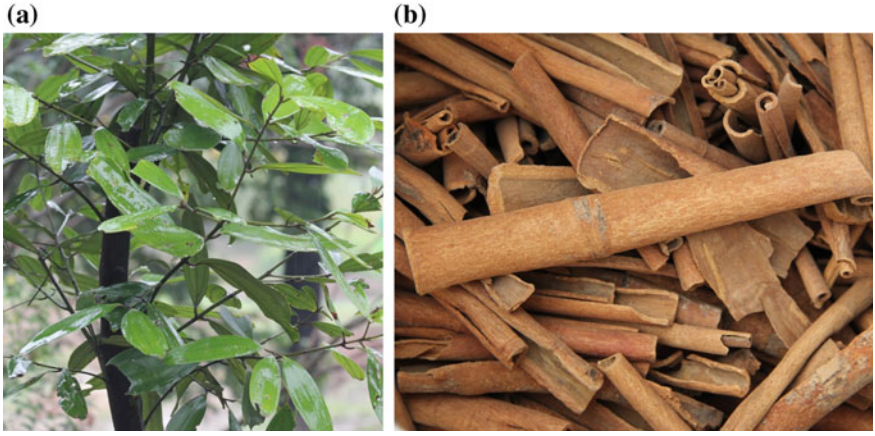

Fig. 67.1 The plant (**a**) and crude drug (**b**) of Rougui

elliptic, with shallow cup-shaped fruit receptacles. Between August and October the bark is peeled from the tree, and stored in dry, cool and shady places, or in sealed tin cases (Fig. 67.1).

67.2 Chemical Constituents

Rougui is a Chinese herb rich in volatile oil, and the bark of Rougui also contains various types of compounds, such as Rougui polysaccharides, sesquiterpenes and sesquiterpene glycosides, diterpenes and diterpene glycosides, flavanols and flavanol polymers [6–8].

67.2.1 Rougui Volatile Oil

Steam distillation of the dried bark of Rougui could give the volatile oil. In the Pharmacopoeia of People's Republic of China [3], the content of volatile oil in Rougui is regulated as a part of the quality standard and its level has to be no less than 1.2 % (mL/g). Cinnamic aldehyde is the main component of volatile oil and is thus required to be above 1.5 % of the volatile oil in Chinese Pharmacopoeia [3]. Besides the main component of cinnamic aldehyde in cinnamon, other common constituents include cinnamyl acetate, ethylcinnamate, coumarin, α-cadinene, calamenene, β-elemane, protocatechuic acid, transcinnamic acid, etc. (shown in Fig. 67.2).

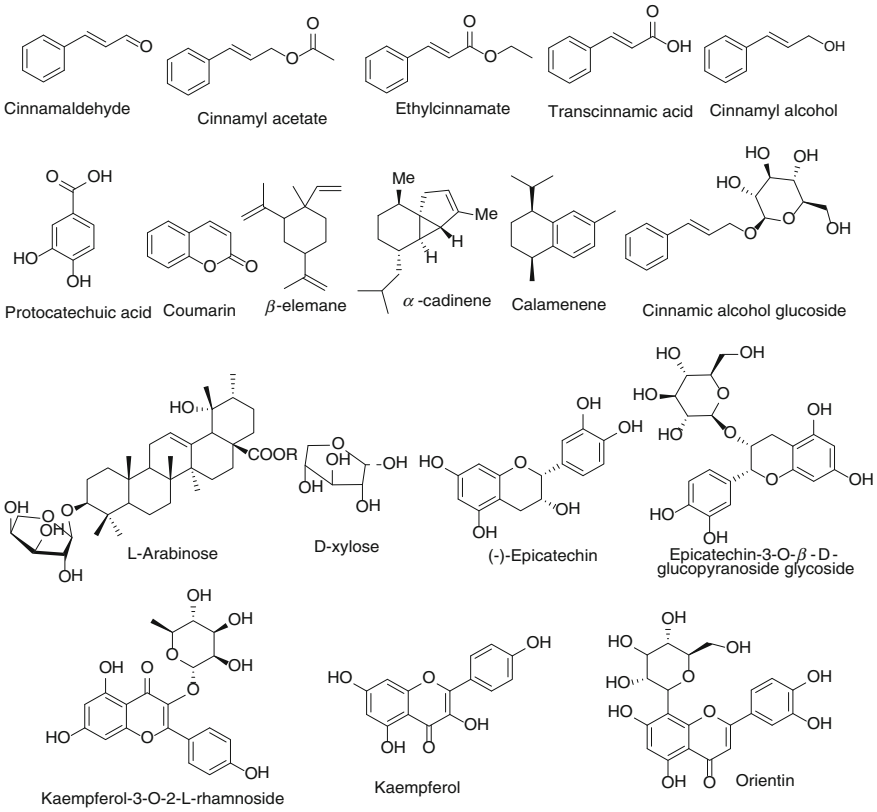

Fig. 67.2 Representative components isolated from Rougui

67.2.2 Other Constituents of Rougui Bark

The main compounds found in Rougui bark include sesquiterpenes and sesquiterpene glycosides, diterpenes and diterpene glycosides. Examples are: cinnamyl alcohol, cinnamic alcohol glucoside, and so forth. Flavonoids, primarily in the forms of flavanols and flavanol polymers such as (-)-epicatechin, epicatechin-3-O-*β*-D-glucopyranoside glycoside, kaempferol, kaempferol-3-O-2-L-rhamnoside, and orientin are also present (shown in Fig. 67.2).

67.3 Pharmacological Studies

As one of the 50 fundamental herbs in China, Rougui is an important ingredient in the traditional Chinese medicine. It tonifies kidney Yang, leads fire back to its source, disperses cold, stimulates generation of Qi and Blood, promotes blood

circulation, and alleviates pain due to cold and dysmenorrhea. During the past number of decades, modern pharmacological studies have indicated that Rougui has many different biological activities. The main bioactivities are: anti-diabetic, cholesterol-lowering, anti-microbial, anti-cancer, immunomodulatory, anti-inflammatory, anti-oxidant, anti-ulcer, anti-viral, etc. [9, 10]. A summary is presented below.

67.3.1 Anti-diabetic Activity

Rougui appears to mimic the effect of insulin through increased glucose uptake by adipocytes and skeletal muscles, and may have potentially useful pharmacological effects for the treatment of diabetes [11]. Volatile oil, alcohol extract and water extract of Rougui have been found to show potent anti-diabetic activity. Methylhydroxychalcone polymer (MHCP), water-soluble polymeric compounds isolated from Rougui was shown to have insulin-enhancing activity, through the increases of glucose uptake, glucose transport across cells, and glycogen syntheses [12].

67.3.2 Cholesterol-Lowering Activity

Rougui reduces serum glucose, triglyceride, LDL cholesterol, and total cholesterol in people with type 2 diabetes and suggest that it will reduce risk factors associated with diabetes and cardiovascular disease [13].

67.3.3 Anti-microbial Activity

The essential oil of Rougui was found to be active against several microorganisms, such as *E. coli*, *Enterococcus faecalis*, *Salmonella anaticum*, *Laetiporus sulphreus*, *Pencillium roqueforti*, *Aspergillus niger*, *Staphylococus aureus*, *Pseudomonas aeruginisa* [10, 14]. Cinnamaldehyde, the main component in the volatile oil of Rougui, is antibacterial and fungistatic [15].

67.3.4 Anti-cancer Activity

Water extract of Rougui was shown to induce apoptosis in the cervical cancer cells through an increase in intracellular calcium signaling as well as loss of mitochondrial membrane potential [16]. 2-Hydroxycinnamaldehyde was reported to be

associated with the down regulation of Wnt signaling in colon cancer cells, indicating that this phenylpropanoid is a promising candidate of natural anticancer agent for the management of human colorectal cancer [17]. Cinnamaldehyde induces apoptosis by ROS-mediated mitochondrial permeability transition in human promyelocytic leukemia HL-60 cells [18]. 2′-Hydroxycinnamaldehyde and 2′-benzoloxycinnamaldehyde isolated from the bark of Rougui show cytotoxicity against several human solid tumor cells such as HCT-15 and SK-MEL-2 cells [19].

67.3.5 Immunomodulatory Activity

2-Hydroxycinnamaldehyde and 2-benzyloxycinnamaldehyde isolated from Rougui, demonstrate immunomodulatory effects by inhibiting lymphocyte proliferation and modulate T-cell differentiation in vitro [19].

67.3.6 Anti-inflammatory Activity

The essential oil of Rougui has excellent anti-inflammatory properties [20]. The triterpenoids and phenolic constituents of the crude methnolic extract of Rougui are active and have anti-inflammatory qualities [21].

67.3.7 Anti-oxidant Activity

The oils and extract from Rougui possess high potential DPPH (2,2-diphenyl-1-picrylhydrazyl), which posses radical scavenging activity similar to those of synthetic antioxidants, which is especially attributed to the presence of phenolic and polyphenolic substances [22, 23].

67.3.8 Anti-ulcer Activity

The hydro alcoholic extract of Rougui was able to protect the gastric mucosa from chemical, stress, and physically induced ulcers [14]. The antiulcerogenic effect of 3-(2-hydroxyphenyl)-propanoic acid isolated from Rougui, is probably attributable to the potentiation of defensive factors through the improvement of the circulatory disorder and gastric cytoprotection [24].

67.3.9 Anti-viral Activity

Cinnzeylanine is the active and anti-viral ingredient in Rougui: it inhibits the proliferation of herpes simplex virus type 1 in Vero cells [25]. Rougui is highly effective against HIV-1 and HIV-2 [26].

67.3.10 Other Activities

Many studies showed that Rougui also have other pharmacological activities, such as anti-obesity, anti-allergic, anti-mutagenic, anti-septic, anti-parasitic, and anti-fagocytic [10].

67.4 TCM Applications and Dietary Usage

67.4.1 TCM Applications

Rougui is used as a spice and medicinal herb throughout the world. Its therapeutic and health-maintaining actions include: slimming, body-temperature-lowering and mental-state-calming. Common Rougui preparations are used clinically in the following forms:

(1) Controlled-release Fengshi capsule [27]: is composed of Rougui (bark of *Cinnamomum cassia*) and Jianghuang (rhizome of *Curcuma longa*). Pharmacodynamic testing of the capsules indicated that it has an anti-inflammation and analgesic effect.
(2) Bawei Rougui tablet/capsule: is composed of eight herbal components: Rougui (bark of *Cinnamomum cassia*), Muxiang (root of *Aucklandia lappa*), Chishao (root of *Paeonia lactiflora*), Doukou (fruit of *Amomun kravanh*), Gaoliangjiang (rhizome of *Alpinia officinarum*), Bichengqie (fruit of *Litsea cubeba*), Xiaohuixiang (fruit of *Foeniculum vulgare*) and Gancao (root and rhizome of *Glycyrrhiza uralensis*). It has the effect of dispersing cold and relieving pain.
(3) Fufang Huanglian Jiangtang tablet: is composed of Dahuang (root and rhizome of *Rheum palmatum*), Huanglian (rhizome of *Coptis chinensis*) and Rougui (bark of *Cinnamomum cassia*), etc. It can lower blood sugar and regulate blood lipids.
(4) Rougui Extract Powder is a convenient form of administration and can be made from single *Cinnamomum cassia* or mixed with other herbs.

67.4.2 Dietary Usages

Rougui is a commonly used ingredient, often as a food additive and condiment. It is used as a spice throughout the world.

67.4.2.1 Rougui Hongtang Teas

Rougui Hongtang tea is composed of Rougui (3–6 g) and Hongtang (brown sugar, 12 g). It may also be mixed with other herbs, such as Shanzha (fruit of *Crataggus pinnatifida*, 9 g).

67.4.2.2 Rougui Powder

Rougui powder is made of Rougui alone. For example, 3 g Rougui is ground to powder and taken twice daily.

67.4.2.3 Rougui Used in Medicated Foods

Rougui can be used to make soups with lamb.

67.5 Clinical Evidences

Rougui is a medicinal plant that has been widely used in alternative medicine and also as a spice worldwide for centuries. Traditionally the use of Rougui as a therapeutic medicine includes its application as an astringent, germicide, and antispasmodic. Rougui was one of the early treatments for chronic bronchitis. Other uses include the treatment of impotence, frigidity, dyspnea, inflammation of the eye, leukorrhea, vaginitis, rheumatism, and neuralgia, as well as wounds and toothaches [28]. Currently, cinnamon oil is used medicinally as a carminative, antidiarrheal, antimicrobial, and antiemetic agent. The indications for Bawei Rougui Capsule include digestive complaints such as flatulence, colic, dyspepsia, diarrhea, and nausea, as well as colds, influenza, fevers, arthritis, and rheumatism. Still under investigation is the use of Rougui as a hypoglycemic and cholesterol lowering agent. A few clinical studies suggest that Rougui supplementation may lower blood glucose concentrations in patients with type 2 diabetes, and may be able to significantly improve blood glucose control in Chinese type 2 diabetic patients [29]. There are many clinically related reports or observational studies published on the hypoglycemic action of Fufang Huanglian Jiangtang tablet, which contains Rougui. Rougui extract in capsule form, Zimt-Kapseln, is sold as dietary

supplement to reduce blood sugar levels in diabetes mellitus. Rougui has always been an important ingredient of Gene-Eden-VIR, which should be used to help a person infected with HSV (herpes simplex virus).

As a spice, cinnamon oil has a delicious aroma along with a sweet, pungent taste that results in its primarily use as a flavoring. It is also used in dental and pharmaceutical preparations, seasonings, sauces, baked goods, drinks, and tobacco. In the United States, Rougui has GRAS (generally recognized as safe) status as a food additive.

67.6 Safety Evaluation and Toxicity Data

A few clinical and animal studies report that Rougui has noticeable toxicity and side effects for various organs when taken orally [30]. The ig LD_{50} of Rougui oil and decoctions for mice were 236.53 and 18.48 g/kg (calculated as crude drug), respectively. The iv LD_{50}, ip LD_{50} and ig LD_{50} of cinnamaldehyde for mice were 132, 610 and 2225 mg/kg, respectively. A review of toxicity studies indicated that the ig LD_{50} of Rougui Gum for mice was 5000 mg/kg, with no noticeable side effects during the chronic toxicity test, long term toxicity test, and carcinogencity study, etc.

The average daily dose of the crude drug (Rougui) is 1–5 g or 0.05–0.2 g of the essential oil [3, 28]. Possible toxins founds in Rougui are coumarin, cinnamaldehyde and styrene, which show toxicity symptoms in a dose-dependent manner. Overdosing may cause some side effects, such as burning sensation in the gastrointestinal tract along with lethargy, double vision, vomiting, and light headedness.

In conclusion, although Rougui is a relative safe herbal medicine, often used for the treatment of diabetes mellitus and dietary supplement for health maintaining purpose, one must pay attention to defined daily dose and use with caution.

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Chapter 68
Dendrobium nobile Lindl. 石斛 (Shihu, Dendrobium)

Hong Xu and Zhengtao Wang

68.1 Botanical Identity

In China, the genus *Dendrobium* is composed of 74 species and two varieties [1], of which the fresh or dried stem of *D. nobile*, *D. chrysotoxum*, *D. fimbriatum* and other related *Dendrobium* species are used as Shihu, and *D. officinale* as Tiepi Shihu [2]. Shihu is mainly divided into two groups Fengdou Shihu and Huangcao Shihu according to different raw materials, processing procedures and morphological characters. The stem of *Dendrobium* species for Fengdou Shihu is soft, fleshy, juicy and rich in mucilage, while the stem for Huangcao Shihu is hard and rich in fiber. *D. nobile* (Fig. 68.1a) is one of the main original sources of group Huangcao Shihu (Fig. 68.1b), and is also one of the most widespread ornamental members of the Orchid Family. Its pedals are multi-colored, ranging from shades of white to pink and purple. Its stem is erect during the flowering period, and during this time inflorescences arise from old stems before or after leaves have fallen, and pedals form along the entire length of the stem.

D. nobile is mainly distributed in the southwest provinces of China. Yunnan, Guizhou, Guangxi, Sichuan, Chongqing, Guangdong and Hainan are the main areas that it is distributed to, and in these provinces it is known to be a nationally protected plant. In recent years, wild *D. nobile* suffered severe damage due to the increased demand for medicine, and since then they have been cultivated in Guangxi, Guizhou, Yunnan and Sichuan provinces, which not only ensure a sustainable medicinal supply, but also ensures the protection of its wild resources.

H. Xu · Z. Wang (✉)
Shanghai University of Traditional Chinese Medicine, Shanghai, China
e-mail: ztwang@shutcm.edu.cn

H. Xu
e-mail: xuhongtcm@163.com

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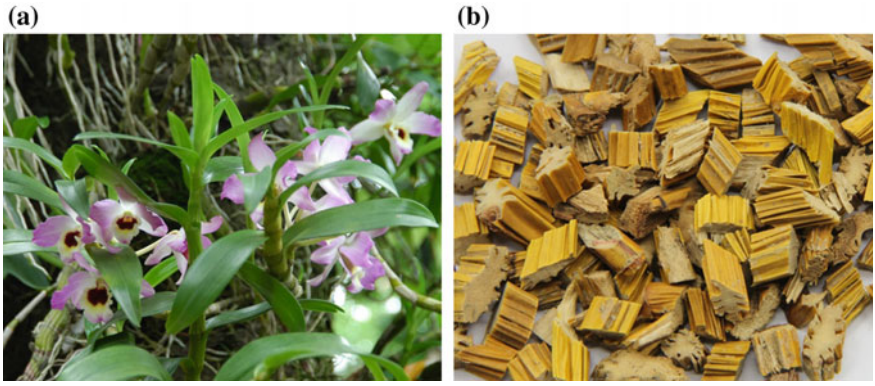


Fig. 68.1 The flowering plant (**a**) Dendrobium nobile and crude drug (**b**) of Huangcao Shihu

Traditional processing methods of Huangcao consist of collecting the stem between the late winter to early spring of the following year. After collection of the stem, it is treated with boiling water, and then left to dry in the sun after leaf sheath is removed using a rubbing motion (Fig. 68.1).

68.2 Chemical Constituents

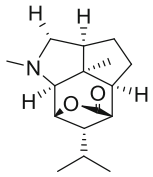
The chemical constituents existing in *D. nobile* mainly consist of alkaloids, phenanthrenes, bibenzyls, lignans, fluorenones and sesquiterpenes. Alkaloids are the major active compounds found in the stem of *D. nobile* [3, 4].

68.2.1 Alkaloids

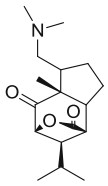
A number of alkaloids were isolated from *D. nobile*. Dendrobine is one of the major active alkaloid components, and was first isolated and structurally determined from *D. nobile* in 1932. It was then used as the standard compound to evaluate the quality of *D. nobile*. So far, there are about 20 alkaloids belonging to sesquiterpene skeleton that have been reported from *D. nobile*. Refer to Fig. 68.2 for review of these alkaloids.

68.2.2 Bibenzyls and Phenanthrenes

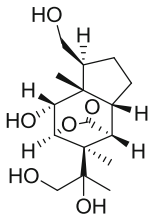
Bibenzyls and phenanthrenes are the two major active compounds existing in *Dendrobium* species. For example, moscatilin and gigantol have been isolated from



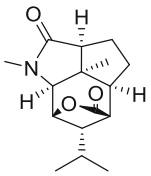
Dendrobine



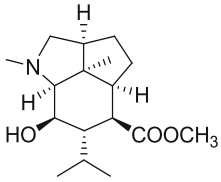
Nobilonine



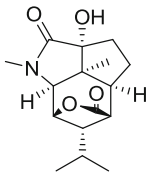
10,12-dihydroxypicrotoxane



Mubironines B



Mubironines C



Dendronobiline A

Fig. 68.2 Typical alkaloids isolated from *Dendrobium nobile*

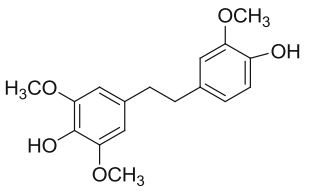
nearly twenty species of *Dendrobium,* which are also isolated from *D. nobile,* and other representative bibenzyls and phenanthrenes found in the stem of *D. nobile* are shown in Figs. 68.3 and 68.4.

68.2.3 Sesquiterpenes

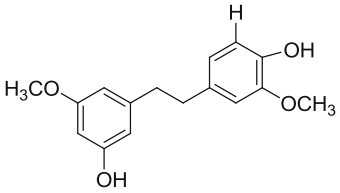
A large number of sesquiterpenes have been found in *D. nobile.* Picrotoxanes are the most common type isolated from *D. nobile*, and some representative sesquiterpenes are shown in Fig. 68.5.

68.3 Pharmacological Studies

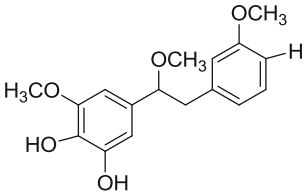
According to traditional Chinese medical theory, Shihu is a herbal stimulant known to aid in the bodies digestive abilities by stimulating the excretion of body fluids, and promoting thermogenesis. Current studies provide evidence that Shihu demonstrates extraordinarily widespread bioactivities that involve the immune, nervous, cardio vascular, endocrine, gastrointestinal and urinary systems [4]. Alkaloids from *D. nobile* are effective in protecting against LPS-induced brain impairment [5]. Three phenanthrenes, denbinobin, fimbriol B and 2, 3, 5-trihydroxy- 4,9-dimethoxyphenanthrene isolated from *D. nobile* were proven to inhibit hepatic stellate cell



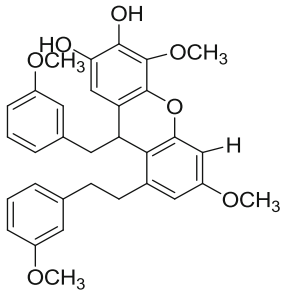
Moscatilin



Gigantol

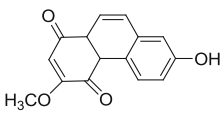


Nobilin A

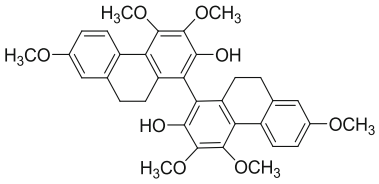


Nobilin E

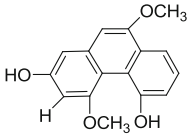
Fig. 68.3 Typical bibenzyls isolated from *D. nobile*



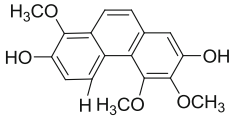
Denbinobin



2,2′-dihydroxy-3,3′,4,4′,7,7′-hexamethoxy-9,9′,10,10′-tetrahydroxy-1,1′-biphenanthrene

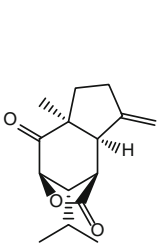


2,5-dihydroxy-4,9-dimethoxyphenanthrene

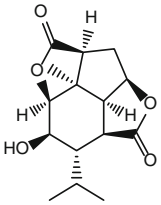


Confusarin

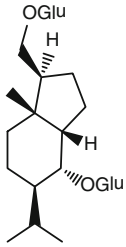
Fig. 68.4 Typical phenanthrenes isolated from *D. nobile*



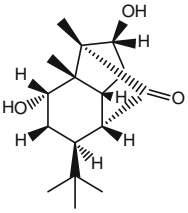
Nobilomethylene



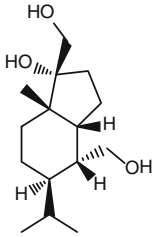
Flakinin A



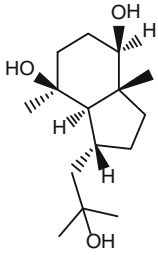
Dendronobiloside A



Dendronobilin A



Dendrodensiflorol



Dendronobilin K

Fig. 68.5 Typica sesquiterpenes isolated from *D. nobile*

proliferation, showing antifibrotic activities [6]. Sesquiterpene glycosides isolated from the stems of *D. nobile* showed immunomodulatory activity in vitro [7]. Polysaccharides from the stem of *D. nobile* exihibted high antitumor activities against Sarcoma 180 in vivo and HL-60 (Human promyelocytic leukemia cells) in vitro [8].

68.4 TCM Applications and Dietary Usage

Shihu, first described in Shennong Bencao Jing (an ancient Chinese medical works) during Han Dynasty (202 BC–220 AD), is a famous and important traditional Chinese medicine that has commonly been used as a stimulant and diuretic in many Asian countries for centuries.

68.4.1 TCM Applications

Shihu is considered an important herb for nourishing and strengthening and is commonly used in Chinese medicine. They are assumed to be effective in some

diseases or syndromes related to thirst, fever, red tongue, faucitis, atrophic gastritis and diabetes.

Shihu Yeguang Wan [2] is a pill that is prepared and used clinically for patients with cataracts, poor eyesight as well as other eye problems. It is composed of 25 herbal components, and mainly used for nourishing Kidney and clearing the Liver Heat to improve vision.

68.4.2 Dietary Usages

Shihu's primary use is typically for the replenishment of bodily fluids. It increases salivation in the mouth and is often prescribed to treat patients with complaints associated with a dry mouths, coughing, as well as those experiencing symptoms associated with severe thirst. Additionally, the plant is effective for treating patients who possess symptoms related to sunstroke. Currently Shihu is listed as a nutritious source of food by the China Food and Drug Administration, and is now a frequently used health food product in China. This product can also provide hydrating benefits to the body such as moisturizing the skin, and because of this it is now used in many cosmetic products. There are many ways to use Shihu as a functional food in dietary supplementation, especially Fengdou Shihu. Examples of these include Shihu wine, Shihu drinks.

68.4.2.1 Shihu Juice

Composition: Shihu (Fresh stem of *D. officinale)* 20 g, Honey 5 g, Water.

Preparation: Cut the stem into pieces, add honey and water, and then stir until crushed. After filtration, the juice could be consumed as a nutritious beverage daily.

Function: Enhancing immunity, relieving fatigue, resisting cancer, prolonging life.

68.4.2.2 Shihu Wine

Shihu can be used alone or combined with other herbs to prepare herbal wine. This product is popular for benefitting physically weak people. One example is Shihu (80 g), Shudihuang (processed root of *Rehmannia glutinosa*, 150 g), Danshen (roots and rhizomes of *Salvia miltiorrhiza*, 90 g), Rougui (stem barks of *Cinnamomum cassia,* 100 g) and Niuxi (roots of *Achyranthes bidentata,* 45 g) in 4 L of Chinese spirit or vodka for more than two weeks. Shake frequently to homogeneous. 25–50 mL daily is recommended.

Function: To nourish the liver and kidney. It can also be used for relieving symptoms of back and knees soreness when walking.

68.4.2.3 Shihu Tea

Composition: Shihu, Maidong (root tuber of *Ophiopogon japonicas*), green tea.

Preparation: Boil all materials with adequate amount of water for 30 min, drink as an ordinary tea.

Function: Promoting the production of body fluid and relieving sore throat.

68.4.2.4 Shihu Porridge

Composition: Shihu (20–30 g), Jinyinhua (flower of *Lonicera japonica*, 20 g)

Preparation: decoct Shihu and Jinyinhua with water. After filtration, pour juice into the pot, add 80 g of japonica rice to boil by slow heat for porridge.

Function: Relieving measles in children effectively.

68.4.2.5 Shihu Soup

Shihu can be used to make soup with pork, duck or fish. The typical way is to boil Shihu with lean pork and other herbs, such as Xiyangshen (roots of *Panax quinquefolium*), Maidong (root tubers of *Ophiopogon japonicus*) or Baishao (root of *Paeonia lactiflora*) on low heat for 60–90 min, add a little salt.

Function: Promoting the production of body fluid and eliminating dryness in the mouth and throat.

68.5 Clinical Use

Studies have shown that Shihu could promote the secretion of acid in the stomach [9]. *Dendrobium* in its prepared compound form could decrease the level of blood glucose and lipids. It was shown to increase insulin sensitivity in 90 cases of type 2 diabetic patients [10]. Shihu Yeguang pill when used with Tears Naturale Forte significantly improved the symptoms of dry eye of patients [11]. Mailuoning injection, is used clinically to dilate blood vessels, which then promotes blood circulation. This is seen to directly correlate to the improvement of overall brain functions [12].

Shihu has also been recently used in the treatment of stomach and lung cancer [3]. If treated with integrated Shihu and anti-cancer western medicine, it could reduce the complication of conventional therapies, stop progression of the condition, and improve the quality of life and prevent relapse from occurring.

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Chapter 69
Epimedium brevicornu Maxim. 淫羊藿 (Yinyanghuo, Barrenwort)

Li-hua Yan

69.1 Botanical Identity

Yinyanghuo, also known as Gangqian, Xianlingpi or Sanzhi Jiuyecao, is an important traditional Chinese medicine and functional food with tonic and anti-rheumatic effects [1]. Yinyanghuo is the dried leaves of four *Epimedium* species, *Epimedium brevicornu* Maxim., *E. sagittatum* (Sieb. et Zucc.) Maxim., *E. pubescens* Maxim., and *E. koreanum* Nakai, which are perennial herbs mainly distributed in East Asia. Wushan Yinyanghuo, the dried leaves of *E. wushanense* T.S. Ying, should be used separately from the other four *Epimedium* species according to Chinese Pharmacopoeia (2010 edition) [2, 3].

Epimedium is a genus of about 50 species of herbaceous plants, which belongs to the Barberry Family. *Epimedium* plants are perennial, deciduous or evergreen. The rhizome is short and stout or horizontally creeping. The leaves are basalor cauline, simple or compound. The leaf blade is usually fibrous. The leaflets are ovate, ovate-lanceolate or suborbicular, usually with spiny margins. The flowering stem have 1–4 leaves or leafless, and can be opposite or rarely alternate. Inflorescences are simple or compound, with terminal raceme or panicle, few or many flowered, glabrous or glandular. The flowers are bisexual and vary in color (yellow, white, purple or pink). The flower has 8 sepals, 4 petals and 4 stamens [3]. *Epimedium* species are also used as ground covers and ornamental plants due to the abundance of colors and patterns in their leaves and flowers [4].

Epimedium species grow mainly on cliffs under moist forests, near streams and wet lands at altitudes ranging from 200 to 3700 m. The vast majority of *Epimedium* species are found in China, although some grow in India, Japan, Korea, Russia, South Europe and North Africa [5]. In China, there are about 40 species that are

L. Yan (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: yanlihua2829@163.com

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mainly distributed in the southwest and central regions such as Guizhou, Sichuan, Shaanxi, Gansu, Henan, Anhui, Hunan, Hubei, Jiangxi and Zhejiang provinces. *E. koreanum* Nakai is mainly distributed in Jilin and Liaoning provinces. *E. sagittatum* (Sieb. Et Zucc.) Maxim. is also distributed in Fujian, Guangdong and Guangxi provinces [3]. Considering the shortage of wild resources and the huge market demand, large scale cultivation is carried out in the last twenty years. *E. wushanense* is distributed in Sichuan, Guizhou, Hubei and Guangxi provinces [3]. Now, entitled national GAP cultivated bases of *E. wushanense* located at Xiuwen, Longli and Leishan counties of Guizhou province.

The leaves of *Epimedium* species should be collected when the vegetation is in its highest abundance like summer and autumn months. After collection it should be removed from foreign matter, and dried in the sun. Upon completion, dried and cleaned leaves can be stored and implemented into markets as raw material. The raw material will be cut into shreds after being watered. Other processing methods for the specific purpose include fried Yinyanghuo, wine processed Yinyanghuo, salt processed Yinyanghuo and mutton oil processed Yinyanghuo. Among them, mutton oil processed Yinyanghuo is recorded in the Chinese Pharmacopoeia for being the most commonly used product. The process is as follows: 20 g mutton oil was melted at about 60 °C, and then 100 g Yinyanghuo leaves were added and stir-fried for 10 min at 60 °C. The finished product was light yellow-green and shining [2]. The flowering plant and crude drug of Yinyanghuo are shown in (Fig. 69.1).

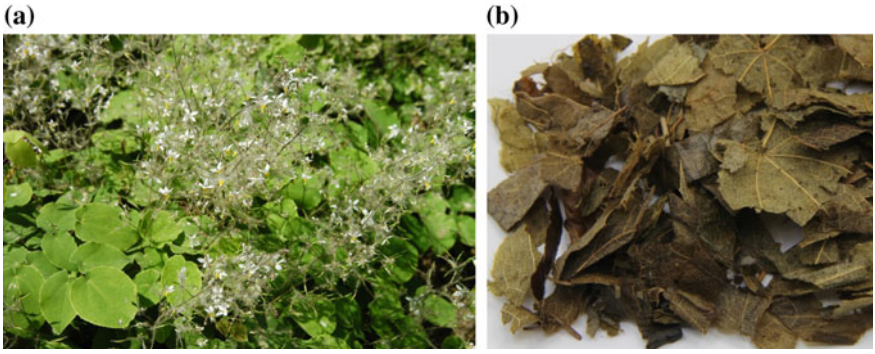

Fig. 69.1 The flowering plant (**a**) and crude drug (**b**) of Yinyanghuo

69.2 Chemical Constituents

Extensive investigations related to phytochemistry have been done on Yinyanghuo. Flavonoids, lignans, phenolic acids, ionones, phenylethanoid glycosides, sesquiterpenes as well as other compounds that have been isolated and identified [5]. Among them, flavonoids are the most prominent constituents and also act as the main active compounds. Today, more than 130 flavonoids have been isolated and identified from the five legal sources of Yinyanghuo or Wushan Yinyanghuo recorded in the Chinese pharmacopoeia. Structures of the typical compounds are shown in Fig. 69.2.

It is widely accepted that 8-prenylflavonoids like icariin (**1**), epimedin A (**4**), epimedin B (**5**), and epimedin C (**6**) are the major pharmacological active constituents in *Epimedium* species. Icariin is the representative component and used as a marker to evaluate the quality of Yinyanghuo [2], the content of which varies among species and sources. Although *E. wushanense* is one of the five botanical sources of Yinyanghuo, the content of icariin was much lower than that of the other four species. On the other hand, *E. wushanense* contained epimedin C as the predominant constituent. Therefore, *E. wushanense* was individually recorded as "Wushan Yinyanghuo" in the latest 2010 edition of Chinese Pharmacopoeia, and epimedin C was selected as a bioactive marker for the quality analysis of *E. wushanense* [6].

In a recent quantitative anaysis, the contents of five marker compounds, epimedins A-C, icariin, and baohuoside I (**2**), as well as total flavonoids of 22 samples from eight official species of *Epimedium* were determined by HPLC and UV, separately. The results demonstrated that the average total flavonoid content of eight species was 6.15 ± 1.55 %, and the amounts of epimedin A, B, C, icariin, and baohuoside I were 0.17 ± 0.10, 0.24 ± 0.18, 1.00 ± 1.55, 0.44 ± 0.34, and

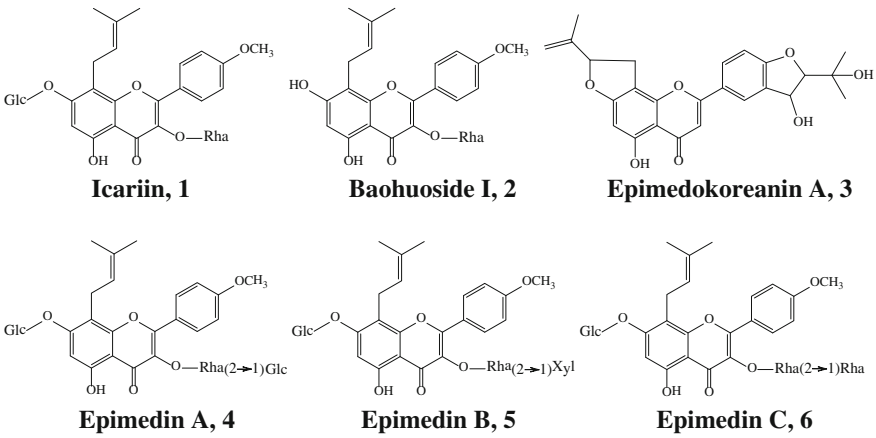

Fig. 69.2 Typical flavonoids isolated from Yinyanghuo

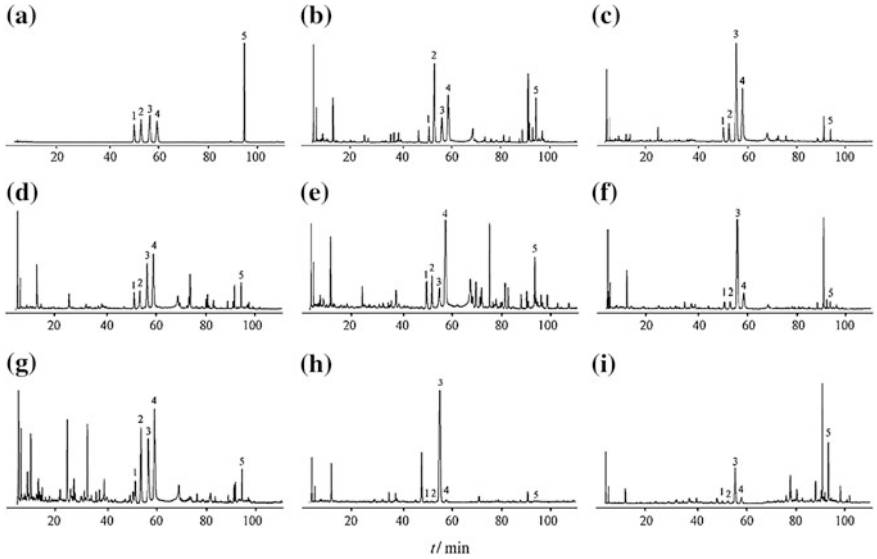

Fig. 69.3 HPLC chromatograms of Yinyanghuo from the main producing areas. **a** Reference standards. **b** *E. brevicornu* Maxim. **c** *E. sagittatum* (Sieb. et Zucc.) Maxim. **d** *E. pubescens* Maxim. **e** *E. koreanum* Nakai. **f** *E. wushanense* T.S. Ying. **g** *E. acuminatum* Franch. **h** *E. myrianthum* Stearn. **i** *E. leptorrhizum* Stearn. 1: epimedin A, 2: epimedin B, 3: epimedin C, 4: icariin, 5: baohuoside I

0.07 ± 0.07 %, respectively. There were significant differences in types and contents of 8-prenylflavonoids in different species [7]. The HPLC chromatograms of different *Epimedium* species from the main producing areas are shown in Fig. 69.3.

69.3 Pharmacological Studies

Modern pharmacological studies have shown that the crude extracts and compounds of Yinyanghuo have extensive biological functions, especially in the improvement of sexual dysfunction, regulation of hormones and modulation of immunological functions as well as anti-osteoporosis, anti-tumor, anti-aging and anti-atherosclerosis activities [5].

The extract of Yinyanghuo has been proven to have a therapeutic effect in animal models of osteoporosis induced by ovariectomy, to increase core binding factor alpha 1 expression in the bone of ovariectomized rat and to stimulate the proliferation of osteoblast and osteoblast-like UMR 106 cells. Research has also shown that the extract of Yinyanghuo can obviously promote the growth of femora, synthesis of proteoglycans and proliferation of chondrocytes in femora of chick embryo in in vitro culture [8]. Many studies have demonstrated that icariin is able to

stimulate the proliferation of osteoblast and induce osteogenic differentiation of marrow stromal cells and pre-osteoblastic MC3T3-E1 cells [8, 9].

69.4 TCM Applications and Dietary Usage

69.4.1 TCM Applications

Yinyanghuo was initially focused on due to its potential effect on the sexual function, and traditionally used as aphrodisiac and kidney tonic. According to legend, this property was discovered by a Chinese goat herder who noticed far more active sexual activity in his goats after they ate the plants. In clinics, Yinyanghuo is widely used as a constituent of many preparations in Chinese medicine, and frequently used to treat osteoporosis, climacteric period syndrome, breast lumps, hyperpiesia and coronary heart disease.

Common Yinyanghuo preparations clinically used include the following forms: (1) Xianlingpi Tablets: It is made from single Yinyanghuo, and used for the treatment of impotence, spermatorrhea, chest tightness, dizziness, shortness of breath, exhausted, rheumatic arthralgia, coronary heart disease, and climacteric hypertension etc. (2) Bushen Qiangshen Tablets: It is composed of five herbal components: Yinyanghuo, Tusizi (seeds of *Cuscuta chinesis*), Jinyingzi (fruits of *Rosa laevigata*), Nvzhenzi (fruits of *Ligustrum lucidum*), and Gouji (rhizomes of *Cibotium barometz*). It is used as a tonifying kidney agent to treat discomfort of the waist, acratia, dizziness, tinnitus, and palpitate. (3) Xianling Gubao Capsules: It is composed of Wushan Yinyanghuo, Xuduan (roots of *Dipsacus asper*), Danshen (roots and rhizomes of *Salvia miltiorrhiza*), Zhimu (rhizomes of *Anemarrhena asphodeloides*), Dihuang (roots of *Rehmannia glutinosa*), and Buguzhi (fruits of *Psoralea corylifolia*). It has been widely used in the clinic for treating osteoporosis. (4) Tiaojing Cuyun Pills: It is an 18-component Chinese patent medicine, which is mainly used for menoxenia, amenorrhea andsterility. (5) Shenbao Heji: It is a 22-component Chinese patent medicine, which is mainly used for lower back pain, diuresis and chilly.

69.4.2 Dietary Usages

Yinyanghuo is not only used as a medicine to cure various diseases, but also as a supplement to prevent disease and strengthen the body. Generally, Yinyanghuo can be soaked in wine, decocted with water, cooked with meat or prepared with other foods for impotence, prospermia, and acratia. To increase its effect, Yinyanghuo was also used with other traditional medicines. The following are some convenient forms that have been developed for consumption.

69.4.2.1 Yinyanghuo Yizhi Soup

Composition: Yinyanghuo 15 g, Yizhi (fruits of *Alpinia oxyphylla*) 15 g, Rougui (barks of *Cinnamomum cassia*) 9 g.

Preparation: Boil all herbs with proper amounts of water for 30 min, and then filtrate for use. Take it twice daily.

Function: Used for frequent micturition.

69.4.2.2 Erxian Concentrated Decoction

Composition: Yinyanghuo 150 g, Xianmao (rhizomes of *Curculigo orchioides*) 150 g, Bajitian (roots of *Morinda officinalis*) 90 g, Zhimu (rhizomes of *Anemarrhena asphodeloides*) 90 g, Huangbai (barks of *Phellodendron chinense*) 90 g, Danggui (roots of *Angelica sinensis*) 90 g, refined honey 259 g.

Preparation: Break the first six herbs into a coarse powder. The powder is to then be immersed in water for 12 h, and then boiled for 3–5 h. The decoction is filtrated and concentrated to paste. Add refined honey, mix together, store in the refrigerator until use. Dissolve two teaspoons of product in hot water to drink. Take it twice daily.

Function: Used for hypertension, chronic nephritis, urinary infection, neurasthenia, soreness and weakness of waist and knees, dizziness and tinnitus, magersucht, acratia.

69.4.2.3 Custard Cream of Yinyanghuo

Composition: Yinyanghuo 50 g, two eggs.

Preparation: Boil Yinyanghuo with adequate amount of water for 20 min. Remove the residues, and cool the soup to room temperature. Add the eggs in the soup and mix well. Then steam the mixture over boiling water until cooked. Add salt and sesame oil to taste.

Function: Used for impotence, prospermia, emaciation, acratia, soreness and weakness of waist and knees, osteodynia, chilly [10].

69.4.2.4 Yinyanghuo Yangshen Gruel

Composition: Yinyanghuo 10 g, a pair of goat kidney, rice 100 g.

Preparation: Boil Yinyanghuo with adequate amount of water for 20 min. Remove residues, add rice, heat water to a boil, add goat kidneys, and continue to heat until cooked. Add ginger, onion, garlic and salt to taste.

Function: Used for teratospermia syndrome.

69.4.2.5 Yinyanghuo Gouqi Noodles

Composition: Yinyanghuo 10 g, Gouqizi (fruits of *Lycium barbarum*) 30 g, Longyanrou (arils of *Dimocarpus longan*) 50 g, noodles 100 g.

Preparation: Boil Yinyanghuo first for 20 min. After filtration, add other two herbs and continue to heat to boiling for 3–5 min. Cook the noodles in another pot. Combine the soup and noodles. Add ginger, onion and salt to taste.

Function: Used for azoospermia.

69.4.2.6 Yinyanghuo Wine

Composition: Yinyanghuo 69 g, wine 500 mL.

Preparation: Put the herb into a container, add wine, seal and soak for 7 days. Take 30–50 mL everynight.

Function: Used for impotence, dysgenesia, acroanesthesia [11].

69.5 Clinical Evidences

Studies of clinical effects on Yinyanghuo principally focused on treatment of various osteopathia like osteoporosis, catagma, and osteoarthritis. The efficacy of Yinyanghuo tea was investigated on patients with osteoporosis. 150 patients were randomly divided into treatment (n = 75, mean age 61.22 ± 7.43 years) and control group (n = 75, mean age 60.78 ± 7.52 years), and both groups were treated with 1.5 g Calcium carbonate and Vitamin D3 tablets once daily for one year. In addition, patients in the treatment group were given Yinyanghuo tea, 6 g per day. At the end of the trial, there was a considerable increase in bone mineral density (BMD), as well as relief of pain in the treatment group [12].

Xianling Gubao capsule is made with Yinyanghuo in the China market. Xianling Gubao capsules were used to treat 100 cases of primary osteoporosis. Patients were randomly divided into treatment and control group. In treatment group (n = 50), patients were given 0.25 g Xianling Gubao capsules each time, two times per day for three months. Patients in the control group (n = 50) were treated with 10 mg Alendronate tablets once daily in the morning. The results revealed that Xianling Gubao capsules can remarkably raise the bone mineral density (BMD) of osteoporosis patients and improve clinical symptoms, and is very effective in preventing and treating primary osteoporosis [13]. Similar results were observed in another trial: administration of 0.25 g Xianling Gubao capsules twice daily for three months considerably relieved pain symptoms caused by osteoporosis [14].

69.6 Safety Evaluation and Toxicity Issue

Yinyanghuo has been used for over 2000 years as an important traditional herb in China. Presently, there is no relevant information reported on the adverse effects or toxicity resulting from uses of Yinyanghuo in humans. According to the record of Chinese Pharmacopoeia (2010 Edition), the clinical dosage of Yinyanghuo recommended for adults is 6–10 g daily. Relative systematic safety evaluation experiments of the water extract of Yinyanghuo were performed in terms of its acute toxicity, cellular toxicity, and genotoxicity. It was found that the LD_{50} of Yinyanghuo was higher than 80 g/kg, and the IC_{50} in Chinese hamster ovary cells and Chinese hamster lung cells were 55.4 and 19.53 mg/mL, respectively. Yinyanghuo did not have mutagenic effects and all toxicity tests were negative [15]. In acute toxicity studies carried out on mice, the total flavonoid of Yinyanghuo (total flavonoid content was 78.24 %) was found to be safe up to 36 g/kg [16]. The long-term toxicity tests showed that administration of the above mentioned total flavonoids of Yinyanghuo at a dose of 1.0 g/kg, 2.0 g/kg or 4.0 g/kg to rats for 12 weeks did not show any toxicological effects [17].

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Chapter 70
Gynostemma pentaphyllum (Thunb.) Makino 绞股蓝 (Jiaogulan, Fiveleaf Gynostemma)

Li-hua Yan

70.1 Botanical Identity

Gynostemm apentaphyllum (Thunb.) Makino, a perennial creeping herb of the Gourd family (Cucurbitaceae), is a well-known edible and medicinal plant in Asia. It is used for heat clearing, detoxification, and chronic bronchitis, lowering blood lipid and blood glucose, regulating blood pressure, strengthening immunity, and inhibiting cancer growth. Common names of *G. pentaphyllum* include Jiaogulan, Qiyedan, Xiaokuyao, Gongluo Guodi, Biandi Shenggen, Amachazuru, Dungkul-cha, and Baan Ja Kahn [1, 2]. The aerial part of *G. pentaphyllum* is the medicinal part, and the leaves are used as tea. Jiaogulan contains numerous dammarane-type saponins (named gypenosides or gynosaponins), which are structurally similar to glycosides found in *Panax ginseng* (Araliaceae). For this reason Jiaogulan has attracted much interest and earned its favorable name of "Southern Ginseng" [3].

Jiaogulan is mainly distributed in China, Japan, Korea, and Southeast Asian countries, and occurs naturally in forests, thickets or roadsides on mountain slopes with an elevation of 200–3200 m. In China, it grows abundantly in the south of the Qinling Mountains and provinces south of the Yangtze River [4]. Owing to its lower retail price and easier availability than ginseng, cultivations of Jiaogulan or its commercialized products such as herbal teas and extracts have been put into production on a large scale. Today there are sweet and bitter taste varieties of Jiaogulan in the market. The national GAP cultivated bases of Jiaogulan located at Pingli county of Shaanxi province in China.

The stem and branches of *G. pentaphyllum* are slender with deep narrow grooves. The leaves are alternate and pedate with 3–9 leaflets (usually 5–7 leaflets). The tendrils are filiform and bifurcate [4]. The flowers are dioecious and the pollen

L. Yan (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: yanlihua2829@163.com

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Fig. 70.1 The plant (**a**) and crude drug (**b**) of Jiaogulan

is dispersed by wind. The fruit consists of a smooth, globular berry about 5–6 mm in diameter and black when ripe. This plant exhibits both sexual reproduction and clonal growth by rhizomes or bulbils [5].

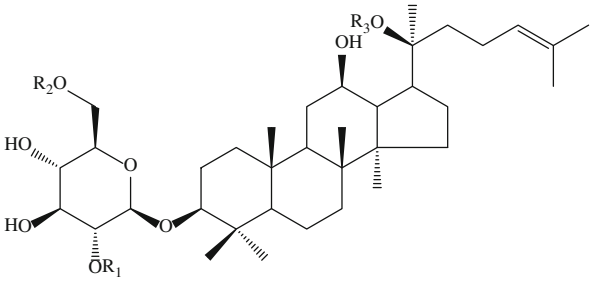
Jiaogulan may be gathered twice every year in June and October, respectively. Cut the aerial parts keeping distance of 5–10 cm from the ground. Cleaned, dried in the shade and baled before packing. Then the products could be stored and marketed as raw material [6]. For Jiaogulan tea, the leaves should be collected from spring to autumn, and August is the best collection time. The process of Jiaogulan tea include fast drying, rolling, baking, packing, etc. [7]. The plant and crude drug of Jiaogulan are shown in Fig. 70.1.

70.2 Chemical Constituents

Jiaogulan contains saponins, flavonoids, polysaccharides, megastigmane glycosides, sterols, vitamins and amino acids.

70.2.1 Saponins

The most abundant components in Jiaogulan are dammarane-type saponins, named gypenosides or gynosaponins, which have been considered as its major bioactive components. To date, approximately 170 gypenosides were obtained from *G. pentaphyllum*. Of these, eight saponins are the same as the protopanaxadiol-type ginsenosides Rb1, Rc, Rb3, Rd, F2, Rg3, malonylginsenosides Rb1 and Rd found in *P. ginseng*. These ginsenosides make up about 25 % of the total gynosaponins in the plant [8]. Total saponins content is reported to be about 2.4 % of the dried herb. The total saponins content is highest before flowering. Some studies also revealed



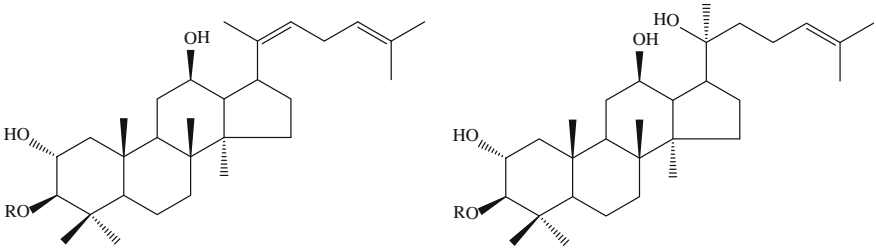
Gypenoside I, 1, R_1=Glc, R_2=Rha, R_3=Glc(6←1)Glc

Gypenoside Ⅱ, 2, R_1=Glc, R_2=Rha, R_3=Glc(6←1)Rha

Gypenoside Ⅲ, 3, R_1=Glc, R_2=H, R_3=Glc(6←1)Glc

Gypenoside Ⅳ, 4, R_1=Glc, R_2=H, R_3=Glc(6←1)Xyl

Gypenoside Ⅷ, 5, R_1=Glc, R_2=H, R_3=Glc



Damulin A, 6, R=Glc(2←1)GlcGypenoside L, 7, R=Glc(2←1)Glc

Fig. 70.2 Representative triterpene saponins isolated from Jiaogulan

that the gypenoside compositions differed in Jiaogulan samples collected from different origins and seasons, sweet and bitter taste variants, and genotypes [2]. Ginsenosides Rb1 (Gypenoside III, **3**), Rb3 (Gypenoside IV, **4**), and Rd (Gypenoside VIII, **5**) were selected as markers for quantitative analysis, because they were regarded as the bioactive saponins of Jiaogulan and commercially available. Structures of some representative compounds are shown in Fig. 70.2 [2, 3].

70.2.2 Other Constituents

Common flavonoids present in Jiaogulan include rutin, quercetin, isorhamnetin and cirsiliol. Recent studies investigated the chemical structures and bioactivities of Jiaogulan polysaccharides. Two acidic polysaccharides (GP-B1 and GP-C1) were

obtained from Jiaogulan. The molecular weights of the two polysaccharides were 79 kDa for GP-B1 and 126 kDa for GP-C1. GP-B1 was composed of Gal, Ara, Man, Rha, Xyl, Glc, GalA and GlcA in a molar ratio of 3.5:3.2:0.6:0.9:0.3:0.5:0.6:0.4. GP-C1 consisted of Gal, Ara, Man, Rha, Glc, and GlcA in the proportions of 2.1:1.0:0.3:0.5:0.4:0.9 [9].

70.3 Pharmacological Studies

Pharmacological studies have revealed that Jiaogulan has a wide spectrum of bioactivities, including lipid-lowering, anti-hyperglycaemia, immuno-potentiating, antitumor, anti-inflammatory, anti-aging, anti-fatigue, anti-gastric ulcer effects, as well as protective effects on cardiovascular system and central nervous system [2]. It is believed that the medicinal properties of Jiaogulan are mainly attributed to the saponin and polysaccharide components. However, mechanisms underlying these diverse effects are still poorly understood.

The intravenous administration of the aqueous extract from Jiaogulan leaves and of the pure gypenosides III and VIII produced a protective effect against vasopressin-induced coronary spasm, arrhythmias and pressor response and a protective and suppressive effect on ouabain-induced arrhythmias in the anaesthetized guinea-pigs. These effects indicate that Jiaogulan extract possesses significant cardiovascular properties similar to those exhibited by verapamil and suggest that gypenoside III and gypenoside VIII are two of its active components responsible of these properties [10].

GP-B1, an acidic polysaccharide obtained from Jiaogulan, had a significant inhibitory effect on the growth of melanoma B16 in vivo and in vitro. Meanwhile GP-B1 could increase the relative spleen weight and stimulate the splenocyte proliferation alone or combined with ConA. Moreover, GP-B1 treatment induced an evident increase in the level of serum TNF-α, IFN-γ, and IL-12 and a reduction for IL-10 production. These results indicate that the antitumor effects of GP-B1 are associated with immunostimulation [9].

70.4 TCM Applications and Dietary Usage

70.4.1 TCM Applications

Jiaogulan has been used in traditional Chinese medicine for heat clearing, detoxification, and as an anti-tussive and expectorant for relieving cough and chronic bronchitis. Modern pharmacological studies and clinical research have indicated a variety of therapeutic qualities of Jiaogulan. Jiaogulan could be used as single form or in combination with other herbs based on TCM theory.

Common Jiaogulan preparations clinically used include the following forms: (1) Jiaogulan Total Saponins tablets: It is made from single Jiaogulan, and used for the treatment of hyperlipemia. (2) Lingzhi Jiaogulan oral liquid: It is composed of Jiaogulan and Lingzhi (sporocarps of *Ganoderma lucidum*), and mainly used for relieving palpitation, shortness of breath, and insomnia. (3) Yinlan Tongluo oral liquid: It is composed of Yinxingye (leaves of *Ginkgo biloba*) and Jiaogulan. It is mainly used for the treatment of dizziness, palpitation, and fatigue. (4) Shen-ling-lan capsules: It is a fourteen-component Chinese patent medicine, which is mainly used before or after radiotherapy and chemotherapy for tumor to improve mental fatigue, feebleness, and emaciation. (5) Jiaogulan total saponins are also prepared and consumed as an active pharmaceutical ingredient in the market.

70.4.2 Dietary Usage

Jiaogulan has been used in food or dietary supplement for hundreds of years. Nowadays, various health foods of Jiaogulan are available in the markets, including tea, beverages, wine, beer, yogurt, bread, biscuits or noodles, which are used for reducing the risk of cardiovascular diseases, diabetes, and cancer. The following are some convenient forms that can be easily made at home.

70.4.2.1 Jiaogulan Tea

Jiaogulan is most often consumed as herbal tea alone or mixed with other herbs. Some examples are: Jiaogulan Shanzha Tea composed of Jiaogulan (15 g) and Shanzha (fruits of *Crataegus pinnatifida*, 30 g); Jiaogulan Yinxingye Tea composed of Jiaogulan (20 g) and Yinxingye (leaves of *G. biloba*, 30 g); Jiaogu Shuiji Tea composed of Jiaogulan (5 g) and Shuifeiji (fruits of *Silybum marianum*, 5 g); Jiaogulan Duzhong Tea composed of Jiaogulan (15 g) and Duzhongye (leaves of *Eucommia ulmoides*, 10 g); Jiaogulan Jueming Huaihua Drink composed of Jiaogulan (15 g), Juemingzi (seeds of *Cassia obtusifolia*, 30 g) and Huaihua (flowers of *Sophora japonica*, 10 g); Jiaogulan Jinqiancao Drink composed of Jiaogulan (15 g) and Jinqiancao (herbs of *Lysimachia christinae*, 50 g). Drinking these herbal teas regularly could improve health and reduce the severity of various illnesses, such as hyperlipemia, hypertension, atherosclerosis, obesity, dizziness, headache, insomnia, palpitation, etc. [11, 12].

70.4.2.2 Jiaogulan Used in Medicated Foods

Jiaogulan can be used to make foods with rice, legumes, mushroom, chicken and pork, etc. Other herbs like Gouqizi (fruits of *Lycium barbarum*), Yuxingcao (herbs of *Houttuynia cordata*), and Juhua (flowers of *Chrysanthemum morifolium*) can be

cooked together with Jiaogulan. Below is an example of a typical recipe. Boil fresh Jiaogulan with proper amount of water for 1–2 min, and then strain off the water through a colander. Immerse Jiaogulan in cold water. Cook rice with adequate amount of water for 20–30 min. When the rice is nearly ready, add finely chopped Jiaogulan. Add rock candy into the rice porridge to taste. This rice porridge is mainly used for the treatment of cough with Lung Heat [12, 13].

70.5 Clinical Evidences

Studies of clinical effects on Jiaogulan principally focused on the treatment of cardiovascular diseases, hyperlipemia and diabetes. Jiaogulan total saponins are the major bioactive constituents in Jiaogulan. In clinical application, there are five main dosage forms, including tablet, capsule, granule, dispersible tablet, and dripping pills. These drugs are widely used in China for lowering blood lipid.

The efficacy of Jiaogulan on lowering blood lipid was evaluated among 80 patients. Patients were randomly divided into treatment and control group. In treatment group (n = 40), patients were given 60 mg Jiaogulan total saponins dispersible tablets, three times per day for two months. Patients in the control group (n = 40) were treated with 0.2 g Vitamin E nicotinicate capsules, twice daily. In both treatment and control group, the levels of total cholesterol (TC) and total triglyceride (TG) were reduced, while high-density lipoprotein (HDL) level was enhanced as compared to baseline. The total efficiency of the treated group (95.0 %) is obviously superior to the control group (87.5 %) [14]. Diarrhea occurred in two patients of treatment group. The side effect is mild and did not stop the patients from taking the medicine. The symptom disappeared two days after finishing the trial. Similar results were observed in another clinical trial among 20 hyperlipemia patients. All patients were given 60 mg Jiaogulan total saponins capsules, three times per day for three months. At the end of the trial total cholesterol and total triglyceride were significantly decreased. Moreover, this drug offered adjutant therapy to hypertension, obesity, and constipation [15].

Diabetic nephropathy is a serious microvascular complication and one of the main causes of end-stage renal disease. The efficacy of Jiaogulan was investigated on patients with early diabetic nephropathy. 86 patients were divided into three groups: 32 patients treated with Jiaogulan total saponins tablets 60 mg each time, three times per day; 28 patients treated with valsartan tablets 80 mg each time, four times per day; 26 patients as the control group without any other treatment. All patients kept receiving their original treatments. The treatment duration was 24 weeks. The results revealed that Jiaogulan total saponins tablets and valsartan tablets can significantly decrease the urine mircoalbuminuria excretion rate (UAER), urinary transforming growth factor-β (TGF-β), and improve the renal function. In addition, Jiaogulan total saponins tablets can significantly remedy blood lipid in the patients with diabetic nephropathy [16].

70.6 Safety Evaluation and Toxicity Data

In traditional medicine practice, the use of Jiaogulan extract for adaptogenic and therapeutic purposes is usually based on gypenoside content, with a recommended daily dose of 60–180 mg (or 1–3 mg/kg) gypenosides for blood glucose and lipid lowering effects [17]. In a recent study, the standardized formulation of water extract of Jiaogulan was used for acute and subchronic toxicity evaluation in rats. Total gypenosides in the standardized Jiaogulan extract were measured by high performance liquid chromatography (HPLC) and found to be 6 %. Total saponins in the extract were also determined and found to be 14.9 %. In acute toxicity test in rats, a single oral administration of the extract at a dose of 5000 mg/kg body weight did not produce mortality or any hazardous effect. In subchronic toxicity test, the dose of the extract was 1000 mg/kg/day, which contained gypenosides of about 20–60 times the human dose. The daily oral treatment of the extract at this dose for 90 days did not cause death or any toxic signs and symptoms [17]. The acute toxicity of Jiaogulan dripping pills was evaluated and showed a LD_{50} of 12.04 g/kg on mice orally [18]. The long-term toxicity tests indicated that the water extract of Jiaogulan given orally with doses up to 750 mg/kg/day did not produce any sign of toxicity in the rats during the 6-month administration period [19]. These results indicate that Jiaogulan is a safe herb for medical and dietary uses.

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Chapter 71
Houttuynia cordata Thunb 鱼腥草 (Yuxingcao, Houttuynia)

Qi-wei Zhang

71.1 Botanical Identity

Houttuynia cordata Thunb, the sole species in the genus *Houttuynia* of the Lizardtail family (Saururaceae), is a perennial herb. Since its stems and leaves smell of fish after rubbing, it earns the nickname Yuxingcao ("fishy grass").

The stems of fresh herb of *H. cordata* are cylindrical, 20–45 cm long, 2.5–4.3 mm in diameter; the upper part is green or purplish-red, the lower part white; the nodes are distinct, glabrous or sparsely pubescent with rootlets on the nodes of lower part. The leaves are alternate; the lamina is cordate, 3–10 cm long, 3–11 cm wide; the apex is acuminate, and the margin is entire; the upper surface of the lamina is green with densely distributed glandular dots; the lower surface often purplish-red; the petioles are slender and can accrete with stipules at the base of petioles to form sheaths. The spike is terminal. The odor of the herb is fishy; the taste is astringent [1].

The Lizardtail family consists of four genera and eight species. They are distributed in the Asia and North America with three genera in China. The genus *Houttuynia* has only one species, i.e. *Houttuynia cordata*. It is broadly distributed in the southeast, southwest and central areas of China, from eastern Taiwan to southwestern Yunnan and Tibet, as well as to northern Shaanxi and Gansu, with a concentration in Sichuan, Hubei, Hunan, Jiangsu, etc. Basic and primary process is to remove foreign matter, wash-cleaning rapidly, cut into sections for fresh herb, and sun-dried [1] (Fig. 71.1).

Q. Zhang (✉)
China Academy of Chinese Medical Sciences,
Institute of Chinese Materia Medica, Beijing 100700, China
e-mail: zhangqw1955@163.com

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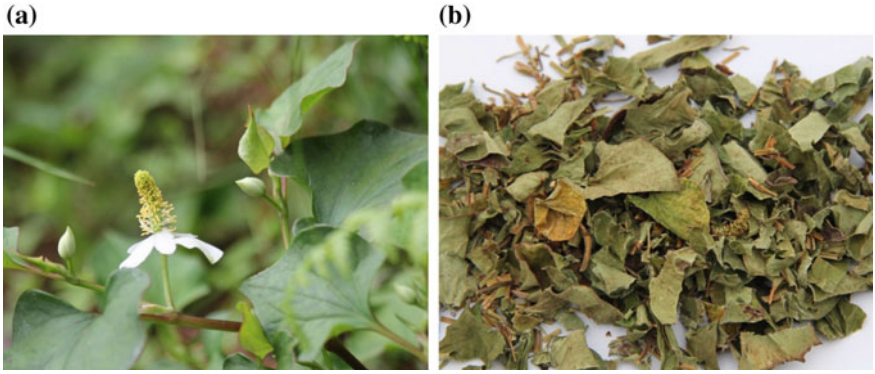

Fig. 71.1 The flowering plant (**a**) and crude drug (**b**) of Yuxingcao

71.2 Chemical Constituents

The chemical constituents in Yuxingcao, except nutrition ones, have also been investigated. The researches have mainly focused on its volatile oils, flavonoids, phenols, and so on. Below is a brief introduction to these research results.

71.2.1 Volatile Oils

The oil extracted by steam distillation is yellowish, and its content is about 0.03 % in the fresh herb, and about 0.04 % in the dried herb.

A GC-MS instrument analyzed the volatile oils. Sixty-eight chemical components were separated from the aboveground part of the herb, and 48 compounds were identified. The sum of peak areas identified was more than 90 % of the total peak areas. The main 17 compounds were decanoyl aldehyde (**1**), 2-undecanone (**2**), decanal, n-tridecylaldehyde, decylformate, β-myrcene, bomeol acetate, geraniol acetate, decanoic acid, α-pinene, tridecyl aldehyde, 1-dodecanol, 2-tridecanone, β-pinene, D-limonene, nonanol, 2-dodecanone. Their peak areas were about 87 % of the total peak areas [2].

71.2.2 Flavonoids

It was reported that the flavonoids in this herb included quercetin, quercitrin, isoquercitrin, hyperin, afzelin, and rutin. In recent years, the chemical constituents were investigated in the water-soluble portion of the fresh herb. Five flavonoid constituents were separated and identified; three of them were quercetin-3-O-β-D-galactoside-

Decanoyl aldehyde, 1 **2-Undecanone, 2**

Fig. 71.2 Representative compounds in Yuxingcao

7-O-β-D-glucoside, kaempferol-3-o-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside, quercetin-3-O-α-L-rhamnopyranosyl-7-O-β-D-glucopyranoside [3].

71.2.3 Phenols

Five phenol compounds were separated in the n-butanol portion from methanol extract of fresh Yuxingcao, and identified as chlorogenic methyl ester, (E)-4-hydroxy-4-[3′-(β-D-glucopyranosyloxy)butylidene]-3,5,5-trimethyl-2-cyclohexen-l-one, 2-(3,4-dihydroxyphenyl)ethyl-β-D-glucopyranoside, p-hydroxyphenethyl-β-D-glueoside, 4-(β-D-glucopyranosyloxy)-3-hydroxybenzoic acid [4].

71.2.4 Others

It was reported that cordarine, chlorogenic acid, palmitic acid, linoleic acid, stigmastan-4-en-3-one, 5α-stigmastan-3,6-dione, and succinic acid were separated and identified from Yuxingcao.

The chemical structures of representative compounds are shown in Fig. 71.2.

71.3 Pharmacological Studies

71.3.1 Antibacterial Effects

The dilute juice of fresh Yuxingcao showed antibacterial activity against *Salmonella typhi, S. paratyphi A, Shigellaflexneri, Pseudomonas aeruginosa, Proteus vulgaris, Peumococcus pneumoriae* and *S. albus*. The volatile oils extracted from fresh Yuxingcao exerted some inhibition against *Streptococcus heamolyticus, S. aureus, Pseudomonas aeruginosa,* and *E. coli*.

71.3.2 Antiviral Effects

Yuxingcao injection (the volatile oil solution) can cause the inhibition of influenza A1 virus nucleoprotein gene expression [5]. Another research showed that Yuxingcao had the in vitro anti-cytomegalovirus effect [6].

71.3.3 Antioxidant Effects

The total flavonoids of Yuxingcao possessed strong antioxidant capacity and high free radical scavenging activities. The total antioxidant capacity of the herb is stronger than that of BHT. The SC50 values of DPPH radical, superoxide anion radical and hydroxyl radical were found to be 12.0, 14.4, and 12.8 μg/mL respectively [7].

The total flavonoids in Yuxingcao extracted with 70 % ethanol exerted high free radical scavenging activities. The concentration of the flavonoids had positive relativity with its antioxidant capacity.

71.3.4 Anti-inflammatory Effects

The anti-inflammatory effects of volatile oils in Yuxingcao were studied, and the results showed that the volatile oils inhibited the mice ear edema, rat paw swollen and rat granuloma. The volatile oils also inhibited the inflammation factors (TNF-α and IL-1).

Another research indicated that 80 % ethanol extract of Yuxingcao decreased the chemotactic ability of HMC-1 cells in response to stem cell factor by inhibiting the NF-kappa B activation, and the herb extracts might be useful for treating mast cell-induced inflammatory diseases [8].

71.3.5 Antipyretic Effects

Yuxingcao injection possessed obvious antipyretic effect on yeast-induced fever rats and the effect was in a dose dependent manner. The antipyretic mechanisms might be due to inhibiting the increase of cAMP in hypothalamus and promoting the release of AVP in ventral septal area (VSA) [9].

71.3.6 Organ Protection Effects

The study indicated that Yuxingcao injection could reduce urinary protein content and renal pathologic changes of membranous nephritis rats. Another research showed that Yuxingcao protected against the renal lesion in diabetic rats through inhibiting the expression of TGF-β1 and enhancing the expression of BMP-7. It was reported that Yuxingcao volatile oils can reduce connective tissue growth factor and improve adiponectin in diabetic rats, which may be the mechanism of the herb on relieving renal impairment in diabetic rats.

71.4 TCM Applications and Dietary Usage

More than two thousand years ago, Chinese ancestors used Yuxingcao as a potherb. From the time of Wei-Jin dynasty (AD 220–316), it was formally accepted for medical use, and was named after *Houttuynia* in the ancient Chinese medical books. Since ancient times, Yuxingcao has played a dual role: as a medicine and as a food, helping people to preserve health, prevent and treat diseases.

71.4.1 TCM Applications

In traditional Chinese medicine, the action of Yuxingcao is to remove toxic heat, promote drainage of pus, and relieve dysuria. It is used to treat lung abscesses with purulent expectoration, heat in the lung with cough and dyspnea, acute dysentery, acute urinary infection, carbuncles and sores [1].

The following is a brief introduction to internal and external use of Yuxingcao. Internal Use:

For treatment of pulmonary abscess and coughing with purulent and bloody sputum, take 250 g of the fresh herb, get juice by pounding, take three times a day for three days.

For treatment of heat cough, take 60 g of the fresh herb (or 20 g of the dried herb), brew in boiling water or decoct with water, add some sugar and drink as tea. For cough with yellow phlegm, it can relieve cough and dispel phlegm.

For treatment of heat stranguria, take 100 g of the fresh herb and some sugar, decoct with water, and take once a day.

For treatment of acute dysentery, take 50–100 g of the fresh herb (a half for the dried herb), decoct with water, take once a day.

For treatment of urinary tract infection, frequent and painful urination, take 50 g of the fresh herb (or 30 g of the dried herb), decoct with water.

External Use:

For treatment of hemorrhoid with swelling and pain, take 100 g of the dried herb (or 300 g of the fresh herb), add 1000 ml of water, decoct the herb to make a soup, fumigate and wash the affected part with the soup once or twice a day for three to four days.

For the treatment of carbuncle and furuncle, take the fresh herb, pound it to apply on affected part; or take the dried herb, grind it into powder and blend with honey to apply. This can cure carbuncle and deep-rooted ulcer, relieve pain and drain pus.

71.4.2 Dietary Usages

Yuxingcao is the plant that can be used as medicine and food. It is on the list of medicine and food materials that ratified by the Ministry of Health of China, and draws attention of the public.

The nutrition constituents in Yuxingcao include proteins, fat, carbohydrates, and minerals. It was reported that the contents of protein, crude fat, soluble carbohydrates and ashes were 2.72, 1.86, 1.42, and 1.08 % respectively. The determination results of mineral elements in the herb show it contains a great deal of Calcium, Magnesium, Potassium, and a little of Iron, Zinc, Copper, Manganese. It contains 574 mg of Calcium, 156 mg of Magnesium, 309 mg of Potassium per 100 g of the herb.

When Yuxingcao is used as food, the fresh stems and leaves are often picked before the plant is abloom in the spring and summer. The underground roots and stems are also edible. Though the stems and leaves of the plant smell of fish, for the people who are used to it, the more concentrated the odor, the greater the preference.

Wash the stems and leaves before serving, use them alone or mix with lettuce and carrots to make cold dishes. They can also be used to stew meat, boil noodles, cook gruel, prepare soups, and make fillings. Here are two commonly used recipes:

Cold dressed “fishy grass”: Take 250 g of the fishy grass. Clean them and slice them into small sections. After pickling in salt, mix in garlic spread, sesame oil, vinegar, and monosodium glutamate.

Stir-fry “fishy grass” and asparagus lettuce: Take 100 g of fresh fishy grass. Clean them, slice into small sections and sprinkle a little salt on them for pickling. Take one asparagus lettuce and peel off its skin. Clean it and cut it into fine shreds. Heat the wok and add oil. Add ginger and green onion, and stir a while. Add fishy grass and asparagus lettuce, and stir-fry. Add garlic and salt to taste.

In Guangdong, Guangxi and Fujian, Yuxingcao is also decocted to make cold tea. The herbal cold tea can help clear away heat and quench thirst.

As a kind of wild vegetable, Yuxingcao can supply human body not only with proteins, fat, carbohydrates, vitamins and minerals, but also with biological active

components, such as volatile oils, flavonoids. These components can help clear away heat, facilitate dieresis, and inhibit pathogenic microorganism. Therefore, it has the food treatment and health care function. Here are some food therapy recipes.

Pork tripe stuffed with fishy grass: Take 150 g of fresh fishy grass (or 50 g of the dried one) and put it into pork tripe. Cook soup with them. Eat the soup once a day for three days. It can cure phthisis, cough and night sweats.

Stir-fry fishy grass: Eating the stir-fried fishy grass can relieve swelling and sore throat for people with amygdalitis and pharyngitis

Fishy grass and egg soup: Take 50 g of fishy grass and decoct with water. Remove the dregs to get the decoction. Put one raw egg in the boiling decoction. Drink once a day for 15 days. It can treat tuberculosis with fever and cough with purulent and bloody sputum.

71.5 Clinical Evidences

Yuxingcao injection (the herb steam distillation liquid plus cosolvent) is often used clinically for the treatment or adjuvant treatment of bacteria- and virus-induced inflammation, such as bronchitis, pneumonia, enteritis, and acute urinary tract infection, epidemic keratoconjunctivitis.

71.6 Safety Evaluation and Toxicity Data

The LD50 of the Yuxingcao decoction in mice by intraperitoneal injection was 51.0 g/kg. For the overall assessment of the safety of fresh Yuxingcao juice, acute toxicity test in mice and rats, Ames test, micronucleus test of bone marrow cells in mice, and sperm shape abnormality test of mice were carried out. The results showed that the fresh Yuxingcao juice was free from toxin, and had no acute toxicity and mutagenicity.

Up to now, there are no reports of adverse reactions for the oral administration of Yuxingcao and its preparations.

In recent years, most ADR (adverse drug reaction) cases were induced by IV drop of Yuxingcao injection. Since Yuxingcao injection was approved for marketing in China in 1988, annual consumption is near 0.3 billion injections, patients who took the injection are more than 5 billion person-time. Up to April 13, 2006, the National Adverse Drug Reaction Monitoring Center has found 494 ADR cases of Yuxingcao injection, including near 100 cases of serious ADRs. This indicates a very low rate of ADR. The clinical manifestations of ADRs include skin swelling, itching, rashes, aversion to cold, fevers, cold shivers, chest distress, palpitation, dyspnea, pulmonary edema, and anaphylactic shock, etc. These symptoms can be relieved soon after the drug is stopped and there are no after-effects.

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Chapter 72
Mentha haplocalyx Briq. 薄荷 (Bohe, Mint)

Feng Zhang, Yin Lu, Wenhui Qian and Zifan Pei

72.1 Botanical Identity

Bohe or mint, the dried aerial parts of *Mentha haplocalyx* Briq, is one of the most popular Chinese herbal medicines in the Lamiaceae family and is used as a raw material in dietary supplements. It is a special plant of economic value and originates from the Mediterranean and Europe and now is commonly grown in America, Spain, Italy and France. In China, the genuine Bohe grows in Yunnan, Jiangsu, Zhejiang and Jiangxi provinces. Its major and legal source is recorded in the Pharmacopeia of People's Republic of China and TCM literature. Stems of Bohe stand erect, about 30–60 cm in height, and are shaped as four diamonds, and the lower section has a number of fine fibres and horizontal creeping rhizome. Elongated leaves are oblong-lanceolate in shape, 3–5 cm in length and 0.8–3 cm in width. They bloom from June to September, and bear fruits in October each year (Fig. 72.1). The stems and leaves of Bohe are usually harvested and dried in summer and autumn, typically twice a year. The first harvest is usually in late June to early July, but no later than mid July, or the second harvest would be affected [1].

72.2 Chemical Constituents

Volatile oils (also known as peppermint oil) are the major bioactive components contained in Bohe. These volatile oils include menthol (**1**), menthone (**2**), menthenone (**3**), isomenthone (**4**), limonene (**5**), decylacetate, menthylacetate, methylbenzoate, pinene, 3-pentol, 2-hexanol, 3-octanol, myrcene, cineole, neterpineol,

F. Zhang · Y. Lu (✉) · W. Qian · Z. Pei
Department of Pharmacology, Nanjing University of Chinese Medicine,
138 Xianlin Avenue, Nanjing 210023, Jiangsu, China
e-mail: luyingreen@126.com; nucmzf@163.com

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Fig. 72.1 Flowering plant (**a**) and crude drug (**b**) of *Mentha haplocalyx* Briq

etc. Bohe also contains flavonoids including isoraifolin, luteolin-7-glucoside and methoside. In addition, organic acids are also found in this medicinal herb, including lusmarinic acid, caffeic acid, aspartic acid, glutamic acid, alanine, asparagine, valine, leuine, isoleucine, phenylalanine, methionine, and lysine [2, 3]. Representative structures of these constituents are shown in Fig. 72.2.

72.3 Pharmacological Studies

A number of pharmacological studies have evaluated the effects of volatile oils, the primary components contributing to the bioactivity of Bohe. Studies showed that peppermint oil was active against *Staphylococcus aureus* with minimal inhibitory

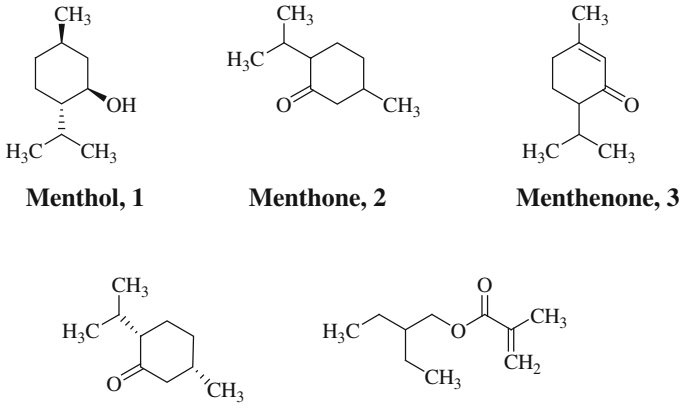

Fig. 72.2 Chemical structures of representative components of *Mentha haplocalyx* Briq

concentrations ranging from 64 to 256 μg/mL, and the production of *S. aureus* exotoxins was decreased by sub-inhibitory concentrations of peppermint oil in a dose-dependent manner. These findings suggested that peppermint oil may potentially be used to aid in the treatment of *S. aureus* infections [4]. Other data showed that peppermint oil significantly promoted the secretion of bile and bile acid in rats, increased bile acid efflux, and decreased cholesterol levels in bile, suggesting that peppermint oil stimulates bile fluid secretion and thus has a choleretic effect [5].

The principal pharmacodynamic effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature due to the interference of menthol with the movement of calcium across the cell membrane. The choleretic and anti-foaming effects of peppermint oil may play an additional role in the medicinal use of Bohe. Peppermint oil is relatively rapidly absorbed after oral administration and eliminated mainly via the bile. The major biliary metabolite is menthol glucuronide, which undergoes enterohepatic circulation. The urinary metabolites result from hydroxylation at the C-7 methyl group and/or at C-8 and C-9 of the isopropyl moiety, forming a series of mono- and dihydroxy menthols and carboxylic acids, some of which are excreted in part as glucuronic acid conjugates. Studies with tritiated I-menthol indicated equal excretion in feces and urine in rats. The main metabolite identified was menthol-glucuronide. Additional metabolites are mono- or di-hydroxylated menthol derivatives [6].

72.4 TCM Applications and Dietary Usage

72.4.1 TCM Applications

Bohe is commonly used in TCM for the treatment of influenza, headache, red eyes, fever, sore throat, etc. It is also used for neuropathic pain, pruritus, rash and eczema. The commonly used formulations of Bohe in clinical context include the following: (a) Compound Menthol injection: as menthol interacts with nerve membrane and narrows sodium channel, the drug is used as a local anesthetic agent; (b) Menthol Calamine lotion: used for treatment of red miliaria in children; (c) Cooling oil: for relieving pain and itching; (d) Compound Menthol nasal drops: used for nasal lubrication, and also for the treatment of atrophic rhinitis and nasal bleeding; (e) Bohe is also clinically used as adjuvant treatment for bronchial pneumonia in inhalation form for infants and young children [7].

72.4.2 Dietary Usages

Since Bohe is a common herb, it has been widely used in daily diet. Its dietary usages include Bohe wine, Bohe soup, porridge, mint herbal tea, mint cake, etc. These dietary forms of preparations can be easily made at home.

72.4.2.1 Bohe Porridge

Fresh Bohe (30 g) or dried Bohe (15 g), put into a span, add water to 1 L, cook with a medium heat until the remaining water is about 0.5 L. After cooling down, the mint material is removed. Then the mint decoction is added to a rice porridge made from 150 g of rice. Add small amount of sugar when the porridge is done. Bohe porridge may stimulate appetite and help with digestion.

72.4.2.2 Bohe Soup

Clean mint leaves, chopped, scalded with boiling water, and then put a little salt and sesame oil. Bohe soup can be used for relieving inflammation.

72.4.2.3 Bohe Cake

Prepare 500 g of rice, 500 g of green beans, 15 g of mint, 25 g of sugar and a small amount of sweet-scented *osmanthus*. First, boil the green beans to be thoroughly cooked, then add some sugar, sweet-scented *osmanthus* and chopped mint leaves to make the stuffing. Then cook the rice, and pack the stuffing with sticky rice bean paste. Bohe cake may help with sore throat.

72.5 Clinical Evidences

Several clinical studies have been carried out to evaluate the therapeutic effects of peppermint oil on some syndromes in humans. Nine studies evaluating 726 patients with irritable bowel syndrome showed that peppermint oil was significantly superior to placebo for global improvement of irritable bowel syndrome (5 studies, 392 patients, relative risk 2.23; 95 % confidence interval, 1.78–2.81) and improvement in abdominal pain (5 studies, 357 patients, relative risk 2.14; 95 % confidence interval, 1.64–2.79). Although patients receiving peppermint oil were more likely to experience some adverse effects, such events were mild and transient in nature. The most commonly reported adverse event was heartburn. These studies

indicated that peppermint oil is a safe and effective short-term treatment for irritable bowel syndrome [8].

There is also a clinical investigation addressing the efficacy and usefulness of peppermint oil as an antispasmodic during upper endoscopy, especially for elderly patients. A total of 8,269 esophagogastroduodenoscopy procedures were performed. There was no significant difference in the antispasmodic score between peppermint oil group and hyoscine butyl bromide group. Among the non-elderly patients, those in peppermint oil group had a worse antispasmodic score than those in hyoscine butyl bromide group. However, among the elderly patients, those in peppermint oil group had similar scores to those in hyoscine butyl bromide group [9]. These data suggest that peppermint oil is useful as an antispasmodic during esophagogastroduodenoscopy, especially for elderly patients.

72.6 Safety Evaluation and Toxicity Issues

Peppermint oil is safe for human within a certain dose range. After mice took pennyroyal (2.3 mL/kg) orally, hepatic functional parameters gradually increased over time, including total bilirubin, alkaline phosphatase (ALP), alanine transarninase (ALT) and aspartate aminotransferase (AST). These trends peaked at 24–48 h, and then gradually decreased, while they could recover to nearly normal levels at 72 h. The studies of dose-effect relationship showed that a single oral medium dose of peppermint oil could lead to elevated serum ALP and liver cell edema, and a single high dose of pennyroyal orally could not only make serum ALP, ALT, AST and liver index rise, but also make liver cells appear serious edema, fatty degeneration, focal necrosis, patchy necrosis, and so on. However, after mice took the low dose of pennyroyal orally, there were no obvious effects on the liver. These results indicate that taking peppermint oil, exceeding a certain amount, can cause acute liver injury. Liver injury could be expressed as changes in liver function and even in liver tissue pathology, and showed a dose-effect relationship, and the damage peak appeared at 24–48 h after taking peppermint oil. In the pathological changes of liver cells resulted from pennyroyal treatment, oxidative damage may be one of underlying mechanisms [10]. According to different time points or different dosages, examination of serum ALT and other liver function parameters were carried out after oral administration in rats. Liver histology and hepatic cell ultrastructure changes were evaluated under light microscope or electron microscope. Compared with the normal group, liver function indexes (e.g. serum ALT) of peppermint oil group increased and peaked at 24–48 h after taking peppermint oil. With the increase of dose, ALT and other liver function indexes increased. In high dose of peppermint oil treatment group, liver injury was obvious, showing ultrastructural changes. The results showed that a single high dose of peppermint oil orally could cause acute liver toxicity and have some toxic limitations [11].

Peppermint oil is easily available as a constituent of medicines. A nearly fatal case due to ingestion of toxic dose of oral peppermint oil has been reported. The

patient came in a comatosed state and was in shock. She was managed with mechanical ventilation and ionotropes. Her vital parameters reached normal levels within 8 h and she became conscious by 24 h. The side effects of peppermint oil were considered to be mild but this case indicates a warning that ingestion of oral toxic doses of peppermint oil could be dangerous [12].

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Chapter 73
Mosla chinensis Maxim. 香薷 (Xiangru, Chinese Mosla Herb)

Zhimin Wang

73.1 Botanical Identity

Xiangru, the aerial part of *Mosla chinensis* Maxim. and its cultivar *M. chinensis* 'Jiangxiangru' (Lamiaceae), is widely distributed in the south of China, such as Anhui, Fujian, Guangdong, Guangxi, Guizhou, Hubei, Hunan, Jiangsu, Jiangxi, Shandong, Sichuan, Taiwan and Zhejiang provinces [1], and Europe, Asia and north Africa as well. The leaves of this plant are frequently used as a raw vegetable or as an additive in foods to give flavor. It was used in traditional medicine for treatment of the common cold, fever, headache, bellyache and edema [2]. Due to the confusion of genus (*Elsholtzia* is also called Xiangru in Chinese) and plant name, *Mosla chinensis* and *M. chinensis* 'Jiangxiangru' were easily published as *Elsholtzia ciliate* and *E. densa* in early papers. By authoritative identification, Xiangru was classified into *Mosla* in China Pharmacopoeia (Fig. 73.1; Table 73.1).

73.2 Chemical Constituents

The chemical ingredients of *M. chinensis* include essential oil, phenols, flavones and organic acids.

The essential oil is about 0.26–0.59 % in fresh aerial part and 0.8–2 % in dried aerial part from *M. chinensis*. The main components in the essential oil are carvacrol (about 58.33 %), thymol (about 22.54 %), p-cymene and humulene [3],

Z. Wang (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: zhmw123@263.net

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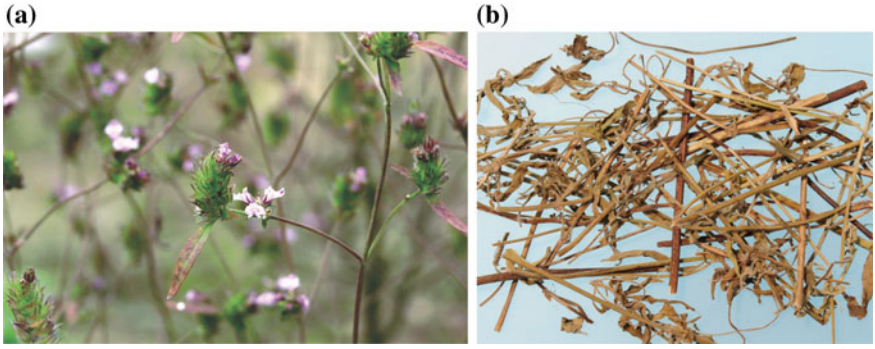

Fig. 73.1 The flowering plant (**a**) and crude drug (**b**) of Xiangru

Table 73.1 The name changes of Xiangru

Lawful species	Chinese name	Confusion names in published papers	
		Latin name	Chinese name
Mosla chinensis Maxim.	*Shi Xiang Ru*	*Elsholtzia ciliate* (Thunb.) Hyland.	*Xiang Ru*
M. chinensis 'Jiangxiangru'	*Jiang Xiang Ru*	*Elsholtzia densa* Bentham	*Mi Hua Xiang Ru*
		Elsholtzia splendens Nakai ex F. Maekawa	*Hai Zhou Xiang Ru*

similar with that in essential oil from *Origanum vulgare* Lina [4]. The percentages of carvacrol and thymol in dried aerial part vary from trace to 0.50 in different growing areas [5].

The water soluble phenols include 4-hydroxy-2,6-dimethoxyphenyl-β-D-glucopyranoside, 4-hydroxy-3,5-dimethoxyphenyl-β-D-glucopyranoside, 3,4,5-trimethoxypheyl-β-D-glucopyranoside, 3-hydroxyestragole-β-D-glucopyranoside, (6S, 9R)-roseoside, adenosine, p-hydroxybenzoic acid glucoside [6], methyl-3-(3′,4′-dihydroxyphenyl) lactate, corchoionoside C, prunasin, sambunigrin, benzyl-D-glucopyranoside and (S)-pencedanol-7-O-β-D-glucopyranoside [7].

Flavones include negletein, luteolin, quercetin, chrysoeriol, apigenin [8], 5-hydroxy-6,7-dimethoxyflavone, 5-hydroxy-6-methylflavanone-7-O-β-D-xylopyranosyl (3 → 1)-β-D-xylopyranoside, 5, 7-dihydroxy-4′-methoxyflavone, apingenin, kaempferol-3-O-β-D-glucoside, morin-7-O-β-D-glucoside and rhamnocitrin-3-O-β-D-apiosyl (1 → 5)-β-D-apiosyl-4′-O-β-D-glucoside [9].

73.3 Pharmacological Studies

Various biological activities of *M. chinensis* and its essential oil have been reported such as antimicrobial activity [10, 11], antioxidant activity [10], anti-inflammation and anti-allergic inflammation [12]. The active ingredients of the crude drug or essential oils are reported to be carvacrol, thymol, and p-cymene [13].

73.3.1 Antimicrobial Activity

The essential oil of *M. chinensis* exhibited great extensively antimicrobial activity against many bacteria [14, 15], such as *Bacterium paratyphosum* B, *Bacillus aeruginosus*, *B. anthrax*, *B. dysenteriae*, *B. diphtheriae*, *B. meningitidis purulentae*, *B. proteus*, *B. typhi*, *B. typhimurium*, *Diplococcus intracellularis*, *Escherichia coli*, *Lactobacillus, Neisseria intracellularis*, *Pseudomonas aeruginosa, Salmonella typhi, Shigella flexneri*, *Staphylococcus aureus*, *S. epidermidis*, *S. mutan, beta-streptococcus,* and fungal strains. Some MIC (μg mL^{-1}) of antimicrobial activities were listed in Table 73.2.

73.3.2 Antioxidant Activity

The essential oil of *M. chinensis* showed significantly higher antioxidant activity than that of the methanol extract. The β-carotene bleaching effects of BHT were found to be 1.88 and 2.53 times greater than the oil and the methanol extract, respectively (Table 73.3).

73.3.3 Antiviral Activity

Essential oil of *M. chinensis* showed a significant inhibitory effect on Asia influenza virus A3 and Orphan virus in vitro [16], and it could postpone the symptom appearance by 72–96 h after being infected by virus in vivo. The essential oil from *M. chinensis 'jiangxiangru'* displayed inhibitory effect on H3N2 subtype of influenza A virus, and displayed remarkable therapeutic effect on mouse pulmonitis induced by influenza virus when the mouse was administered with the essential oil (100 mg kg^{-1}) [14].

Table 73.2 Antimicrobial activity of the essential oil of *M. chinensis* [10]

Microorganisms	Essential oil		Gentamicin		Nystatin	
	DD	MIC	DD	MIC	DD	MIC
Gram-positive						
S. aureus	14.7 ± 0.58	62.5	24.3 ± 1.53	6.3		
S. albus	9.0 ± 1.00	250.0	24.0 ± 1.00	6.3		
E. faecalis	12.3 ± 1.53	125.0	28.0 ± 1.00	3.1		
L. monocytogenes	14.0 ± 0.00	62.5	29.3 ± 0.58	3.1		
Gram-negative						
E. coli	8.0 ± 1.00	250.0	22.0 ± 0.00	6.3		
K. pneumoniae	11.3 ± 0.58	125.0	18.0 ± 1.00	12.5		
P. aeruginosa	10.0 ± 0.00	125.0	19.0 ± 0.00	12.5		
S. typhimurium	9.0 ± 0.00	250.0	24.0 ± 0.00	6.3		
Fungi						
A. niger	14.0 ± 0.00	62.5			20.3 ± 1.53	31.3
A. fumigates	12.0 ± 0.00	125.0			13.3 ± 1.53	62.5
A. flavus	15.0 ± 1.00	62.5			18.0 ± 0.00	31.3
A. terreus	14.3 ± 0.58	62.5			16.3 ± 0.58	31.3
C. indicum	12.0 ± 1.00	125.0			14.0 ± 1.00	62.5
C. globosum	16.3 ± 0.58	31.3			18.0 ± 1.00	31.3
M. racemosus	14.0 ± 1.00	62.5			19.0 ± 1.53	31.3
Yeast						
C. albicans	15.0 ± 1.00	62.5			24.0 ± 0.00	7.8
C. rugosa	16.0 ± 0.00	62.5			25.0 ± 1.00	7.8

MIC minimum inhibitory concentration (as μg/ml)

Table 73.3 IC_{50} or EC_{50} values (μg/mL), total phenolic contents of *M. chinensis* essential oil and methanol extract [10]

Sample	DPPH (IC_{50})	β-Carotene bleaching (EC_{50})	Reducing power (EC_{50})	Total phenol contents (μg GAE*/mg)
Methanolic extract	1482.5 ± 10.9	789.4 ± 1.3	313.5 ± 2.5	47.3 ± 0.4
Essential oil	1230.4 ± 12.5	588.2 ± 4.2	105.1 ± 0.9	80.7 ± 0.5
BHT	181.2 ± 7.5	312.3 ± 2.8	20.8 ± 0.1	–

*Calculated as gallic acid equivalents

73.3.4 Anti-inflammation and Relieving Fever Activity

The essential oil from *M. chinensis* showed significant anti-inflammatory activities against rat's foot swelling induced by 5-HT or carrageenan, and against chronic arthritis induced by formaldehyde [12]. The decoction of *M. chinensis* 'Jiangxiangru' displayed antipyretic activity [14].

73.3.5 Immune Enhancement Effect

The essential oil of *M. chinensis* 'Jiangxiangru' showed increased specific and nonspecific immune response and improved defense system. The oil made the weight of spleen increased: this suggested that it could promote the proliferation of T and B lymphocyte. The essential oil displays enhancement effect on antibody forming cell of spleen, and increases the total amount of antibody for anti-SRBC (sensitization red blood cell, SRBC). In the aspect of nonspecific immune response, the essential oil of *M. chinensis* 'Jiangxiangru' showed that it could increase the amount of lysozyme in serum [17].

73.3.6 Other Activities

The essential oil of *M. chinensis* 'Jiangxiangru' displayed a significant inhibitory effect on spontaneous contraction of ex vivo ileum of mouse, rat, guinea pig and rabbit, among which their EC_{50} were 35.1, 14.2, 3.6, and 7.6 μg mL^{-1}, respectively.

Allergic inflammatory diseases such as food allergy, asthma, sinusitis, and atopic dermatitis are increasing worldwide. The aqueous extract of *M. chinensis* inhibited compound 48/80—induced systemic and immunoglobulin E (IgE)—mediated local anaphylaxis, and reduced intracellular calcium levels and downstream histamine release from rat peritoneal mast cells activated by compound 48/80 or Ig E [18].

73.4 TCM Applications and Dietary Usages

73.4.1 TCM Applications

Xiangru is a common herbal medicine traditionally used for treatment of epidemic viral diseases and gastrointestinal disorders. Preparations clinically used include.

73.4.1.1 Xianru Decoction

This prescription is from HejiJu Fang, an ancient herbal medicine works (1102–1106 AD). The decoction can ease symptoms of influenza, such as nausea, vomit and whole body aches. It is composed of five dietary medicines: Xiangru (aerial part of *M. chinensis*), Gancao (root and rhizome of *Glycyrrhiza uralensis*), Baibiandou (seed of *Dolichos lablab*), Houpo (bark of *Magnolia officinalis)* (to strip the shuk) and Fuling (sclerotium of *Poriacocos*), (2:0.5:1:1:1, w/w), decocted with water.

73.4.1.2 Xianru Decoction from Jiuji Fang

This decoction can alleviate symptoms of cholera, bellyache, vomit and diarrhea. It is composed of four dietary medicines: Xiangru (aerial part of *M. chinensis*), Xiebai (bulb of *Allium macrostemon*), Houpo (bark of *Magnolia officinalis)* and Ganjiang (rhizome of *Zingiber offcinale)*, decocted with water.

73.4.1.3 Xiangru Juice from Zhouhou Fang

This juice can treat the bleeding on the tongue.

73.4.2 Dietary Usages

Because of the good effects on diaphoresis, relieving fever, stimulating peptic secretion, promoting gastrointestinal peristalsis and diuretic effects, Xiangru can be used to take concoction with a common food or drink for preventing heatstroke and promoting appetite. The following drinking or eating forms can be easily made in home.

73.4.2.1 Xiangru Soup

Composition: Xiangru 10 g, Baibiandou (seed of *Dolichos lablab*) 5 g, Houpo (bark of *Magnolia officinalis*) 5 g.

Preparation: Decoct herbal medicines with proper amount of water, and drink it per day.

Function: The soup will benefit for easing symptoms of influenza, such as nausea, vomit and bellyache.

73.4.2.2 Xiangru-Bohe Tea

Composition: Xiangru, Bohe (leaf of *Mentha haplocalyx*), Danzhuye (stem and leaf of *Lophatherum gracile)*, each 5 g, and Cheqiancao (herb of *Plantago asiatica*) 10 g.

Preparation: Decoct herbal medicines with proper amount of water, and drink as tea.

Function: The tea will benefit for alleviating uncomfortable feeling vexed, red urine, thirst and halitosis.

73.4.2.3 Xiangru Porridge

Composition: Xiangru 10 g, rice 100 g and proper sugar.

Preparation: Decoct Xiangru with water, use the decoction and rice to cook the porridge, add sugar for eat. Eat once a day for three to five days.

Function: The porridge will benefit for alleviating symptoms of cold in summer, edema and urination obstruction.

73.4.2.4 Xiangru-er'dou Soup

Composition: Xiangru 15 g, Baibiandou (seed of *Dolichos lablab*) 30 g and Baibiandouhua (flowers of *D. lablab*) 5 g.

Preparation: Decocted together and drink the juice.

Function: The soup will treat the fever and vomit of heatstroke.

73.5 Safety Evaluation and Toxicity Issue

The LD_{50} of essential oil from *M. chinensis* and its cultivar *M. chinensis* 'Jiangxiangru' were 1.304 ± 0.126 and 1.333 ± 0.106 mL kg^{-1} by oral administration, and no obvious pathological changes were observed in animal organs by macroscopic [19]. *M. chinensis* was detected no mutagenic activity by using the Ames test, the bone marrow micronucleus test and the testicle chromosome aberration test [20].

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Chapter 74
Portulaca oleracea L. 马齿苋 (Machixian, Purslane)

Raorao Li and Hui-Min Gao

74.1 Botanical Identity [1, 2]

Machixian is the dried aerial part of *Portulaca oleracea* L. from the Purslane family (Portulacaceae). It was first recorded in the book "Bencao Jing Jizhu" and called Wuxing grass or Long life vegetable. It is listed as a medicinal and edible wild plant by the Ministry of Health of China, and has been used in China for many years.

The plant of *P. oleracea* L. is an annual succulent herb with cylindrical stems, up to 30 cm long, 1–2 mm in diameter; yellowish-brown in colour and furrowed longitudinally. The leaves are opposite or alternate and are easily broken. When whole, it is 1–2.5 cm long, 0.5–1.5 cm wide; greenish-brown in colour, obtuse or slightly notched at the apex. There are 3–5 small yellow flowers with 5 conical shaped petals that are 5 mm long.

P. oleracea L. originated in India and gradually became popular around the world. It has been cultivated as a vegetable in Britain, France, Netherlands, Russia and etc. It grows in most of China except alpine regions.

Machixian is collected in the summer and autumn. It is removed from the roots, washed, steamed briefly or treated with boiling water, and then dried in the sun. Its processed product is obtained by softening briefly and cutting into sections. The characteristics of the slices are as followed: stems cylindrical, externally yellowish-brown, distinctly furrowed longitudinally. Leaves are mostly broken, when whole, obovate, obtuse or slightly notched at the apex. It has a slight odour and has a delicate slightly sour taste (Fig. 74.1).

R. Li · H.-M. Gao (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: huimin_gao@126.com

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Fig. 74.1 Flowering plant (**a**) and crude drug (**b**) of Machixian

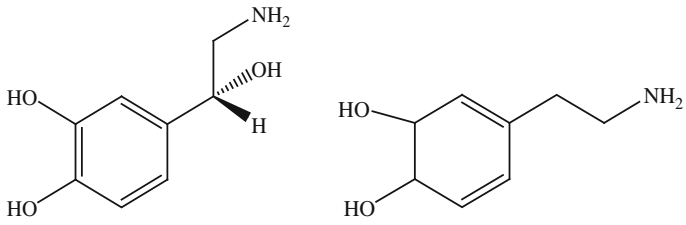
74.2 Chemical Constituents [3, 4]

74.2.1 Alkaloids

Large amount of noradrenaline (**1**) was found in the whole plant. Dopamine (**2**), dopa, oleracein A–E, adenosine, and so on, were also isolated from this plant (Fig. 74.2).

74.2.2 Organic Acids

Machixian is a rich source of unsaturated fatty acids, such as α-linolenic acid, which belongs to *ω*-3 unsaturated fatty acid and is the important nutrient for brain nerves. In the whole plant, linolenic acid, linoleic acid and palmitic acid are the main organic acids, whereas in the seed, linoleic acid and linolenic acid have relatively high amounts.



Noradrenaline, 1 **Dopamine, 2**

Fig. 74.2 The structures of compound 1 and 2

74.2.3 Protein and Amino Acids

The content of protein is 19.1 % in the dried herb. Most of amino acids have higher amounts than those in the cultivated vegetables. The essential amino acids for human body, including aspartic acid, alanine, tyrosine, threonine, phenylalanine, serine, valine, histidine, glutamic acid, methionine, lysine, proline, isoleucine, arginine, glycine and leucine, are detected in this herb.

74.2.4 Minerals

A lot of potash, such as potassium chloride, potassium nitrate, potassium sulfate, etc., was found in the whole plant. The content of potash, equivalent to K_2O, was about 1 % in the fresh plant and 17 % in the dried crude material.

74.2.5 Flavonoids

The content of total flavonoids in this plant is 6.37 %. The isolated pure compounds are mainly quercetin, kempferol, myricetin, apigenin and luteolin, etc.

74.2.6 Other Compounds

Volatile oils and polysaccharides are reported in the whole plant.

74.3 Pharmacological Studies

Purslane is popular as a traditional medicine in China for the treatment of hypotension and diabetes. Most studies in vivo and in vitro have verified that Machixian extract diaplayed the antihypertension and antidiabetic activity, which are related with polysaccharides, ω-3 unsaturated fatty acids and noradrenaline, enriched in this drug. Additionally, Machixian showed various pharmacological effects including antitumor, anti-atherosclerotic, antibacterial and anti-viral, anti-aging activities and immune enhancement function.

74.4 TCM Applications and Dietary Usage [1]

74.4.1 TCM Applications

Machixian is a commonly used herbal medicine and health-maintaining products as it is rich in nutrients and has great medicinal value.

It clears Heat and removes toxins, cools the Blood to restrict bleeding and dysentery. It is useful for treating Heat-toxin blood dysentery, swelling abscess, deep-rooted boil and sore, eczema, erysipelas, bite wound of insect, worm or snake, bloody stool, hemorrhoid bleeding, flooding and spotting.

74.4.2 Dietary Usages

Machixian can be used in many ways, such as Machixian Juice. The following drinks or foods can easily be made at home.

74.4.2.1 Purslane Porridge

The porridge is made from fresh purslane (100 g), rice (50 g) and onion (5 g). The cleaned purslane is blanched and then cut into pieces, fried with oil and onions. The rice is then added with some water and a little salt and then boiled. The porridge has the effect of clearing the heat away, eliminating toxic materials, restoring transportation and transformation of the spleen and stomach. It is suitable to treat enteritis, diarrhea, urinary tract infections, carbuncle, abscesses, furuncle, etc.

74.4.2.2 Purslane Dish

The dish is prepared from fresh purslane (500 g), garlic, a teaspoon of soy sauce, sesame oil and salt. Purslane is blanched and cut into segments, and then mixed with mashed garlic, soy sauce, sesame oil and salt. The food is used to clear the heat away and relieve dysentery. It is the secondary therapeutic dish for treating dysentery due to Damp-Heat, vitiligo patients and white hair because of copper element deficiency.

74.4.2.3 Soup of Purslane and Pig Liver

The soup is composed of purslane (45 g), day lily (30 g), pig liver (50 g), an egg, and a teaspoon of salt. Purslane is washed and cut into segments. Pig liver is washed and cut into pieces. Day lily is soaked in water for about 30 min, and cut

into segments. Purslane and day lily were boiled for 15 min then the pig liver was added. Boiling continues for 10 min and the egg paste was added. Some salt was added before eating. The soup is used for nourishing the liver, improving eyesight and lowering the adverse-rising Qi of stomach. It is the secondary therapeutic dish for nyctalopia, etc.

74.4.2.4 Purslane Bun

The bun is prepared from flour (500 g), dried purslane (200 g), fried bean curd (100 g) and a teaspoon of salt as well as oil. The dried purslane was soaked in water for 10 min and washed, and then mixed with minced curd. The salt and oil were added to the mixture and stuffed into the bun, then steamed for 15 min. The food is used for nourishing the liver, improving eyesight, clearing the heat away and relieving toxin. It is the secondary therapeutic dish for the treatment of carbuncle, furuncle, and dysuria.

74.5 Clinical Evidences

The effectiveness of seeds of *P. oleracea* L. has been evidenced by two recent reports. A pilot clinical trial described its effect on the abnormal uterine bleeding (AUB). Ten premenopausal women with AUB comprising menorrhagia, metrorrhagia, polymenorrhea and intermenstrual bleeding who had not responded to standard drugs and were candidates for hysterectomy, participated in the clinical trial. The subjects took 5 g of purslane seeds powder in a glass of water every 4 h orally 48 h after the onset of menstruation for 3 days. The results suggest that purslane seeds could be effective and safe in the treatment of AUB [5]. Another case reported the effects of *P. oleracea* L. seeds in treatment of type-2 diabetes mellitus patients as adjunctive and alternative therapy. A thirty subject with type-2 diabetes divided into two groups, to receive 5 g of PO seeds twice daily while in the second group, their participants receive 1500 mg of metformin/day. The results indicated purslane seeds possessed notable hypoglycaemic, hypolipidaemic and insulin resistance reducer effects; possibly due to its contents of polyunsaturated fatty acids, flavonoids, and polysaccharides [6].

74.6 Safety Evaluation and Toxicity Issue

The LD_{50} of the water extract of purslane is 1040 mg kg^{-1} by intraperitoneal injection in mice [4].

This drug is both cold and cool in property and can easily injury the spleen and stomach. So, it is contraindicated for the patients with deficiency and cold of the spleen and stomach. It is also not suitable for the pregnant women.

It is not recommended to be eaten together with pepper powder and soft-shelled turtle. Otherwise, the indigestion and food poisoning easily happened.

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Chapter 75
Taraxacum mongolicum 蒲公英 (Pugongying, Dandelion)

Chun Hu

75.1 Botanical Identify

In China, *Taraxacum* (Pugongying, dandelion) was originally compiled in the Newly Revised Materia Medica (657–659 AC) in the Tang dynasty. This herb was also recorded in Compendium of Materia Medica in 16th century. For food use, dandelion was first compiled in Materia Medica for Famine during the Ming dynasty. Whole herbs of *Taraxacum mongolicum* Hand.-Mazz. and *T. borealisinense* Kitam. (also known as *T. sinicum* Kitag) or other species are used with medicinal applications in TCM [1]. This is slightly different from the dandelion used in western herbal medicine, where *T. offincale* is more commonly known as medicinal dandelion [2].

The genus of *Taraxacum* is a member of the Asteraceae family, Cichorioideae subfamily and Lactuceae tribe, which is widely distributed in northern hemisphere. Dandelion has been historically used in herbal medicine around the world. In traditional Chinese medicine, medicinal dandelion refers to the dried whole plants of *Taraxacum mongolicum* Hand.-Mazz, *Taraxacum borealisinense* Kitam and others species in the *Taraxacum* genus [1]. Quality of the dandelion herb is determined by the caffeic acid content (>0.02 % dry weight is required).

Dandelion is a perennial weed without a stem; the green leaves are clustered in a rosteele at the base of the plant, and the whole herb contains white latex. The flowering stalks stick out with yellow flowers. The conical achenes fruits are brown and crowned by white hairy pappus, allowing seeds to be spread with wind. The dandelion plant is deeply rooted, which means that the plant is also capable to produce a new plant—even if its aerial part is clearly cut.

Dandelion herb is collected between spring and autumn, before or when the plant starts to bloom (Fig. 75.1). Traditionally, quality is considered to be lower

C. Hu (✉)
Nutrilite Health Institute, 5600 Beach Blvd, Buena Park, CA 90621, USA
e-mail: charles.hu@amway.com

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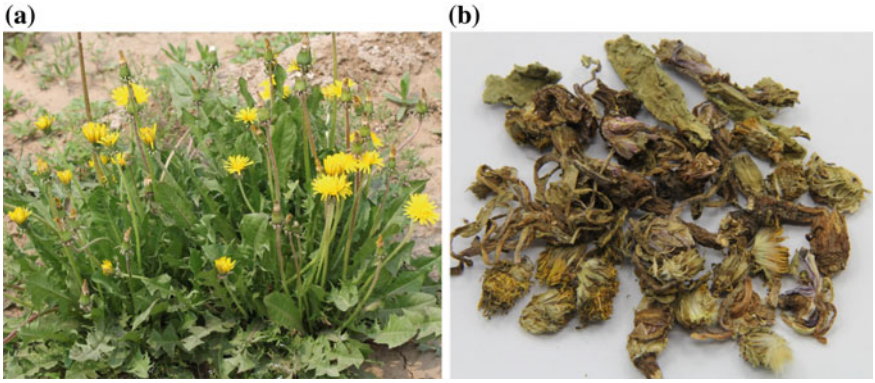

Fig. 75.1 Representative plant (**a**) and crude drug (**b**) of dandelion

after full bloom. After harvest, whole herbs are cleaned and dried (traditionally by sun dry method) to moisture content no greater than 13.0 %. Dandelion herb should match its botanical identity and TLC profile against a standard specimen; currently China Pharmacopeia requires that caffeic acid content is not less than 0.020 % of dry weight determined by HPLC method [1].

The northern region is the primary production area of *Taraxacum* in China, and is especially common in the central and east part of China. Table 75.1 shows the *Taraxacum* with medicinal use grown in different regions [3–5] and nine sections are also listed for *Taraxacum*. It's also worthwhile to point out that *Elephanpus scaber*, *Embelia sonchifolia* (L.) DC, *Pieris divaricate* Vant., *Ixerisdebilis* Gray, *Ixeri schinensis* Nakai, *hemisteeptalayrata* Bunge, *Sonchusoleracens* L and *Youngia japonica* DC are sometimes mislabeled as *Taraxacum* in some regions in China [3], though economic adulteration is not common for *Taraxacum* herb.

75.2 Chemical Constituents

Many phytochemicals have been found and identified in *Taraxacum* whole herb [6], these include:

Sesquiterpenoid, triterpenoid and *phytosterol*—Triterpenes such as taraxasterol, arnidiol, ψ-taraxasterol, faradiol, α-amyrin and β-amyrin were found in *Taraxacum* root [2, 7] (Fig. 75.2). Shi et al. [6] identified mongolicumin A (6,9,10-trihydroxyl-benzoxanthene-1,2-dicarboxylic acid), mongolicumin B (11-hydroxyl-2-oxo-guaia-1(10),3,5-trien-8,12-lactone), isodonsequitin A, taraxacin and sesquiterpeneketo-lactone from *T. mongolicum* (Fig. 75.3). β-sitosterol and stigmasterol were found in *T. mongolicum* and *T. officinale* [2, 6] (Fig. 75.4).

Flavonoid—Sixteen flavonoids have been identified from *Taraxacum mongolicum,* including artemetin (5-hydroxyl-3,6,7,3′,4′-pentamethoxyl flavone), quercetin,

Table 75.1 Taraxacum varieties and distribution in China [3–5]

Name	Medicinal use	Sections	Heilongjiang	Jilin	Liaoning	Inner Mongolia	Hebei	Shaanxi	Shanxi	Gansu	Sichuan	Qinghai	Shandong	Anhui	Guizhou
T. mongolicum Hand-Mazz	*	Mongolica (Dahlst.) R. Doll	+	+	+	+	+	+	+	+	+	+	+	+	+
*T. brassicaefolium*Kitag	*	Brassicafoo Y. R. Lin et X. J. Ge	+	+	+	+	+	+		+	+	+			
T. platypecidum Diels	*	Calanthodia (Dahlst.) R. Doll	+	+	+	+	+	+	+						
T. cumoreanum Nakai	*	Mongolica (Dahlst.) R. Doll	+	+	+	+									
T. variegatum Kitag	*	Mongolica (Dahlst.) R. Doll	+	+	+	+	+								
T. parvulum (wall) DC	*	Parvula Hand.-Mazz							+		+	+			
T. bessarabicum(Hornem) Hand-Mazz	*	Piesis (DC.) A. J. Rich. Ex Kirschn													
T. asiaticum Dahlst	*	Sinensia Soest	+	+	+	+	+	+	+	+	+	+			
T. borealisinense Kitam	*	Sinensia Soest	+	+	+	+	+	+		+	+				
T. officinale F.H. Wigg	*	Taraxacum													
T. tibetanum Hand-Mazz	*	Tibetana Soest									+	+			
T. calanthodium Dahlst	*	Calanthodia (Dahlst.) R. Doll						+		+	+	+			
T. ohwianum Kitam	*	Calanthodia (Dahlst.) R. Doll	+	+	+	+									
T. heterolepis Nakai et Koidz ex Kitag	*	unknown	+	+	+										
T. altaicum Schischk		Arctica Dahlst													
T. lilacinum Krassn.		Arctica Dahlst													
T. nutans Dahlst		Bienna R. Dollin Fedde					+	+	+						
T. repandum Pavl		Brythrocarpa Hand-Mazz													
T. sumneviczii Schischk		Brythrocarpa Hand-Mazz													

(continued)

Table 75.1 (continued)

Name	Medicinal use	Sections	Heilongjiang	Jilin	Liaoning	Inner Mongolia	Hebei	Shaanxi	Shanxi	Gansu	Sichuan	Qinghai	Shandong	Anhui	Guizhou
T. tianschanicum Pavl		Brythrocarpa Hand-Mazz													
T. grypodon Dahlst		Calanthodia (Dahlst.) R. Doll									+				
T. lanigerum Soest		Calanthodia (Dahlst.) R. Doll										+			
T. licentii Soest		Calanthodia (Dahlst.) R. Doll							+						
T. lugubre Dahlst		Calanthodia (Dahlst.) R. Doll								+	+	+			
T. compactum Schischk		Dissecta Soest													
T. dissectum (Ledeb) Ledeb		Dissecta Soest													
T. erythrospermum Andrx. ex. Bess		Etythrosperma (H. Lindb. F.) Dahlst													
T. glabrum D.C.		Glabra Dahlst													
T. pseudoratum Oraz		Glabra Dahlst													
T. subglaciale Schischk		Glabra Dahlst													
T. dealbatum Hand-Mazz		Leucantha Soest													
T. leucanthum (Ledeb) Ledeb		Leucantha Soest								+		+			
T. luridum Hagel		Leucantha Soest													
T. bicorne Dahlst		Macrocornuta Soest								+		+			
T. koksaghyz Rodin		Macrocornuta Soest													
T. lipskyi Schischk		Macrocornuta Soest													
T. longipyramidatum Schischk		Macrocornuta Soest													
T. monochlamydeum Hand-Mazz		Macrocornuta Soest													+
T. multiscaposum Schischk		Macrocornuta Soest													

(continued)

Table 75.1 (continued)

Name	Medicinal use	Sections	Heilongjiang	Jilin	Liaoning	Inner Mongolia	Hebei	Shaanxi	Shanxi	Gansu	Sichuan	Qinghai	Shandong	Anhui	Guizhou
T. pingue Schischk		Macrocornuta Soest													
T. stanjukoriczii Schischk		Macrocornuta Soest													
T. breirostre Hand-Mazz		Oligantha Soest								+		+			
T. loskocii Schischk.		Oligantha Soest													
T. oliganthum Schottet Kotschy ex Hand-Mazz		Oligantha Soest													
T. pseudoaminutilobum S Koval		Oligantha Soest													
T. dasypodum Soest		Parvula Hand.-Mazz													
T. indicum Hand-Mazz		Parvula Hand.-Mazz									+				
T. antungense Kitag		Sinensia Soest			+										
T. lamprolepsis Kitag		Sinensia Soest	+	+	+	+									
T. stenolobum Stschegl		Sinensia Soest										+			
T. terolepos Nakai et Koiz ex Kitag		Sinensia Soest	+	+	+	+									
T. pseudoalpinum Schischk. ex Oraz		Spectabilia Dahlst													
*T. ecornutum*Koval		Taraxacum													
T. xinyuanicum D.T. Zhai et Z.X.An		Taraxacum													
T. apargiaeforme Dahlst		Tibetana Soest									+				
T. acumeriopoduum (D.Don) DC		Tibetana Soest								+	+	+			
T. alatopetiolum D.T. Zhai et Z.X. An		Tibetana Soest													
T. forrestii Soest		Tibetana Soest													
T. mitalii Soest		Tibetana Soest													
		Tibetana Soest								+		+			

(continued)

Table 75.1 (continued)

Name	Medicinal use	Sections	Heilongjiang	Jilin	Liaoning	Inner Mongolia	Hebei	Shaanxi	Shanxi	Gansu	Sichuan	Qinghai	Shandong	Anhui	Guizhou
T. pseudostenoceras Soest															
T. qirae D.T. Zhai et Z.X. An		Tibetana Soest													
T. Sikkimense Hand-Mazz		Tibetana Soest									+	+			
T. stenoceras Dahlst		Tibetana Soest								+	+	+			
T. suberipodum Soest		Tibetana Soest													
T. centrasiaticum D.T. Zhai et Z.X. An															
T. chionophill Dahlst											+				
T. glaucophyllum Soest															
T. ludlowii															
T. maurocarpum Dahlst											+	+			
T. pseudoroseum Schischk															
T. sherriffii Soest												+			

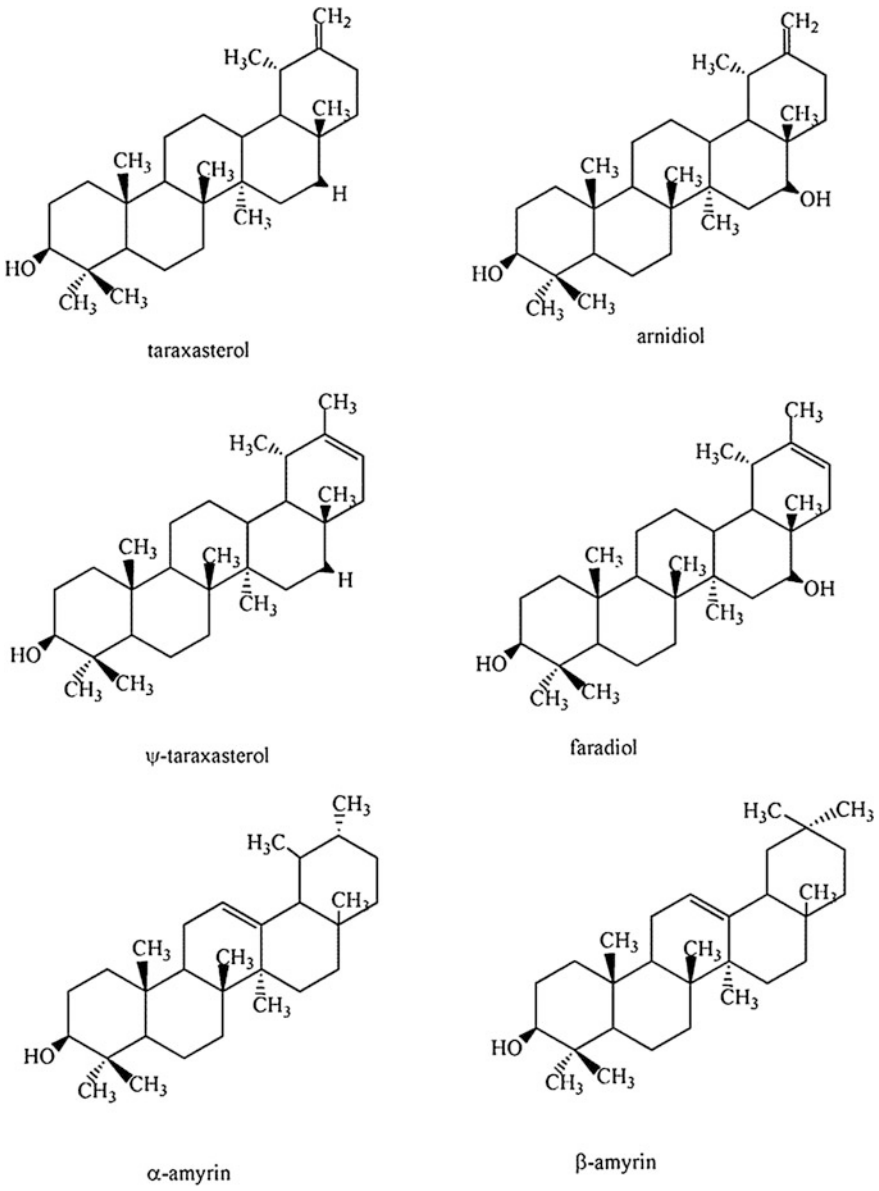

Fig. 75.2 Triterpenes found in dandelion

queretin-3′,4′,7-trimethyl ether, luteolin, luteolin-7-O-β-D-glucopyranoside, luteolin-7-O-β-D-glucopyranoside, genkwanin (apigenin-7-methyl ether), isoetin (5,7,2′,4′,5′-pentahydrxy flavone), hesperetin, genkwarnin-4′-O-β-D-lutinoside, hesperidin, quercetin-7-O-[β-D-glucopyranosyl (1→6)-β-D-glucopyranoside,

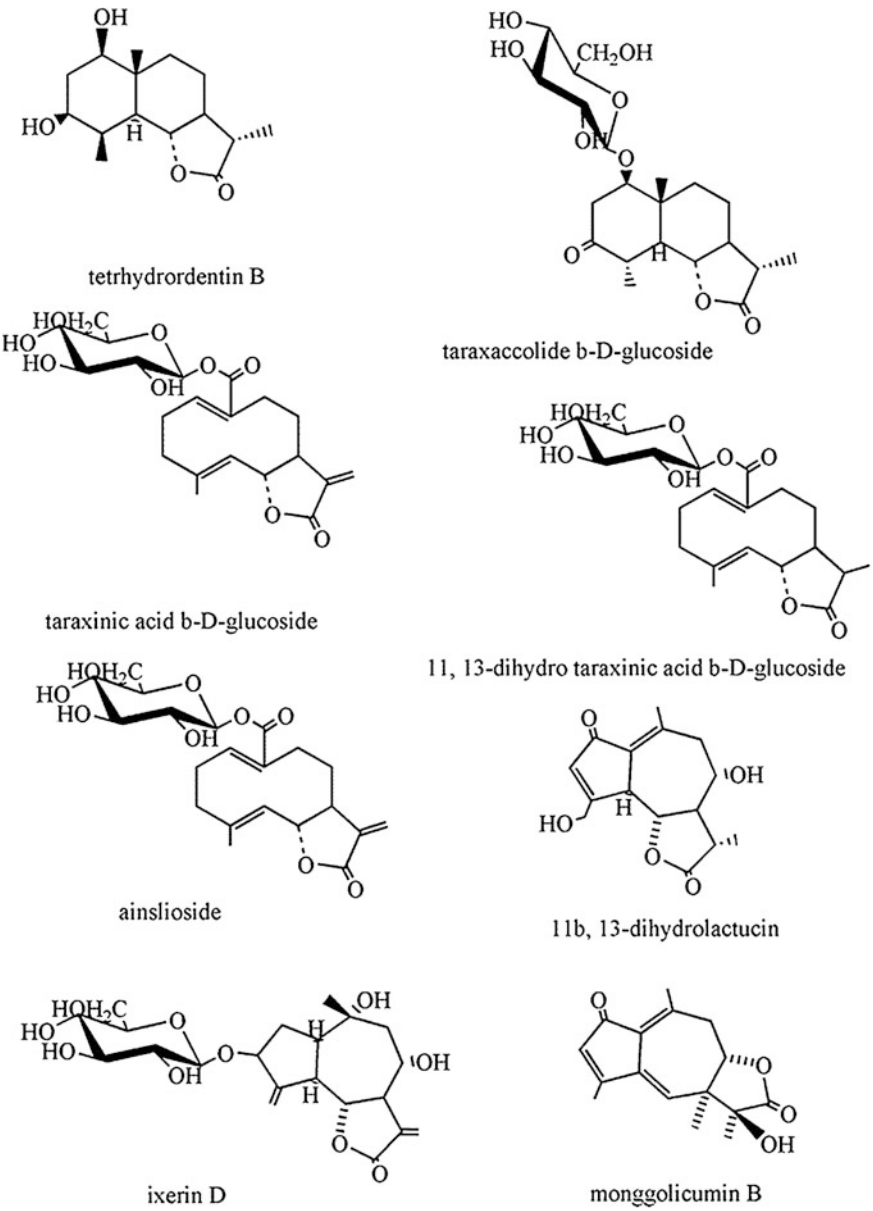

Fig. 75.3 Sesquiterpene lactone found in dandelion

quercetin-3,7-O-β-D-diglucopyranoside, isoetin-7-O-β-D-glucopyranosyl-2′-O-α-L-arabinopyranoside, isoetin-7-O-β-D-glucopyranosyl-2′-O-α-D-glucopyranoside, isoetin-7-O-β-D-glucopyranosyl-2′-O-β-D-xyloypyranoside [6, 8]. Chrysoeriol

(4′,5,7-trihydroxy-3′-methoxyflavone) was identified from flower of *T. officinale*, and authors did not identify any flavonol glycosides or luteolin-4′-glucoside or luteolin 7-rutinoside [9]. On the other hand, Schütz et al. [10] identified chrysoeriol diglycoside from the juice of *T. officinale* root, and the same group also identified several quercetin and luteolin triglycoside and diglycoside from same preparation from root. Flavonoids are more abundant in leaves and flowers than roots [9]. Structures of identified flavonoid aglycone are illustrated in Fig. 75.4.

Phenolic acid—Caffeic acid was found in *T.mongolicum* root [7]. In addition, ferulic acid, chlorogenic acid (3-O-caffeoylquinic acid), 3,5-di-*O*-caffeoylquinic acid, cichoric acid (3,4-di-*O*-caffeoylquinic acid), 4,5-di-*O*-caffeoylquinic acid, *p*-hydroxybenzoic acid, *p*-coumaric acid, 3,5-di-hydroxylbenzoic acid, syringic acid, gallic acid, gallicin, 3,4-di-hydroxybenzoic acid and caffeic acid ethyl ester were identified from the whole herb of *T.mongolicum* [6] (Fig. 75.4). Cichoric acid, monocaffeyltartaric acid and chlorogenic acid were the most abundant phenolic compounds in leaf and flower part of *T. officinale* [9]. Cichoricacid, monocaffeoyltararic, 4-caffeoylquinic acid, chlorogenic acid, caffeic acid, p-coumaric acid, ferulic acid, p-hydroxybenzoic acid, protecatechuic acid, vanilic acid, syringic acid and *p*-hydroxyphenylacetic acid were found in the root of *T. officinale* [2]. Though, cichoric acid is abundant in dandelion leaves, its content is negatively correspondent to air drying temperature with retention of cichoric acid and chlorogenic acid [11].

Other components—Inulin was found in dandelion root as a storage carbohydrate, with content up to 40 % in autumn versus only 2 % in spring. Vitamin A, B, C and D as well as potassium were found in both root and leaves, as well as was potassium [12]. Meanwhile, 1,3-dimethylbenzene, 1,2-dimethylbenzene, 1-ethyl-3-methylbenzene, heneicosane and tricosane were identified as the primary volatile compounds from the *T. officinale* flower [13].

75.3 Pharmacological Studies

75.3.1 Antioxidant Activity

Antioxidant activities of dandelion have been demonstrated in various models with various parts of the plant (Table 75.2). All parts of dandelion plant possessed antioxidant activities, though leaf extract had a stronger hydrogen donating capacity than its radix extract, due to the higher polyphenol content in leaves [14]. All evidence suggested that the whole dandelion herb might be a potential candidate for antioxidant use in health foods or in pharmacological application.

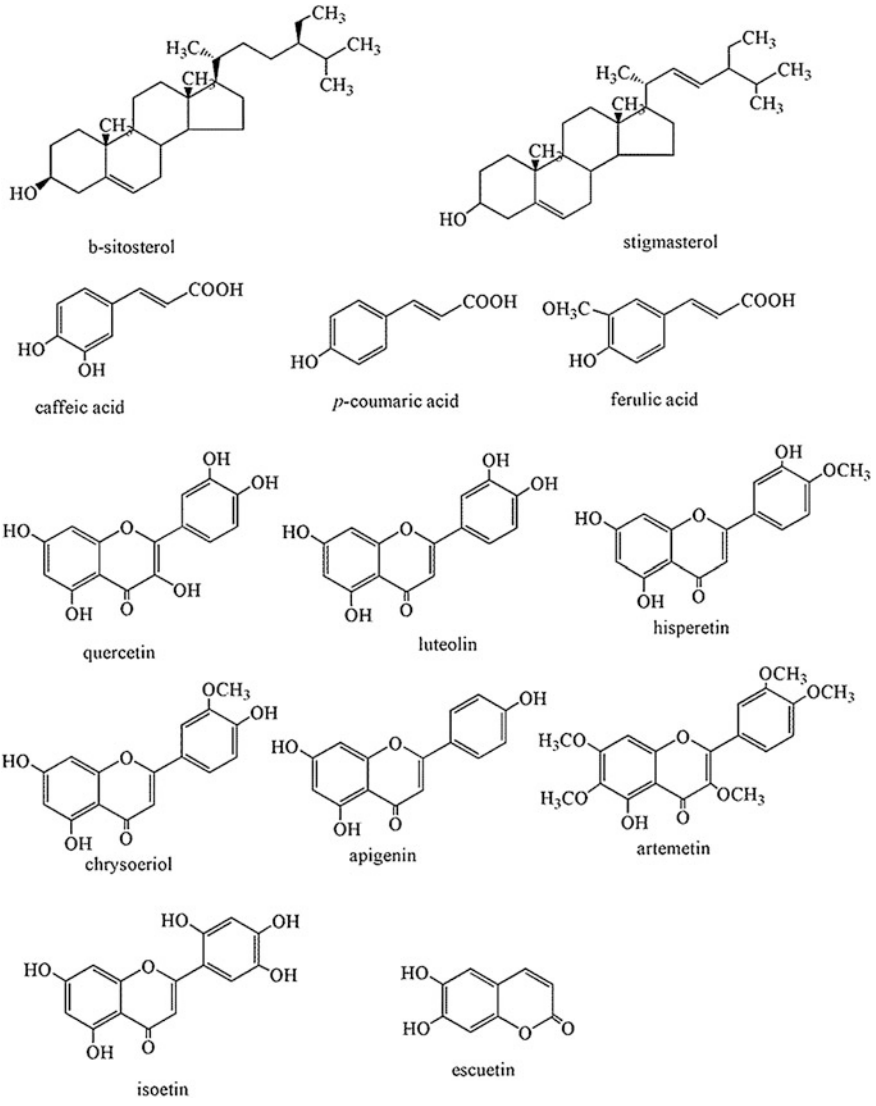

Fig. 75.4 Phytosterol, phenolic acid and flavonoid from dandelion

75.3.2 Anti-inflammatory Activity

The potential anti-inflammatory activities of dandelion were demonstrated in both cell culture and animal models. Using LPS-activated mouse macrophage RAW264.7 cell, Hu and Kitts found that dandelion flower extract and its primary flavone components suppressed the inducible nitric oxide synthase (iNOS) and cyclooxygenase-2

Table 75.2 Antioxidant activities of dandelion

Parts	Antioxidant activities
Flower	*T. officinale* flower inhibited the peroxyl and hydroxyls radical induced supercoiled DNA breakage, as well as liposome oxidation induced by peroxyl radical [15], and suppressed peroxyl radical induced intracellular oxidation in RAW264.7 cell [16]. Luteolin and its glycoside isolated from dandelion flower, inhibited the production of nitric oxide and prostaglandin E_2 in bacterial lipopolysaccharide-activated mouse macrophage by suppressing the expression of inducible nitric oxide synthase and cyclooxygenase-2 protein [17]
Leaf and stem	*T. officinale* leaf and stem extract suppressed the lipid peroxidation in rat liver microsome model and influenced the microsomal NADPH-cytochrome p-450 reductase activity [18]. Dandelion leaf supplement prevented the liver glutathione depletion in a high cholesterol diet fed rabbit model, and maintained the normal hepatic glutathione transferase, glutathione peroxidase, catalase and superoxide dismutase activities [19]. Leaf extract suppressed the oxidative stress in nonalcoholic steatohepatitis C57BL/6 mice derived from methionine and choline deficient diet [20]. Dandelion water extract significantly improved hepatic superoxide dismutase and catalase activity without impact on their mRNA expression in diabetic rats; dandelion supplement helped to suppression of lipid peroxidation [21]
Root	*T. officinale* root extract protected mice from alcohol-induced hepatic toxicity by suppressing lipid peroxidation [22]; dandelion root supplement inhibited the hepatic glutathione depletion in rabbit fed with high cholesterol diet and improved the antioxidant enzyme activities [19]

(COX-2) protein expression and production of pro-inflammation cytokine PGE_2 [17]; the similar activity was further revealed with dandelion leaf extract [23, 24], and the reduction of expression of iNOS and COX-2 expression was confirmed through the inactivation of the mitogen-activated protein kinase pathway [24]. The anti-inflammatory effect of dandelion was confirmed in mice with acute lung injury-induced by LPS, dandelion was orally administrated for five consecutive days followed by LPS challenge. Results showed that dandelion treatment resulted in the suppression of lung tissue injury and inhibited the production of TNF-α and IL-6 in bronchoalveolar lavage fluid in a dose-dependent manner [25]. Dandelion extracts (*T. officinale* and *T. platycarptum*) significantly inhibited 12-O-tetradecanoylphorbol-13-acetate induced ear oedema in mice [26]. In addition to the flavone fraction of dandelion [17], taraxasterol isolated from *T. officinale* exhibited in vitro anti-inflammatory activity in LPS induced RAW264.7 macrophage model by inhibiting the productions of nitric oxide, PGE_2, TNF-α, IL-1β and IL-6 in a dose-dependent manner through preventing NF-κB translocation [27].

The anti-inflammatory activity was also tested in herbal supplement formulated with other materials, herbal supplement containing dandelion leaf significantly inhibited IL-1β induced nitric oxide production and glycosaminoglycan release, suggesting that such supplement possesses chondroprotective properties in IL-1 stimulated cartilage [28]. Using Chinese herbal formula Jinying Tang containing Jinyinhua (flower of *Lonicera japonica*), Pugongying (Herb of *Taraxacum*

mongolicum), Gualou (fruit of *Trichosanthes kirilowii*), lianqiao (fruit of *Forsythia suspensa*), Dahuang (root and rhizome of *Rheum palmatum*), Huangqi (root of *Astragalus membranaceus*) and Danggui (root of *Angelica sinensis*), Wang et al. [29] found that Jinying Tang formula significantly decreased TNF-α and IL-6 in serum and mammary glands and reduced inflammatory response to the incidence of mastitis in rabbits challenged with *Staphylococcus aureus.* An herbal extract mixture containing Baiputaogan (fruit of *Vitis vinifera*), Wuweizi (fruit of *Schisandra chinensis*) and Pugongying (herb of *Taraxacum officinale*) lowered serum level of TNF-α, IL-6 and COX-2 protein, and suppressed the translocation of NF-κB and c-Jun phosphorylation in a D-galactosamine induced hepatitis rats model [30].

75.3.3 Diuretic Effect

T. officinale is known for its diuretic function [12, 31]. The diuretic effect of dandelion was confirmed in a clinical observation in a group of health female subjects (18–65 years old) taking 8 ml of dandelion tincture (1 ml equivalent to 1 g of dandelion) three times per day [31]. Compared to the baseline, the day-time urination frequency and excretion ratio (output/input volume) were significantly increased ($p < 0.05$) after first day dose (8 ml at 8:00 am, 1:00 and 6:00 pm), but such effect was not observed in the following dose. The authors acknowledged that the lack of blinding and small subject numbers as well as self-monitoring of fluid input/output without correction of water content in food consumed, therefore suggesting that a better designed and controlled study is warranted. However, this observation demonstrated the potential diuretic effect of dandelion in the traditional application, and warranted the necessity of future larger scale double-blind placebo controlled clinical trial on this matter.

75.3.4 Hypolipidemic Activity

The implication of dandelion on attenuating lipid metabolism has been demonstrated both in vitro and in vivo. Pancreatic lipase is a critical enzyme in regulating dietary fat metabolism, dandelion was found to significantly inhibit pancreatic lipase activity in vitro with an IC_{50} of 78.2 μg/ml [32]. Flavonoids associated with *Taraxacum*, such as quercetin and luteolin both exhibited inhibition on porcine pancreatic lipase activity in vitro [33]. When mice were fed with dandelion extract and corn oil, the postprandial plasma triglyceride was significantly lower than the control group [32]. Dandelion leaf extract feeding resulted in the lower serum triglyceride and total cholesterol in high-fat fed C57BL/6 mice compared the control group [34]. Using air-dried dandelion leaf or root in rabbit chow for 4 weeks in a diet containing 1 % cholesterol, rabbit serum triglyceride level was significantly lower in the treatment group than control group [19].

75.3.5 Hypoglycemic Activity

Alpha-glucosidase catalyzes the hydrolysis of oligosaccharide and disaccharide, playing an important role in carbohydrate metabolism and diabetic management. Dandelion extract exhibited a weak inhibition on α-glucosidase [35, 36] and α-amylase [37] in vitro, whilst several phytochemicals such as luteolin, luteolin-7-glucoside, chlorogenic acid all exhibited various extent of inhibition on these enzymes [37, 38].

Using rats insulinoma cell line INS-1, Hussain et al. [39] demonstrated the ethanol extract of *T. officinale* significantly suppressed insulin secretion at 40 μg/ml. In a streptozotocin-induced diabetic rat model, dandelion water extract administration lowered the postprandial blood glucose [21, 36] with no effect on insulin level and glucose infusion rate, and such effect was attributed to its inhibition on α-glucosidase and inhibition of maltose hydrolysis and glucose absorption [36]. In an early study, a proprietary herbal formula containing *T. officinale* radix (other ingredients were *Myrtilli folium, Cichorii radix, Juniperi fructus, Centaurii herba, Phaseoli pericarpium, Millefolii herba, Morii folium, Valeriane radix, Urticae herba* et *radix*) administration for 7 days significantly reduced the serum glucose and fructosamine in alloxin-induced non-obese diabetic mice, though it was unclear which herb was the primary contributor to such effect [40].

75.3.6 Liver Protection

In a methionine and choline deficient diet induced nonalcoholic fatty liver C57B/L6 mice model, dandelion leave feeding was found to relieve the severity of clinical signs of steatohepatitis and reduced the serum ALT, hepatic triglyceride and malondialdehyde, as well as expression of TNF-α and IL-6, whilst increased glutathione (reduced form) level, suggesting the beneficial effect of dandelion on NASH is due to the its antioxidant and anti-inflammatory activities [20]. The same group also found the dandelion feeding led to lower body and liver weight in high fat diet fed C57BL/6 mice; serum triglyceride, total cholesterol and fasting glucose were also lower in dandelion feeding group compared to high fat diet control group. The activation of adenosine monophosphate-activated protein kinase in liver and muscle protein was improved by dandelion whilst the hepatic lipid accumulation was suppressed, suggesting that dandelion leaves may present a preventive effect in obesity-related nonalcoholic fatty liver disorder [34]. The serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and lactate dehydrogenase activities were all suppressed when mice fed with dandelion root extract (extracted by hot water) and alcohol, meanwhile hepatic antioxidant enzymes (including catalase, glutathione-S-transferase, glutathione peroxidase and glutathione reductase) activities were higher than those with alcohol alone [22]. Administration of dandelion contained herbal mixture HV-P411 containing Baiputaogan

(fruit of *Vitis vinifera*), Wuweizi (fruit of *Schisandra chinensis*) and Pugongying (herb of *Taraxacum officinale*) reduced D-galactosamine-induced hepatotoxicity in rats [30]. In CCl_4—induced mice hepatic fibrosis model, *T. officinale* root extract is (i.p.) helped to recover hepatic fibrinous deposits, and histological architecture was restored, hepatic SOD activity was improved through the inactivation of hepatic stellated cells and improvement of hepatic regenerative capacity, providing the evidence to substantiate traditional use of dandelion in liver disorder and liver protection [41]. Similarly, polysaccharide fractions from *T. officinale* root exhibit hepatoprotection in an acute CCl_4-induced damage in Sprague-Dawley rat model by attenuating inflammatory mediators and suppressing oxidative stress [42].

75.3.7 Anti-microbial Activity

Dandelion has a wide spectrum of anti-microbial activities. Ethanol extract fraction of *T. mongolicum* aerial part inhibited *Staphylococcus aureus, Escherichia coli*, *Pseudomonas aeruginosa* [43]. Hsueh et al. [44] found that only *T. mongolicum* maceration instead of decoction exhibits the inhibition on *E. coli,* suggesting the preparation of herb is important for the antimicrobial activity of this herb. Besides its inhibition on the bacteria, *T. mongolicum* also inhibits on fungus such as *Aspergillus niger*, *Paecilomyces variotii* and *Cladosporium herbarum.* Granules made from *Isatidis radix* (*Isatis indigotica* Fort)*, Violae herba* (*Viola yedoensis* Makino) and *Taraxaci herba* (*Taraxacum mongolicum*) suppressed the *S. Aureus*, *Streptococci pneumococcus*, *Klebsiella pneumococcus*, *Haemphilus influenzae*, *E. coli* and *Pseudomonas aeruginosa* [45]. Taraxasterol was found to be the only tripenoid from *Asteraceae* species to inhibit *S. aureus* [46]. Combined with *Laggera pteroldonta*, pomegranaterind, dandelion water extract inhibited *Helicobacter pylori* metronidazole resistant strains, suggesting dandelion may be beneficial for *H. pylori* induced gastric ulcer [47].

75.4 TCM Applications and Dietary Usage

Dandelion is consumed in many cultures as an edible vegetable [48]. Dandelion leaves (100 g raw) contains 85.6 g water, 2.7 g protein, 0.7 g lipids, 9.2 g carbohydrate (3.5 g fiber), 187 mg calcium and 397 mg potassium, 35 mg vitamin C, 508 μg RAE vitamin A, 3.44 mg vitamin E, and 778 μg vitamin K (USDA national nutrient database for standard reference release 25). Young leaves are typically consumed as salad alone or mixed with other green leafy vegetables, as well as cooked vegetable dishes. Dandelion is sometimes formulated into an alcoholic or non-alcoholic beverage with other ingredients. Dandelion root is collected in autumn and roasted after being sliced and consumed as coffee substitute with its unique flavor. In China, the Ministry of Health has approved the whole herb of

dandelion as one of botanical ingredients used as both food and medicine application, meaning that dandelion is allowed to be used for both general food and medicinal purpose. In addition, health (functional) foods are required to be approved by State Food and Drug Administration prior to marketing with 27 allowed functional claims using standard testing protocol defined by government. By the end of March 2013, 61 health foods containing dandelion have been approved for various functional claims. The most popular health claims related to dandelion contained formulas were "to assist protecting chemical induced hepatic injury", "to improve immunity" and "to clear throat". In addition, dandelion is also found in the health food with functional claims for cosmetic and digestion health.

In traditional Chinese Medicine, *T. mongolicum* is used for relieving heat and detoxification, reducing swelling and act as a diuretic, with a typical daily dose of 10–15 g [1]. In China, dandelion herb, alone or with other herbs, has been developed as solid dose (including granule, hard-shell capsule and tablet) and injection format in the applications of heat relief and detoxification, anti-inflammation and diuretics. In other culture, Germen Commission E monograph lists both dandelion (*T. officinale* G. H. Weber ex Wiggers) herb and root and their preparation for therapeutic use, where the whole herb is used for "loss of appetite" and "dyspepsia", whilst root is used for "disturbance in bile flow, stimulation of diuretics, loss of appetite and dyspepsia", and the typical dose is 4–10 g raw material equivalent [49]. British Herbal Pharmacopeia characterized dandelion leaf and root with bitter taste, with leaf being used for diuretic and choleretic, whilst root for hepatic function, typical recommended dose for leaf is 3–5 g or 5–10 ml leaf tincture twice per day. Health Canada published its dandelion monograph with leaf is used for diuretic, and root is used for diuretic, help to treat digestive disturbance (dyspepsia), increase bile flow (cholagogue), stimulate appetite and as an alternative to help relieve dermatological condition such as eczema.

75.5 Clinical Evidences

Randomized double blind placebo controlled clinical studies regarding efficacy of *Taraxacum* is limited. In a non-placebo controlled pilot study, *T. officinale* tincture significantly improved the frequency of urination and ratio of excretion within the first 5-hour, but the observed effect disappeared with further dose within the same day compared to the baseline [31]. *T. officinale* ethanol extract showed promise as a diuretic in humans. However, further well-designed studies are needed to establish the value of this herb for induction of diuresis in human subjects as well as other clinical applications. Clinical trials with *Taraxacum* alone is very limited, most of the clinical trials were conducted for the recipes or formula with other botanical ingredient. In a group of outpatients with clinical functional dyspepsia, a commercial mixture of extracts of artichoke leaf, dandelion root, turmeric and rosemary was found to significantly reduce severity of dyspepsia symptom after one month, and blood chemistry profile also improved over baseline after 2 months [50]. In a

pilot and feasibility study, intervention of blend of turmeric, global artichoke, rosemary, Schisandra, milk thistle and dandelion in combination of dietary change did not show substantial effects on estrogen in premenopausal women, though early-follicular phase androgens decreased with the blend of botanical extracts [51]. Overall, well designed clinical trials are needed for the future understanding of any potential therapeutic and health benefits of *Taraxacum.*

75.6 Safety

Dandelion has been consumed, as part of a diet and herbal medicine, its adverse effects is rare. Dandelion root and dandelion fluid extract are both granted for "generally recognized as safe" status by US FDA for dietary supplement use. No negative effect has been reported during pregnancy and lactation, in children or in combination with pharmaceutical drugs [52]. Oral administration of dandelion leaf didn't cause any toxic sign or death in mice for 2 weeks and LD_{50} was estimated greater than 20 g/kg bw, and neither mutagenic effect was found [53]. Neither did four month feeding with dandelion leaf (33 % in diet) cause toxic effect in rats [52]. No acute toxicity was found in rabbits with oral administration of dehydrated dandelion plant at 3–6 gram/kg body weight. LD_{50} (I.P) for mice is 28.8 and 36.6 g/kg for fluid herb and root extract, respectively. Though *Taraxacum* is generally safe, contact dermatitis is known for dandelion due to the presence of taraxinic acid ester [2]. Those with acute gastrointestinal inflammation or obstruction or nonatonic reflux esophagitis should be cautioned when using dandelion, as the bitter component may aggravate these conditions [52].

In conclusion, *Taraxacum* is widely used as both vegetable and traditional medicine with some promising preclinical evidence and good safety data, however, the clinical evidence is very limited, suggesting that future clinical trials are warranted.

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Part V
Flower or Flower Bud Materials

Chapter 76
Carthamus tinctorius L. 红花 (Honghua, Safflower)

Zhuju Wang and Xidan Zhou

76.1 Botanical Identity

Honghua originates from the annual or biannual herbal plant *Carthamus tinctorius L.* in the Compositae family. The medicinal part is the red tubular flower without ovary, which is called Honghua. The crude medicine Honghua, is 1–2 cm long, feels soft and its surface appears reddish yellow or red. It smells slightly fragrant and tastes slightly bitter.

C. tinctorius L. is a glabrous plant and grows to the height of 30–180 cm. Stems are upright and cylindrical, and leaves are pinnatilobed, pinnatisect or undivided, and margin is usually spiny. Terminal inflorescences are large with numerous tubular flowers, which are usually bisexual and orange or yellow. Achenes with three ribs are elliptic or obovate, and white [1].

In China, the long history of cultivation of *C. tinctorius L.* can be traced back to the Han dynasty (206 BC–220 AD). In early stages, it has been used as dye and medicine. Later on it was also employed as oil crops. The resources of *C. tinctorius L.* are very abundant in China, and its areas of cultivation are almost scattered across the country, ranging from Heilongjiang to Guangdong and from Qinghai-Tibetan plateau to Jiangsu-Zhejiang coastal regions. Yet it's mainly produced in the areas of Henan, Sichuan, Zhejiang and Xinjiang [2]. Among them, Henan province is a famous production area in history, and Honghua produced in city Weihui, Henan province has been enjoying good fame in home and abroad.

Due to its special character of medicinal part, Honghua can only be harvested by hand. Generally, Honghua is picked in summer when the colour of the flowers changes from yellow to red. The optimal time for collecting is in morning before the dew evaporates. The orange flowers should be collected, and then dried in a

Z. Wang (✉) · X. Zhou
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: wangzhuju@sina.com

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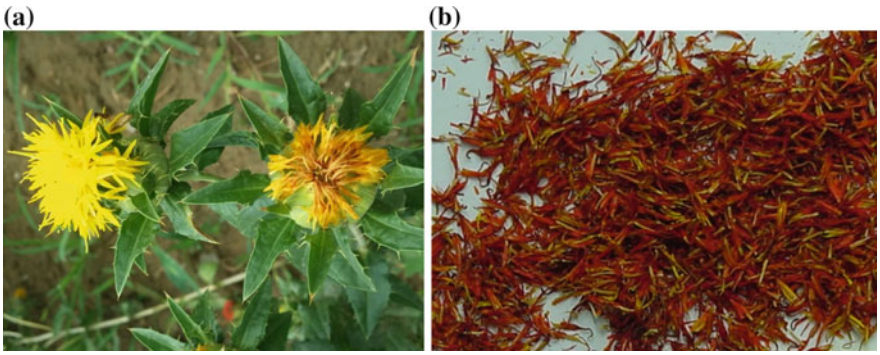


Fig. 76.1 The flowering plant (**a**) and crude drug (**b**) of Honghua

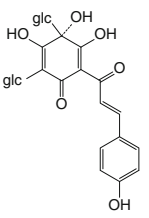
shady and well-ventilated place. This is to prevent the medicinal material from moisture and worms. It's important to note that proximal ovary can't be damaged when the pollinated tubular flowers are being collected. It is important to be careful in regards to avoiding bright light, raging fire and repeatedly touching, because it will have an impact on the quality of Honghua (Fig. 76.1).

76.2 Chemical Constituents

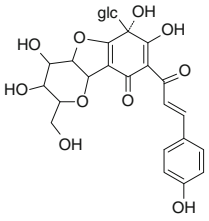
Up to date, many constituents, such as quinochalcones, flavonoids, polyacetylenes [3], alkane-diols [4], fatty acids, steroids, lignans, etc. have been isolated from Honghua. Among them, quinochalcones and flavonoids are considered as the characteristic and active constituents of Honghua.

76.2.1 Quinochalcones

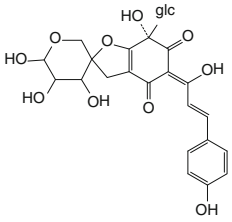
Quinochalcones are the main pigments from Honghua, including the yellow pigments and the red ones [5]. It's reported that such constituents have been turned out to be the effective materials for the pharmacological action of Honghua on the cardiovascular and cerebrovascular systems. Many components of this kind have been isolated and identified, including hydroxylsafflor yellow A (HSYA), safflor yellow B, safflomin C, tinctorimine, and precarthamin, etc. Among them, HSYA is used as one of the standard compounds to evaluate the quality of the crude drug Honghua and related preparations containing Honghua. These compounds have been classified into the quinochalcone family for having a unique structure with a C-glycosylated cyclohexanonedienol moiety that occurs only in this plant. Some of them are shown in Fig. 76.2.



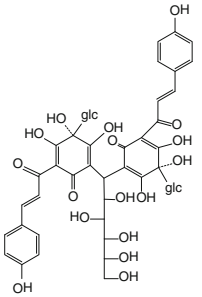
Hydroxy safflor yellow A, 1



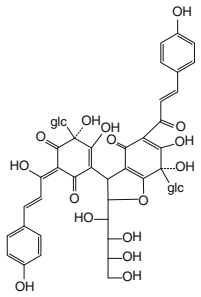
Safflor yellow A, 2



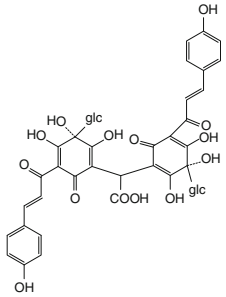
Saffloquinoside A, 3



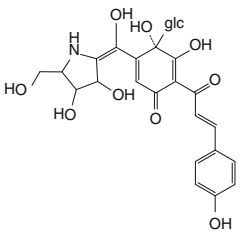
Safflor yellow B, 4



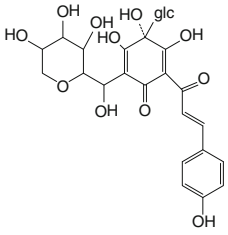
Anhydrosafflor yellow B, 5



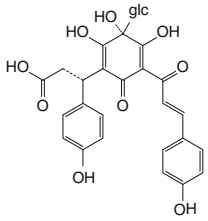
Precarthamin, 6



Tinctorimine, 8



Safflomin, 9

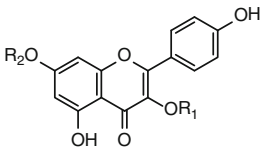


Safflomin C, 10

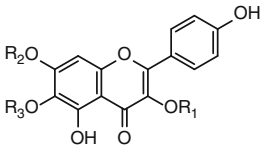
Fig. 76.2 Key quinochalcones isolated from Honghua

76.2.2 Flavonoids

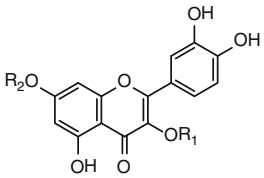
Except for quinochalcones described above, flavonoids are also closely concerned because of their definite pharmacological activities, including flavonols, flavones and chalcones [6]. Among them, flavonol glycosides are the most extensively studied components, which have been evidenced to have antioxidative activity. The structure-activity relationship has been studied, demonstrating that the ability of antioxidative activity is relevant to the structure of sugar moiety. Kaempferide is used as the other standard component to evaluate the quality of crude drug Honghua. Some of them are as follows (Fig. 76.3).



Kaempferol, 1, R_1=R_2=H
Kaempferol 3-β-D-glucoside, 2, R_1=glc, R_2=H
Kaempferol 3-β-rutinoside, 3, R_1=Rutinose, R_2=H
Kaempferol 3-β-sophoroside, 4, R_1=Sophorose, R_2=H
Kaempferol 3-β-D-glucoside-7-β-D-glucuronide, 5, R_1=glc, R_2=gluA



6-hydroxykaempferol, 6, R_1=R_2=R_3=H
6-hydroxykaempferol-3-β-D-glucoside, 7, R_1=glc, R_2=R_3=H
6-hydroxykaempferol-3,6-di-β-D-glucoside, 8, R_1=R_2=glc, R_3=H
6-hydroxykaempferol-3,6,7-tri-β-D-glucoside, 9, R_1=R_2=R_3=glc
6-hydroxykaempferol-3,6-di-β-D-glucoside-7-β-D-glucuronide, 10, R_1=R_3=glc, R_2=gluA



Quercetin, 12, R_1=R_2=H
Quercetin 3-β-rutinoside, 13, R_1=Rutinose, R_2=H
Quercetin 3 -α-L-rhamnoside-7-β-D-glucuronide, 14, R_1=rha, R_2=gluA

Fig. 76.3 Key flavonoids isolated from Honghua

76.3 Pharmacological Studies

It's generally known that Honghua and its related preparations have been widely used in clinical practice and daily life. Under the guidance of the TCM theory, Honghua is mostly applied for blood-stasis syndrome because of its capacity to promote blood circulation. Modern pharmacological studies have also proved that Honghua has certain effects on diseases of the cardiovascular system and the blood system. For example, Honghua has the efficacy of dilating coronary artery and improving myocardial ischemia, anticoagulation and anti-thrombosis, and quinochalcones are proved to be the major effective constituents for such function. In addition, Honghua has shown a wide range of bioactivities, including anti-free radical, anti-oxidation, anti-aging, anti-hypoxia, anti-fatigue, anti-inflammation, analgesia, exciting uterine, anti-hepatic fibrosis, modulating immune system, anti-tumor, etc. [7]. As a single compound isolated from Honghua, HSYA has the effect of antagonizing cerebral ischemia injury, protecting neurons and inhibiting the activation of platelet.

76.4 TCM Applications and Dietary Usage

76.4.1 TCM Applications

In the theory of Traditional Chinese Medicine (TCM), Honghua is pungent in flavor, warm in nature and attributive to the heart and liver meridians. Honghua has

the power to promote blood circulation to remove blood stasis, promote menstruation and alleviate pain. In the aspect of clinical practice, Honghua is mainly applied for blood-stasis syndrome with dysmenorrheal, amenorrhea, postpartum abdominal pain and mass, trauma and pain of joints, etc. Besides, Honghua can also be used for darkish skin eruptions due to stagnation of heat and blood stasis [8]. Clinically, Honghua can be employed in a single form or in a combination with other herbs based on TCM theory.

Single Honghua preparations used frequently mainly include "Honghua injection" and "Honghua dripping pill", which can both be used for occlusive cerebrovascular diseases and coronary heart disease. Compound Honghua preparations involve three kinds of formulation [9]. (1) "Shuxiong tablets" and "Shuxiong pellets" composed of three herbal medicines: Honghua (flower of *C. tinctorius*), Chuanxiong (rhizome of *Ligusticum chuanxiong*), and Xiyangshen (root of *Panax quinquefolium*), are mainly used for the treatment of thoracic obstruction, cardiodynia, angina, and arrhythmia. Recently, "Shuxiong pellets" are receiving increasing attention due to special merits. (2) Dan Hong preparations composed of flower of *C. tinctorius* and root of *Salvia miltiorrhiza* can effectively relieve the clinical symptoms of angina pectoris and improve myocardial ischemia. They mainly have the following four forms: "Dan Hong injection", "Dan Hong frozen-dried powder" (for injection), "Dan Hong orally disintegrating tablets" and "Compound Dan Hong Dripping Pill". Every formulation has its unique advantages and disadvantages, so appropriate formulation should be chosen when it comes to clinical application. (3) Preparations made from active components, such as "HSYA orally disintegrating tablets", "HSYA-phospholipid compound".

76.4.2 Dietary Usage

Honghua not only has high medicinal value, but also has great edible value. The content of linoleic acid from the safflower oil is higher than that from other plants, so safflower oil can be used as healthy edible oil. In many areas of Asia, safflower pigments are used to dye food such as bread, candy and alcohol. Nowadays, Honghua is found to appear on dinner tables as food. Several diet therapy methods are introduced here, so people have a good knowledge of Honghua.

76.4.2.1 Honghua Wine

Composition: Honghua 200 g, low-alcohol-content wine 1000 ml, brown sugar in moderation.

Preparation: Put Honghua and brown sugar in a clean gauze bag, seal the bag and place it into the wine jar. The Honghua wine is made after soaking for seven days.

Function: Nourishing blood and skin and promoting blood circulation. The Honghua wine is indicated for blood-insufficiency, blood-stasis, and dysmenorrhea.

76.4.2.2 Huangqi Honghua Wine [10]

Composition: Huangqi (root of *Astragalus membranaceus*) 15 g, Dangshen (root of *Codonopsis pilosula*) 15 g, Yuzhu (rhizome of *Polygonatum odoratum*) 15 g, (the three herbal medicines are chopped), Gouqizi (fruit of *Lycium bararum*) 15 g, Honghua 9 g, Chinese spirit 500 ml.

Preparation: Chopped three herbal medicines, Gouqizi, and Honghua are put in a cloth bag, then place it in a container. Add Chinese spirit, seal, and soak for 30 days. Huangqi Honghua wine is made after filtration.

Function: Benefiting kidney and strengthening spleen. Huangqi Honghua wine is indicated for physical fatigue, mental weariness, and disharmony of Qi and blood.

76.4.2.3 Gouqi Honghua Wine

Composition: Gouqizi (fruit of *Lycium bararum*) 50 g, Honghua 20 g, low alcohol Chinese spirit 300 ml.

Preparation: Soak Gouqizi and Honghua in 300 ml of Chinese spirit for a month.

Function: Promoting blood circulation and nourishing blood, keeping ears clear. Gouqi Honghua wine is indicated for deafness and tinnitus.

76.4.2.4 Honghua Jupi Seaweed Soup [11]

Composition: Honghua 10 g, Jupi (pericarp of *Citrus reticulata*) 50 g, seaweed 10 g.

Preparation: Boil all herbs above with an adequate amount of water for 15 min.

Function: Promoting flow of Qi and circulation of blood, eliminating sputum and softening hard mass. Honghua Jupi seaweed soup is indicated for hyperthyroid patients with stagnation of Qi and blood.

76.4.2.5 Honghua Tea

Composition: Honghua 5 g, water 300 ml.

Preparation: Put the dried Honghua in a water pot, add boiling water and steep for five minutes. According to personal taste, honey or haw flakes can be added to enrich its flavor.

Function: Regulating menstruation and relieving pain. Honghua tea is indicated for irregular menstruation and amenorrhea.

76.4.2.6 Black Beans Honghua Drink

Composition: Black beans 30 g, Honghua 6 g, brown sugar 30 g.

Preparation: Boil black beans, Honghua with proper water for 4 min by anintense fire, and then continue boiling until black beans are cooked thoroughly by a slow fire. Remove the black beans and Honghua, and add brown sugar to regulate flavor.

Function: Activating blood and dissolving stasis, relieving pain. Black beans Honghua drink is used for the treatment of dysmenorrheal.

76.4.2.7 Xing Ju Honghua Drink [12]

Composition: Kuxingren (seed of *Prunus armeniaca var. ansu*) 6 g, Honghua 6 g, Juhua (flower of *Chrysanthemum morifolium*) 6 g, sugar 30 g.

Preparation: Boil the three herbal medicines with 250 ml water by an intense fire, and then continue boiling for 15 min by a slow fire. Add sugar, and mix up.

Function: Tranquilizing liver and dispelling wind, clearing away heat. Xing Ju Honghua drink is indicated for chronic hepatitis with eye redness and headache.

76.4.2.8 Honghua Shanzha Pudding [13]

Composition: Honghua 15 g, Shanzha (fruit of *Crataegus pinnatifida*) 500 g, rock candy 500 g.

Preparation: Boil Honghua with water and collect decoction, and add Shanzha and rock candy to cook thoroughly. Then the mixture will be congealed into a hard lump after cooling.

Function: Promoting blood circulation and fluid production. Honghua Shanzha pudding is indicated for sjogren syndrome.

76.5 Clinical Evidences

It's demonstrated that Honghua and its related preparations have significant efficacy through repeated and long-term validation of clinical practice. As reported, 36 patients with acute ischemic apoplexy were observed to investigate the clinical effect of HSYA injection on acute ischemic apoplexy, and the effectiveness rate of HSYA injection was 94.4 % [14]. Honghua injection was used to treat 40 patients with coronary disease and angina pectoris, and the total effectiveness rate was 90 % [15]. Hot moist compress with Honghua alcohol was utilized to prevent the occurrence of chemotherapy-induced phlebitis of 28 patients, and the effectiveness rate was 92.86 % [16]. Dan Hong injection was applied for the treatment of acute cerebral infarction, and it suggested that the significantly effectiveness rate and the

effectiveness rate of the treatment group were obviously higher than that of the control group [17]. Honghua injection was used to treat acute gouty arthritis, and it turned out to be extremely effective with no obvious adverse effect [18]. Furthermore, it's also reported that Honghua preparations can be used in combination with other drugs to prevent and treat other diseases or to increase the therapeutic effects. For example, Safflower Yellow was used to treat unstable angina in combination with low molecular weight heparin, and its effect was affirmative, superior to that of regular anti-angina drugs [19]. Honghua injection was used to treat stroke when connected with Bezoar Xingnao injection [20].

76.6 Safety Evaluation and Toxicity Issue

There are very few clinical reports on the toxicity issue of Honghua. Ames experiments were conducted to explore the acute toxicity and genetic toxicity of Honghua, as a result, Honghua was found to have low toxicity and no genetic toxicity [21]. The different dosage groups were set up to investigate the long-term toxicity of Compound Honghua Dripping Pill in rats, and it demonstrated that the difference among the three dosage groups was not significant [22]. However, in the theory of TCM, Honghua can promote blood circulation and remove blood stasis; meanwhile it also can consume Qi and blood. Hence, pregnant women are not allowed to use Honghua. Modern pharmacological experiments on rats have also shown that Honghua decoction is toxic to the mother and embryo when used in pregnant rats. It can lead to maternal abortion, loss of weight and increase risk of embryonic mortality [23]. Therefore, Honghua should be forbidden or used with caution during pregnancy.

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Chapter 77
Chrysanthemum morifolium Ramat 菊花 (Juhua, Florists Chrysanthemum)

Chun Hu

77.1 Botanical Identification

Juhua is the dried flower head of chrysanthemum plant (*Chrysanthemum morifolium* Ramat). *Chrysanthemum morifolium* is a perennial herb covered with white villous hairs, cultivated in many areas in China for medicinal and food applications as well as for ornamental use. The *chrysanthemum morifolium* plant is about 60–100 cm high, densely covered with white villous hairs and has ovate or ovate-lanceolate shaped leaves (3.5–5 cm long, 3–4 cm wide), which are obtuse at the apex and subcordate at the base. Flower heads are at terminal or axillary of stem, with outer flower ligulate shaped petals in white or yellow color, withthe center of the flower being yellow and tubular in shape. The flowers are harvested during the blossoming season, followed by drying to produce Juhua herbal material which is characterized as a mixture of plain to sweet and bitter taste (Fig. 77.1).

Chinese Pharmacopoeia lists four major cultivars based on the areas where they are produced and post-harvest processing methods. These cultivars are known as Boju, Chuju, Gongju and Hangju. The edible chrysanthemum is widely cultivated and produced in Zhejiang, Anhui, Sichuan, Henan, Hebei and Shandong provinces in China. Flower heads are harvested from September to November when flowers are in blossom. Traditionally chrysanthemum flowers are naturally sun dried or dried in shade with or without pretreatment. Boju (traditionally produced in Bo Zhou area of Anhui province) flowers are cut with stems and dried in shade, flower heads are then collected after they are dry, with 1.5–3 cm (diameter) in off-white color; Chuju (1.5–2.5 cm diameter, off-white color, traditionally produced in Chu Zhou area of Anhui province) flowers are collected and fumigated with sulfur, followed by sun drying; Gongju (1.5–2.5 cm, white or off-white, traditionally produced in Xin county of Anhui province) flowers are dried to 90 % dryness at

C. Hu (✉)
Nutrilite Health Institute, 5600 Beach Blvd, Buena Park, CA 90621, USA
e-mail: charles.hu@amway.com

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Fig. 77.1 Representative flowering chrysanthemum (**a**) and chrysanthemum crude drug (**b**)

60 °C followed by sun drying; Hangju (2.5–4 cm diameter, white or yellow; white chrysanthemum is traditionally for food consumption as tea alternative and yellow chrysanthemum is for medicinal use, traditionally produced in the area around Hangzhou of Zhejiang province) flowers are steamed for 4–5 min followed by sun drying. Chinese Pharmacopeia requires that chrysanthemum commodity contain less than 15 % of moisture, no less than 0.20 % (dry weight) of chlorogenic acid, no less than 0.080 % (dry weight) of luteolin glycoside and no less than 0.70 % (dry weight) of 3,5-caffeoylquinic acid [1].

Chrysanthemum is used as traditional Chinese medicine for "expelling wind and clearing away heat", "clearing heat and eliminating toxic substances" and "brightening eyes" in many traditional Chinese medicine formulas and also for daily food consumption as tea alternative. Juhua has sweet and bitter tastes and a slightly cold property, acting on lung and liver meridians, with functions such as "Expelling wind and heat, used for upper respiratory infections", "subduing hyperactivity of the liver and improving acuity of vision, used for inflammation of the eyes and blurred vision" and "calming the liver, used for headache and dizziness". The typical daily dose is 5–10 g [1].

77.2 Chemical Constituents

Flavonoids have been identified from *Chrysanthemum morifolium* flower, including flavones (apigenin, acacetin, luteolin, diosmetin and eupatorin), flavanone (eriodictyol), flavonols (quercetin, isorhamnetin, kaempferol, kaempferide, chrysosphenol C and chrysosphenol D) as well as their glycosides and acetyl glycosides [1–6] (structures are shown in Fig. 77.2), of which, luteolin glycoside is also used as a quality control marker for this herb [1].

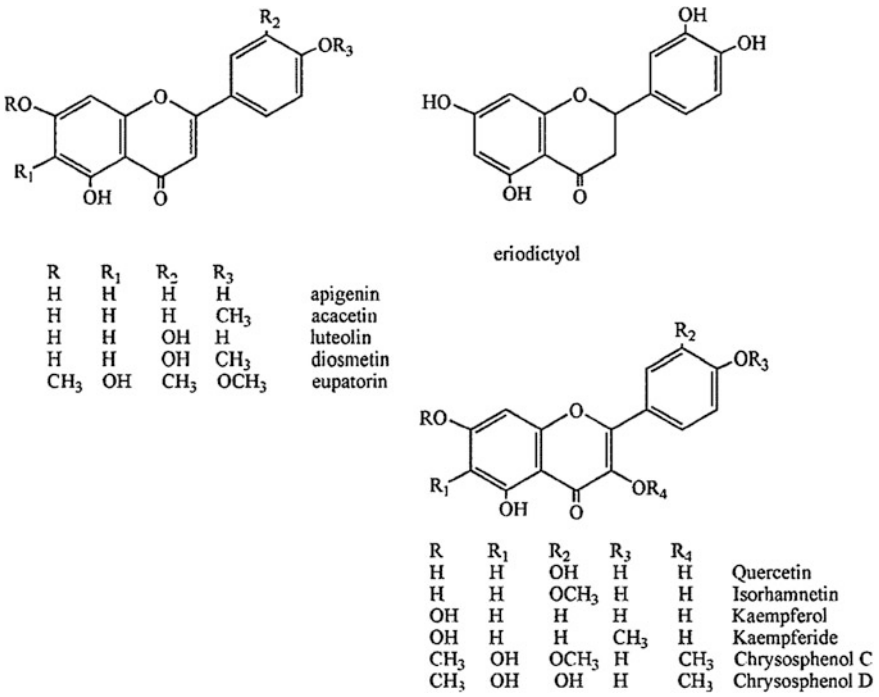

Fig. 77.2 Structure of flavonoid aglycones in *Chrysanthemum morifolium* ramat

Phenolic acids are another class of phytochemicals identified from chrysanthemum. Chlorogenic acid and 3,5-di-caffeoylquinic acid (Fig. 77.3) are known phenolic acids in *Chrysanthemum morifolium* flower, and serve as quality check markers for this herbal material in current China Pharmacopeia [1]. In addition, 1-caffeoylquinic acid, 3-caffeoylquinic acid, caffeic acid 4-glucoside, 4-caffeoylquinic acid, 5-sinapoylquinic acid, caffeic acid, 1,3-di-caffeoylquinic acid, 3,4-di-caffeoylquinic acid, 1,4-di-caffeoylquinic acid, 1,5-di-caffeoylquinic acid, 3-methyoxaloyl-1,5-di-caffeoylquinic acid, 4,5-di-caffeoylquinic acid, 4-caffeoyl-5-feruloylquinic acid, and 3,4,5-tricaffeoylquinic acidare also found in chrysanthemum flower [3] (Fig. 77.3). Caffeoylquinic acid content reaches its peak value when 50 % tubular florets and 70 % ray florets open, which is consistent with the traditional harvest practice [5].

Terpene, sesquiterpene and their oxidized derivatives are the primary volatile compounds from *Chrysanthemum morifolium* flowers. Terpene includes borneol, camphor, α-pinene, β-pinene and 1,8-cineole; sesquiterpene includes farnesene, farnesol, α-cubebene and muurolol, etc. Of the identified volatile compounds from Hangju (Chrysanthemum produced in Zhejiang region), volatile compounds with relative content greater than 1 % include 2-methyl-1-pentene, camphor, borneol, bornyl acetate, β-elemene, α-cubebene, curcumene, α-bergamotene, β-bisabolene,

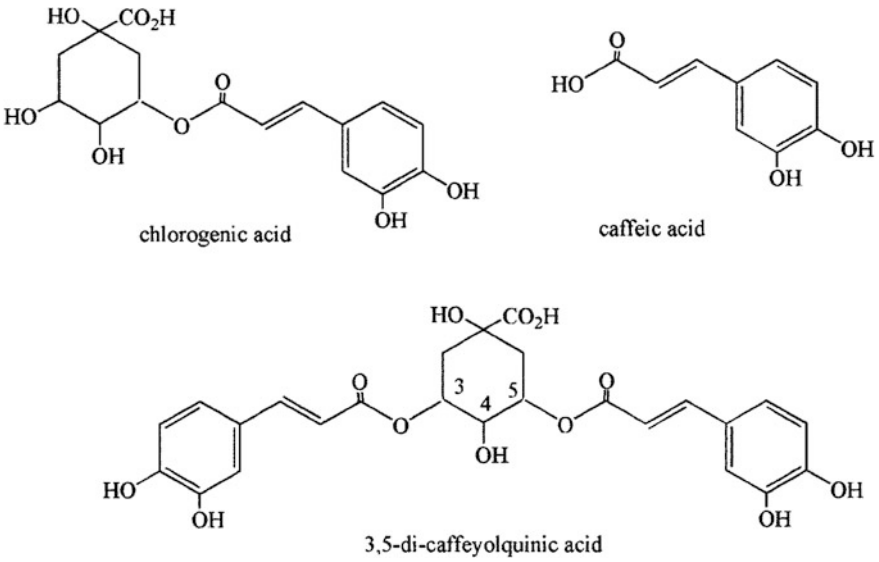

Fig. 77.3 Structures of caffeic acid and its derivatives found in *Chrysanthemum morifolium* ramat

β-cadinene, caryophyllene oxide, β-maaliene, alloaromadendrene, α-costol, hexadecanoic acid, hexadecanoic acid, heneicosane, 9,12-octadecadienoic acid, tricosane, tetracosane and pentacosane according to their retention time on GC/MS [7]. Similarly, another group of researchers identified 58 volatile compounds from *chrysanthemum morifolium,* with β-humulene as the most abundant compound, other significant compounds including ledene oxide, *cis*-Z-α-bisaboleneepoxide, 3,4-dihydro-,2,2-dimethyl-2H-1-benzopryan, *trans*-limonene oxide, 2-methyl-5-(1-methylethenyl)-cyclohexanone, 2,6-dimethyl-1,3,6-heptatriene, 1,6-dibromo-hexane, β-elemene, bromo-cyclohexane, 1-(1,5-dimethyl-4-hexenyl-4-methylbenzene, 3,3,6,6-tetraethyl-tricylco[3.1.0.0(2,4)]hexane, 3-cyclohexene-1-methanol,6-isopropenyl-4,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-ol, caryophyllene, 1-tert-butyl-1,5,-cyclooctadiene, α-farnesol, α-farnesene, limonene, α-pinene, 2-methyl-1-pentene, camphor, borneol, bornyl acetate, β-elemene, α-cubebene, curcumene, α-bergamotene, β-bisabolene, β-cadinene, caryophyllene oxide, β-maaliene, alloaromadendrene, α-costol, hexadecanoic acid, heneicosane, 9,12-octadecadienoic acid, tricosane, tetracosane, astaured hydrocarbons (n-nonadecane, n-eicosane, n-heneicosane, n-docosane, n-pentoacosane, n-hexacosane, n-heptacosane, n-octacosane, n-nonacosane, n-triaceontrane, n-hentriacontane, and n-tritriacontane) [4]. It seems that the volatile compounds vary with the growing area, harvest season, post-harvest process as well as the freshness of the chrysanthemum materials.

Phytosterols, such as campesterol, stigmasterol, β-sitosterol, α-amyrin and β-amyrin, are identified from *Chrysanthemum morifolium*. Ukiya et al. identified and

characterized 24 triperpenediols and triols from n-hexane extraction fraction of *Chrysanthemum morifolium* flower, including arnidiol [taraxast-20(30)-ene-3β,16β-diol]; brein (urs-12-ene-3β,16β-diol); calenduladiol [lup-20(29)-ene-3β,16β-diol]; (24R)-cycloart-25-en-3β,24-diol; dammarenediol II [(20S)-dammar-24-ene-3β,20-diol]; 3-epicabraleadiol [(20S, 24S)-20,24-epoxydammarane-3β,25-diol]; erythrodiol (olean-12-ene-3β, 28-diol); faradiol (taraxast-20-ene-3β,16β-diol); maniladiol (olean-12-ene-3β,16β-diol); (24S)-25-methoxycycloartane-3β,24-diol; (24R)-saringosterol [(24R)-stigmasta-5,24^1(24^2)-diene-3β,24-diol]; (24S)-saringosterol [(24S)-stigmasta-5,24^1(24^2)-diene-3β,24-diol]; (24R)-cycloartane-3β,24,25-triol; (24S)-cycloartane-3β,24,25-triol; faradiol α-epoxide [(20R,21S)-20,21-epoxytaraxastane-3β,16β-diol]; heliantriol A1 [olean-olean-13(18)-ene-3β,16β,28-triol]; heliantriol B2 [lup-20(29)-ene-3β,16β,28-triol]; heliantriol C (taraxast-20-ene-3β,16β,28-triol); (24S)-lanost-9(11)-ene-3β,24,25-triol; longispinogenin (olean-12-ene-3β,16β,28-triol); (24S)-25-methoxycycloartane-3β,24, 28-triol; 22α-methoxyfaradiol (22α-methoxytaraxast-20-ene-3β,16β-diol); (24S)-29-norcycloartane-3β, 24,25-triol [8]. In addition, endoperoxysequitepene lactone and 10α-hydroxy-1α,4α-endoperoxy-guaia-2-en-12,6α-olide have also been identified from chrysanthemum [6].

77.3 Pharmacological Studies

77.3.1 Antioxidant Activity

The antioxidant potential of chrysanthemum extract has been demonstrated in oil emulsion [9], liposome model system with radical scavenging activity [10] and protecting erythrocyte membrane from superoxide radical induced damage [11]. Many phenolic phytochemicals found in *Chrysanthemum morifolium* are known to exhibit antioxidant activity and free radical scavenging capacity in various in vitro models. For example, luteolin and its glycoside suppress free radicals and inhibit lipid oxidation and nitric oxide production [12, 13]. Phenolic acid, 3,5-di-caffeoylquinic acid and 1,3-di-caffeoylquinic acid isolated from *Chrysanthemum morifolium* inhibited superoxide radical (IC_{50} = 2.0 ± 0.1 μg/ml and 2.6 ± 0.4 μg/ml, respectively) in xanthine/xanthine oxidase system [14]. Using hot water extract of *Chrysanthemum morifolium* Ramat, Lii et al. found that chrysanthemum extract and phytochemical associated with chrysanthemum (apigenin and luteolin) suppressed the reactive oxygen species, ICAM-1 and E-selectinin human umbilical vein endothelia cells induced by oxidized LDL (low-density lipoprotein) in a dose-dependent fashion [15].

A flavonoid enriched chrysanthemum extract was found to support oxidative stress status in a cerebral ischemia/reperfusion rats model, and improve neurological deficit score, percentage of infraction and brain edema and maintain superoxide dismutase activity, suggesting that the antioxidant activity of chrysanthemum played an

important role in protecting the animal from cerebral ischemia/reperfusion injury [16]. Similarly, after five days of gauge feeding with flavonoid rich chrysanthemum extract, the myocardial ischemia reperfusion injury in rat model was attenuated, which was attributed to the improvement of antioxidant defense mechanism [17]. Chrysanthemum extract feeding reduced the lipid peroxidation and improved antioxidant enzyme levels in a lead-induced mice oxidative model, and significantly lowered the lead level in blood, brain and other organs [9].

77.3.2 Anti-Inflammatory Activity

Chrysanthemum extract suppressed, bacterial lipopolysaccharide (LPS) induced production of prostaglandin E_2 (PGE_2) in mouse macrophage RAW264.7 at IC_{50} of 0.6 mg/ml [18]. Luteolin and its glycoside inhibited the production of PGE_2 and suppressed the expression of cyclooxygenase-2 (COX-2) in the same cell model [12]. Chrysanthemum methanolic extract was found to significantly inhibit 12-O-tetradecanoylphorbol-13-acetate induced edema in mice [19].

Lipid fraction of chrysanthemum flower extract was shown to contain triterpene diols and triols in their 3-O-fatty acid esters forms, and many of these triterpene diols and triols exhibited anti-inflammatory activity against 12-*O*-tetradecanoylphorbol-13-acetate induced inflammation in mice in the range of IC_{50} between 0.03 and 1.0 mg per ear [8].

77.3.3 Antibacterial and Antiviral Activity

Essential oil obtained from whole herb exhibited strong inhibition on *Streptococcus aureus* and *E. coli* [20]. The minimal inhibition concentration of chrysanthemum extract against oral pathogens *Streptococcus mutans, S. sanguinis* and *S. sobrinus* was greater than 8 mg/ml [21]. Flavonols (quercetin and kaempferol) and flavone (luteolin) exhibited inhibitory activity against methicillin-resistant *Staphylococcus aureus* [22]. In addition, 3-hydroxyl triterpenoids from non-saponifiable lipid fraction of chrysanthemum flower extract exhibited anti-tubercular activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$ [23]. Hu et al. found acetin-7-galatoyranoside from *Chrysanthemum morifolium* was the most effective HIV inhibitor among eight flavonoids isolated from this plant in H0 cell model and the structure-activity relationship showed that a structure with hydroxyl groups at C-5 and C-7 with C2-C3 double bond was more effective in inhibiting HIV growth [24].

77.3.4 Cardiovascular Health

Vasorelaxant effect was found when chrysanthemum extract was incubated with rat thoracic aorta in vitro. Chrysanthemum extract induced both endothelium dependent and independent relaxation using rat thoracic aorta, attributed to the its regulation on the nitric oxide as well as Ca^{2+}-channel and K^{+}-channel [25]. Chrysanthemum extract attenuated the reduction of contraction of isolated rat heart and cardiomyocytes induced byischemia/reperfusion by improving superoxide dismutase activity [26].

77.3.5 Antiglycation and Diabetic Benefit

The non-enzymatic browning reaction between amino acid and carbonyl group (reducing sugar) leads to the accumulation of the advanced glycation end products (AGEs). The glycation process occurs not only in food processing (Mallard reaction in thermal process) but also in biological systems, resulting in the modification of macromolecules with biological importance. Therefore prevention of overly occurred glycation is critical in preventing diabetic complications and the aging process. In a bovine serum albumin/glucose model, chrysanthemum flower effectively inhibited the formation of AGEs (measured by pentosidine) and N^{ϵ}-(carboxymethyl) lysine (CML), attributing to antioxidant and antiglycation activities of phenolic components such as chlorogenic acid and flavonoids in the extract [27, 28]. Though chrysanthemum extract inhibited glycation in an in vitro model, the measurement of skin elasticity improvement after eight weeks of daily oral intake of up to 150 mg chrysanthemum extract failed to show efficacy in a randomized controlled clinical trial, which the author speculated it was possibly due to post-translation modification of collagen [29].

Endoperoxysequiterpene lactone (10α-hydroxyl-1α,4α-endoperoxyl-guaia-2-en-12,6α-olide) showed strong inhibitory effect against α-glucosidase and lipase activity at IC_{50} of 229.3 and 161.0 μM level. While acacetin-7-glucsoide and rhamnoside inhibited both α-glucosidase and α-amylase, eriodictyol only effectively inhibited α-glucosidase [6]. This suggests that chrysanthemum may possess potential health benefits for diabetics.

77.3.6 Other Effects

Being used in Korea for the treatment of insomnia, chrysanthemum extract was found to extend the sleep time in mice induced by pentobarbital by increasing glutamic acid decarboxylase expression. However there was no effect on expression of $GABA_A$ receptor in the hippocampus of the mouse's brain, which was attributed to the Cl^{-} channel activation [30].

77.4 TCM Applications and Dietary Usage

77.4.1 TCM Application

Chrysanthemum is used with Sangye (leaf of *Morus alba*), Bohe (herb of *Mentha haplocalyx*) and Lianqiao (fruit of *Forsythia suspensa*) as *Sangjuyin* decoction to treat exogenous disease due to wind and heat or early stage of seasonal febrile disease manifested such as fever, headache and cough. Chrysanthemum is used with Sangye (leaf of *Morus alba*), Juemingzi (seed of *Cassia obtusifolia*) and Longdan (root and rhizome of *Gentiana manshurica*) to treat red and painful eyes due to wind and heat attacking liver meridian or flaming-up the exuberant liver-fire. Qi Ju Dihuang pill formulated with Gouqizi (fruit of *Lycium barbarum*), Shudihuang (prepared root tuber of *Rehmannia glutinosa*) and Shanzhuyu (pulp of *Cornus officinalis*) is used to treat blurred vision due to weakness of liver and kidney. Chrysanthemum is formulated with Shijueming (shell of *Haliotis Diversicolor*), Baishao (root of *Paeonia lactiflora*) and Chinese cat's claw (*Amulusuncarriae cum uuncis*) to treat dizziness and headache resulted from overly expressed liver-*Yang*. Fresh chrysanthemum flower juice can be used orally and residual used externally to treat furuncle and furunculosis, and this can also be achieved in combination with Zihuadiding (herb of *Viola yedoensis* Makino) and Pugongying (herb of *Taraxacum mongolicum* L).

77.4.2 Dietary Usage

In China, chrysanthemum has been considered as ingredient used as both food and traditional Chinese medicine material by the Ministry of Health, therefore chrysanthemum has been widely used in food and beverages in China. Chrysanthemum is used alone or with other traditional Chinese herbs as a tea alternative and is widely consumed in summer to relieve damp hot. Chrysanthemum tea beverage, sweetened or non-sweetened, is widely available in China as ready-to-drink herbal tea. *Sang Ju Yin* (herbal tea drink formulated with mulberry leaf and chrysanthemum) is also popular in summer and such drinks are commercially available in both aseptic package (ready-to-drink) or as a drink granule. Fresh or dried chrysanthemum flower are sometime used in Chinese cooking too.

Chrysanthemum is also used widely in China in health foods applications with a functional claim. About 220 health foods containing chrysanthemum or its extract have been approved by State Administration of Food and Drug by middle of 2013. About 20 % of products carry a claim for "relieving vision fatigue", and are typically formulated with Sangye, Juemingzi and Gouqizi. Some of these products are formulated with bilberry extract and lutein, which is well aligned with traditional Chinese medicine principles of the usage of chrysanthemum.

77.5 Clinical Evidence

Published double-blind placebo-controlled studies using only *chrysanthemum morifolium* Ramat alone is limited. In a randomized controlled clinical trial, eight week oral administration of 50 and 150 mg chrysanthemum extract per day was proven to be safe, though the primary clinical outcome (improving skin condition) was not demonstrated [29]. In China, Juhua formulated with other traditional Chinese medicines have been clinically studied. In a non-placebo controlled study, granule containing extracts of fleecewood, Gouqizi, Juemingzi, Shanzha (fruit of *Crataegus pinnatifida*), Juhua and Jiaogulan (herb of *Gynostemm apentaphyllum*) (30 g raw material equivalency, twice per day) for stage 1 and 2 hypertensive patients resulted in the reduction of systolic pressure from 159.2 ± 13.5 mmHg to 136.9 ± 8.4 mmHg and diastolic pressure from 100.2 ± 8.4 mmHg to 86.2 ± 5.2 mmHg over 30 days [31].

77.6 Safety Evaluation and Toxicity Data

Chrysanthemum is considered to be safe and of low toxicity, the Ministry of Health of China listed chrysanthemum as one of 80 botanical ingredients used in "both food and medicine". Very few adverse events have been reported from consumption of chrysanthemum. Oral administration of 15 g/kg body weight chrysanthemum extract (containing 7.0 % luteolin and 5.19 % apigenin) did not lead to any observable toxicity in SD rats, and a daily gavage of up to 1280 mg/kg body weight of the same chrysanthemum extract did not lead to any toxicological change in body weight, food and water consumption, or hematologic and histopathologic changes, confirming the high tolerance to chrysanthemum [32]. Using an oral dose of 6.09 g/kg body weight chrysanthemum extract to feed pregnant rats (equivalent to 300 times the recommended human dose in China Pharmacopeia) for 10 days, no significant differences ($p > 0.05$)were found between the treatment group and the placebo group in term of body weight gain of the pregnant rats, average live fetus, absorptive fetus ratio, or body weight and length of fetus, indicating that chrysanthemum had no apparent teratogenicity and embryotoxicity [8]. The high tolerance to chrysanthemum was also confirmed in an eight-week oral administration of 150 mg/day chrysanthemum extract [29]. The primary flavone (luteolin 85.56 mg and apigenin 65.04 mg through administration of 12 *chrysanthemum morifolium* tablets per day) was excluded in urine in the forms of aglycone, sulfurate and glucuronate within 12 h of administration, the mean ($n = 8$) concentration of luteolin and apigenin in urine 6 h after administration were 1.239 ± 0.90 and 1.337 ± 0.91 μg/ml respectively [33]. On the other hand, contact dermatitis was reported from chrysanthemum plant, and the intensity to chrysanthemum is flower > leaf > whole plant > stems [34].

In summary, C*hrysanthemum morifolium* flower contains flavonoids, phenolic acids and volatile compounds, possessing antioxidant, anti-inflammatory, antibacterial and antiviral properties, and exhibits cardiovascular benefits mainly attributed to the phytochemical profiles. Chrysanthemum is safe and has been widely used in food and traditional Chinese medicine. Though chrysanthemum has been formulated and applied in traditional Chinese medicine, well-designed clinical trials are needed to demonstrate efficacy of chrysanthemum.

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Chapter 78
Lonicera japonica Thunb 金银花 (Jinyinhua, Honey Suckle)

Haixia Li and Chunbo Lu

78.1 Botanical Identity

Jinyinhua, a sprawling and twining lianas in the family of Caprifoliaceae, is a popular Chinese herbal medicine used for the treatment of inflammatory diseases and as a well-known dietary supplement that has been used for many centuries. The medicinal part of the plant is the dried flower buds or flowers before blooming. The bloomed flowers undergo six stages, i.e. the juvenile bud stage, green stage, white stage, complete white stage, silver flowering stage, and golden flowering stage [1]. The color of the last two stages are silvery and golden respectively, so the medicinal material is called Jinyinhua becuase Jin means gold in Chinese, Yin means silver in Chinese and Hua means flower in Chinese. Although four other species of genus *Lonicera,* similar to Jinyinhua, have been used for medicinal purposes [2], only *Lonicera japonica* Thunb. has been used as a legal source of Jinyinhua, recorded in The Pharmacoepia of People's Republic of China [3]. As the typical botanical traits, *L. japonica* has young stems with pubescence; leaves ovate, elliptic, oblong or broadly lanceolate, blades 3–8 cm long, 1–3.5 cm wide; flowers in axillary cymes; corolla white, turning yellowish or tinged pink, 2-lipped. Figure 78.1 showed the flowering plant and crude drug of *Lonicera japonica*.

Besides natural wild growth, Jinyinhua is cultured as a ground cover for ornamental and conserving water and soil due to its beautiful flowers and strong roots. Both wild and cultured materials are the source of supply. The flowers are typically harvested between May to June when they change from green to white and are in buds. The quality of medicinal materials will be lowered if the harvest is too early or too late. After drying 1–2 days and picking up impurities, cleaned and dried raw

H. Li (✉) · C. Lu
School of Pharmaceutical Sciences, Zhengzhou University,
Zhengzhou 450002, China
e-mail: lihx1024@zzu.edu.cn

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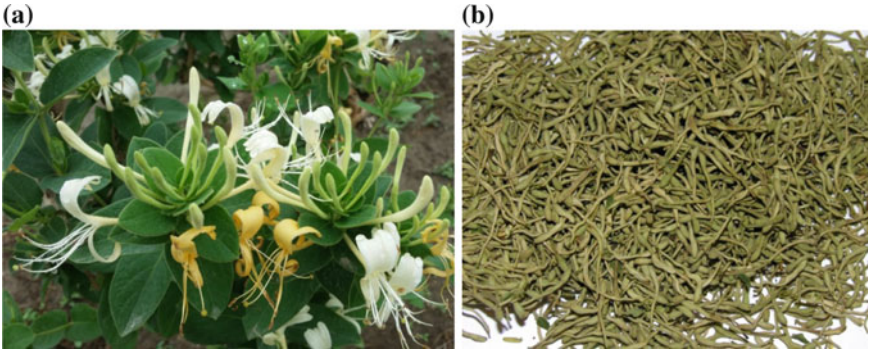

Fig. 78.1 Flowering plant (**a**) and crude drug (**b**) of *Lonicera japonica*

material can be obtained and marketed. During drying procedures, do not direcctly expose the flowers to strong sunlight because it will darken the flowers. Other processing methods are further performed for some specific medicinal purposes, such as fried Jinyinhua and charcoaled Jinyinhua etc. In recent years, sulfur-fumigation has been used to replace natural drying processing for efficiency and pest control [4].

78.2 Chemical Constituents

Organic acids, flavonoids and volatile oil are the three major classes of bioactive compounds found in Jinyinhua [1]. In addition, shuangkangsu (shown in Fig. 78.2 (8)), which has the marked anti-viral activity against influenza B virus, influenza A3 virus and respiratory syncytial virus, is an important chemical constituent with a novel skeleton structure of cyclic peroxide. It was found in 2008.

78.2.1 Organic Acids

Organic acids are the main and effective components of *L. japonica*. Chlorogenic acid (**1**), isochlorogenic acid (**2**), neochlorogenic acid (**3**), and caffeic acid (**4**) (shown in Fig. 78.2) are representative compounds. Among them, chlorogenic acid is received considerable attention for its part in the human diet with potential biological effects [5], and is used as a standard compound for evaluation of the quality of Jinyinhua and related pharmaceutical or natural health product containing the herb. According to the Chinese Pharmacopoeia, its content must be not less than

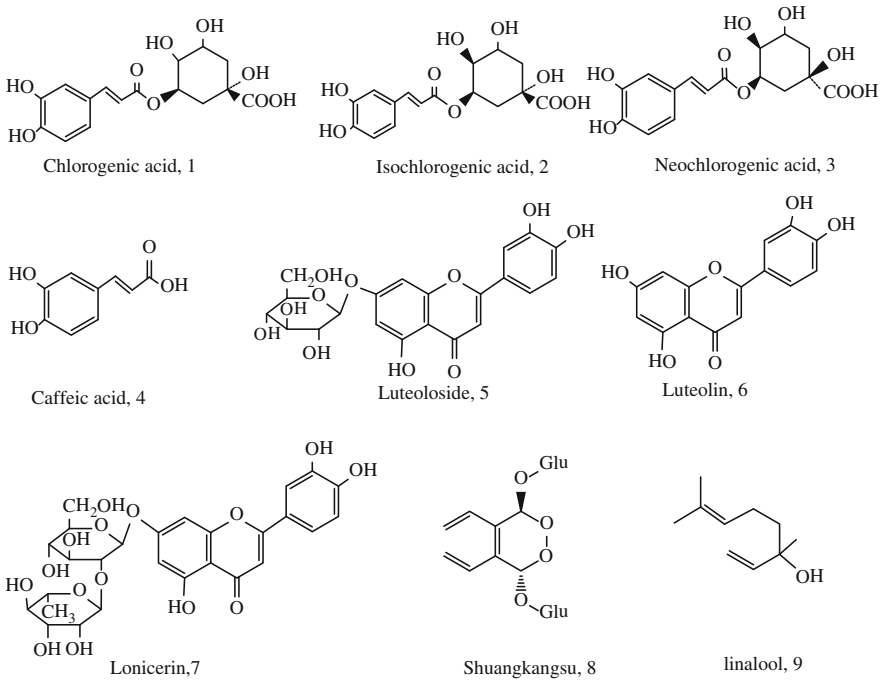

Fig. 78.2 Representative organic acids, flavonoids, and volatile component isolated from Jinyinhua

1.5 % in the dried crude drug. The highest level of chlorogenic acid was found in the white and complete white flowering stages. So far, about 32 organic acids have been isolated from Jinyinhua [1]. Figure 78.2 illustrated the representative organic acids, flavonoids and volatile components isolated from Jinyinhua.

78.2.2 Flavonoids

Because flavonids have a wide spectrum of biological activities, especially with antioxidative and anti-inflammatory properties, they play a part in the qualitative and quantitative analysis of Jinyinhua. Luteoloside (**5**) was added in Chinese Pharmacopoeia with chlorogenic acid to control the quality of medical material by HPLC method. The content of luteoloside in the Jinyinhua should be not less than 0.05 %. Besides luteoloside, other flavonoids, such as luteolin (**6**) and lonicerin (**7**) (shown in Fig. 78.2), have exerted anti-inflammatory activity [6]. Up to now, about 30 flavones have been isolated from *L. japonica*.

78.2.3 Volatile Oil

As one of the important compositions, volatile oil is significant in both the wide activity and utilization of Jinyinhua. A total of about ninety compounds of volatile oil were identified, the main compound being linalool [7]. Due to the differences in harvesting time and processing technics, the contents and components of volatile oil are different. Existing research showed that the complete white and silver flower period are the preferable harvest times for volatile oil, which match with the best time to harvest for chlorogenic acid. Low temperature and no-lighting were in favor of the volatile oil in the dry and extract processes [1].

78.3 Pharmacological Studies

As described previously, Jinyinhua is one of widely used herbs in TCM, especially for almost all infectious diseases, due to its antimicrobial and anti-inflammatory activities. The two activities act synergistically to accelerate wound repair [8]. Moreover, the modern pharmacological studies showed that Jinyinhua and its active principles also possess the wide pharmacological actions, such as antiendotoxin, antipyretic, antihyperlipidemic, antithrombotic, anti-oxidative and anti-carcinogenic activities, and hepatoprotective etc. [1]. In addition, anti-lipase, insecticidal and acaricidal activities were also found in the crude extract of Jinyinhua. In recent years new bioactivities, such as the potent anti-Parkinsonism activity [9] and protecting neuronal cells against glutamate excitotoxicity via antioxidative activity [10], inhibition of the allergic contact dermatitis [11], and a possible use for antidiabetes, have been discovered and suggested to be in the compounds isolated from Jinyinhua due to its potent inhibitor action for maltase [12]. Researchers thought most of these effects may be related to the active compositions of volatile oil, chlorogenic acid, and flavones. Chlorogenic acid and luteoloside, officially used as the indicator compound to characterize the quality of this herb and its related preparations, were shown to have beneficial effects in the aspects of anti-oxidation and antitumor [1, 13]. Moreover, chlorogenic acid showed the antibacterial, antiviral, anti-inflammatory, hypoglycemic activities, and allergy-preventive properties [1, 14]. Meanwhile, luteolin, another major flavonoid in Jinyinhua, and volatile oil also showed significant anti-inflammatory activity. Luteolin has significant bioactivities in the aspects of antifibrotic and anti-5-lipoxygenase activities [6, 15]. Taken together, most of these activities matched to traditional usage.

78.4 TCM Applications, Dietary, and Daily Life Usage

78.4.1 TCM Applications

Jinyinhua with heat-clearing and detoxifying effect has been called little fairyhood of herb store. In TCM clinical practice, Jinyinhua is usually used to treat various infectious diseases. As the most famous herb of anti-inflammatory, it is constantly used for upper respiratory tract infections. 1500 years ago, Jinyinhua had been used for the treatment of exopathogenic wind-heat, epidemic febrile diseases, carbuncles, sores, furuncles and infection diseases. Also, it has also been made in preparations to treat chronic enteritis, pneumonia, acute tonsillitis, nephritis, acute mastitis, and leptospirosis in clinic. More than 500 prescriptions containing Jinyinhua have been used to treat various diseases [1]. Common Jinyinhua preparations clinically used include the following forms:

78.4.1.1 Oral Liquids

Yinhuang Oral Liquid and Shuanghuanglian Oral Liquid [9, 12] are two typical examples of oral liquid. Yinhuang Oral Liquid is composed of two herbal components: Jinyinhua and Huangqin (roots of *Scutellaria baicalensis*), where Shuanghuanglian Oral Liquid has an additional component: Lianqiao (fruits of *Forsythia suspensa*) besides Jinyinhua and Huangqin. There are hundreds of manufacturers making these two products based on the same formula in China, These two products are two of the best-selling drugs on market. They are mainly used for the treatment of fever, cough, sore throat, acute and chronic tonsillitis, acute and chronic pharyngitis through its function clearing away the heat and toxic material, antibacterial, anti-inflammatory and antiviral effects.

78.4.1.2 Buccal Tablets

Yinhuang buccal tablets and Shuanghuanglian buccal tablets have the same compositions as oral liquid but are in a different form. The buccal table form is particularly suitable for swelling and pain of the throat caused by acute and chronic tonsillitis, pharyngitis and upper respiratory tract infections.

78.4.1.3 Injections

Yinhuang Injection, Shuanghuanglian Injection, and Compound Acetaminophen Jinyinhua Injection are three common used preparations containing Jinyinhua. Compound Acetaminophen Jinyinhua Injection is composed of the extract of Jinyinhua, baicalin, and acetaminophen. These products have been used clinically for

the treatment of upper respiratory tract infections, sore throat, tonsillitis, mumps and pneumonia, and Compound Acetaminophen Jinyinhua Injection has also been used to relieve moderate pain, such as arthralgia, headache, and toothache. Adverse reactions of these products after intravenous injection were detected so these injections are better to be administered by intramuscular injection.

78.4.1.4 Granular Form

Jinyinhua granula prepared by itself is an extract in a convenient form that is used by being mixed with other herbs.

Recently, Jinyinhua, as 'bouvardin', has been used extensively to prevent and treat some serious viral diseases of humans and animals, such as SARS corona virus, H1N1 (Swine) flu virus [16].

78.4.2 Dietary Usages

Jinyinhua is a well-known dietary supplement due to its valuable bioactivies and because it's easy to obtain since it is planted in many areas as one of ornamental groundcover. It can be used in many ways historically. These include Jinyinhua beverage, Jinyinhua candy, and Jinyinhua soup etc. The following dietary forms can be easily bought at a market or made at home.

78.4.2.1 Jinyinhua Beverage and Wine

Jinyinhua has been used to make healthy beverage through various technologies, such as Jinyinhua tea, Jinyinhua dew, Jinyinhua nutritive dew, Jinyinhua nutritive beverage, and Jinyinhua yogurt etc. These beverages are employed to improve the body and prevent illnesses in China [1].

Jinyinhua tea has a variety of practices, such as Jinyinhua by itself, combined with tea, combined with honey, or combined with other herbs. All of them are popular ways to use Jinyinhua. They are typically drunk in the hot season for clearing heat, detoxicating and strengthening the body's response against disease by improving the activity of the immune system. Some examples are: Jinyinhua dew composed of the distilled liquid of Jinyinhua and water. Jinyinhua Tea can be drunk after boiling water of 150 ml to soak Jinyinhua (5 g) and green tea (3 g) for 5–10 min. According to further needs, Jinyinhua can be combined with other herbs with bioactivities for enhancing its effect. Jinyinhua Shanzha Tea composed of Jinyinhua (10 g), Juhua (flowers of *Chrysanthemum morifolium*, 10 g), and Shanzha (fruits of *Crataegus pinnatifid*a, 10 g) for headache, fever and thirst caused by hotness. Jinyinhua Bohe Tea composed of Jinyinhua (15 g), Bohe (aerial parts of *Mentha haplocalyx*, 5 g), and Gouqi (fruits of *Lycium chinense* or *L. barbarum*, 15 g).

Jinyinhua itself or combined with different herbs can be used to make herbal wine for various specific needs of functions. Some examples are: the extracting solution of Jinyinhua (alcohol content 55 %) is added before fermentation, the following process is the same as used to brew wine [17]; Jinyinhua (45–55 g), Gancao (roots and rhizomes of *Glycyrrhiza uralensis*, *G. inflate*, or *G. glabra*, 5–10 g), Gouqi (fruits of *Lycium chinense* or *L. barbarum*, 25–30 g) and Baizhi (roots of *Angelica dahurica*, 5–10 g) are soaked in 500 ml wine of alcohol content between 55–60 % for more than 25–50 days, then it can be adjusted into different contents of alcohol according to needs.

78.4.2.2 Jinyinhua Candy

Jinyinhua, the material which can be used as medicine and food, is often made into candy together with other herbs. Some examples are: Jinyinhua Qingguo Pipa candy composed of Jinyinhua, Qingguo (Chinese olives, fruits of *Canarium album*), Pipa (fruits of *Eriobotrya japonica*), Jiegeng (roots of *Platycodon grandiflorum*) and Baimaogen (rhizomes of *Imperata cylindrica*); Jinyinhua cool candy is composed of Jinyinhua, Qingguo, Luohanguo (fruits of *Siraitia grosvenorii*), Pangdahai (seeds of *Sterculia lychnophora*) and Bohe (aerial parts of *Mentha haplocalyx*); Jinyinhua Juhua candy is composed of Jinyinhua, Bohe and Juhua (flowers of *Chrysanthemum morifolium*). White granulated sugar and liquid glucose are usually added to adjust the taste. You can buy the candy in the supermarket for the purpose of moistering and clearing the throat.

78.4.2.3 Jinyinhua Used in Medicated Foods

Jinyinhua can be used to make soups or porridge with rice, or mung bean etc. A typical way is to boil 100 g mung bean and a piece of ginger in 1 liter of water before adding 30 g Jinyinhua, then continuously boil until the mung bean cracks and are fully cooked. Other ingredients, such as wax gourd, lily bulbs, lotus root, almond, pears, and ham etc., can be boiled together with Jinyinhua. Beautiful white and yellow color, nutrient, and health-maintaining effect of Jinyinhua can be employed simultaneously. The taste of Jinyinhua-contained foods can be adjusted by adding honey, white granulated sugar or licorice.

In addition, the oil and extracts from Jinyinhua may be a potential source of preservatives for the food industries [1].

78.4.3 Jinyinhua Used in Daily Life

In Qing dynasty of China, about 375 year ago, Jinyinhua was used to moisturize the skin and for rejuvenation. Recently, the extract of Jinyinhua, as natural source of

bioactive compounds, have been applied in cosmetics, extensively to exert its marked antibacterial and antisepticize activities, such as Jinyinhua facial mask, Jinyinhua facial cleanser, and Jinyinhua shower Gel. It could be made into toothpaste which could have the effects of preventing and treating the oral cavity's diseases [1]. In addition, the volatile oil isolated from Jinyinhua would cover the smell from cigarettes. And chlorogenic acid and its analogues, which are beneficial to health, are rich in Jinyinhua. It can be added into cigarettes to serve a useful role in improving the quality of cigarettes and preventing disease.

78.5 Clinical Evidences

Jinyinhua is mostly used in combination with other herbs with heat-clearing and detoxifying effect, such as Huangqin (roots of *Scutellaria baicalensis*), Lianqiao (fruits of *Forsythia suspensa*) etc. More than 12 preparations, in which Jinyinhua was the main and active compositions, were listed in Chinese Pharmacopoeia (2010 edition) and used to cure fever, cough and pharyngalgia and the swell of throat, constipation, conjunctival congestion, etc. Except the aforementioned preparations: injection, oral solution, granular, or suppository of Yinhuang, Shuanghuanglian and Yinzhihuang, SimiaoYongan decoction, Yinqiao Jiedu Tablets, and Xiaoyin Tablets etc. are the most commonly used preparations.

There are large numbers of clinical related reports or observational studies published on the effects of Jinyinhua and its related preparations for various diseases. Clinical report showed Shuanghuanglian oral solution's effect of antipyretic on wind and warm syndrome was 100 % within 72 h in 48 cases [18]; and the preparation could effectively relief the cold symptom of cough, headache, nasal discharge, sore throat. It could also stop the cheek swelling of child with epidemic parotitis [19]. Yinzhihuang oral solution, which is composed of four herbal components: Jinyinhua, Yinchen (aerial parts of *Artemisiae scopariae* or *A. capillaris*), Huangqin (roots of *Scutellaria baicalensis*), and Zhizi (fruits of *Gardenia jasminoides*), may inhibit further increase in bilirubin levels, and reduced the phototherapy requirement in 1177 cases of neonatal indirect hyperbilirubinemia in term newborn infants [20]. Simiao Yongan (Trade name: Mailuoning) is used in treating ischemic cardiovascular and cerebrovascular diseases for many years in clinical and comprises Jinyinhua, Xuanshen (roots of *Scrophularia ningpoensis*), Danggui (roots of *Angelicae sinensis*) and Gancao (roots and rhizomes of *Glycyrrhiza uralensis*, *G. inflate* or *G. glabra*), clinical studies have shown that it can inhibit the inflammatory response and antagonize the blood clotting process [21].

78.6 Safety Evaluation and Toxicity Data

Because Jinyinhua is an edible herb and commonly used as raw material in health food, clinical reports on the toxicity or side effects were done to determine its safety at least 10 years ago. The extract of Jinyinhua was found to be fairly nontoxic when oral taken by rats or mice. The detail was as follow. Acute toxicity test showed its LD_{50} was more than 15 g/kg body weight on mice orally. According to the classification standard of chemicals acute toxicity, it belongs to non-toxic level. Micronucleus test of bone marrow cells up to 7.5 g/kg in mice orally and Ames test/mammals microsomal enzyme test showed it was safe without mutagenesis. Meanwhile, sperm abnormalities and antifertility effect were undetected on male mice and SD female rats, respectively [22]. In addition, Jinyinhua combined with the dried Zhimu (rhizomes of *Anemarrhena asphodeloides*) showed no signs of acute or chronic toxicity in terms of general behavior, gross appearance of the internal organs, blood chemistry, or mortality in male or female rats when orally administered a single dose of 5,000 mg/kg in acute toxicity test or 500, 1000 or 2,000 mg/kg daily for 13 weeks in chronic toxicity test. They didn't cause significant gastric mucosal damage after single or repeated doses, instead appearing to protect the mucosa from diclofenac-induced gastric damage [23].

To sum up, as a material of being used as medicine and food, Jinyinhua is definitely a safe herbal medicine, and often used for the treatment of infectious diseases and health maintaining purpose. It can also be used for relieving cold and cleaning away poison. But the close attention must be paid when deciding to use this herb for cold because it is obvious that the cold treated by Jinyinhua refers only to a pyretic cold rather than a frigid cold, and this herb is inapplicable for the hypofunction of person's constitute with cold manifestation consideration of its strong clearing heat activity.

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Chapter 79
Sophora japonica L. 槐花 (Huaihua, Japanese Pagodatree Flower Bud)

Raorao Li and Hui-Min Gao

79.1 Botanical Identity [1]

Huaihua is the dried flower and flower bud of *Sophora japonica* L. in the Leguminosae family. It is collected in the summer at flowering (Fig. 79.1) or when flower buds are formed, and then it is dried in time and removed from branch, pedicel and foreign matter. The former is known as "Huaihua" and the latter "Huaimi". Huaihua has a crumpled and rolled appearance. Its petals have mostly fallen off. For the whole flower, the yellowish-green calyx campanulate was observed, with a 5-lobed at the apex. Huaimi takes on the ovoid and ellipsoidal shape, 2–6 mm long, about 2 mm in diameter.

S. japonica L, the origin plant of Huaihua, is a deciduous tree. It is often planted in homes and on the roadside. It blossoms from April to May each year, and flowering period is about 10–15 days. It is widely cultivated in most places around China, such as Shanxi, Gansu, Qinghai, Ningxia, Henan, Hebei, Shandong, Anhui, and Jiangsu provinces, etc.

Traditionally, Huaihua has three kinds of medicinal forms with different therapeutic actions, such as the crude drug and its processed products, stir-baked or carbonized slices. The latter two are commonly used in clinical practice. Stir-baked slice is prepared by stir-baking the crude material till a dark yellow color is produced externally, while carbonized slice is cooked until a charred brown color is produced externally under the same procedure.

R. Li · H.-M. Gao (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: huimin_gao@126.com

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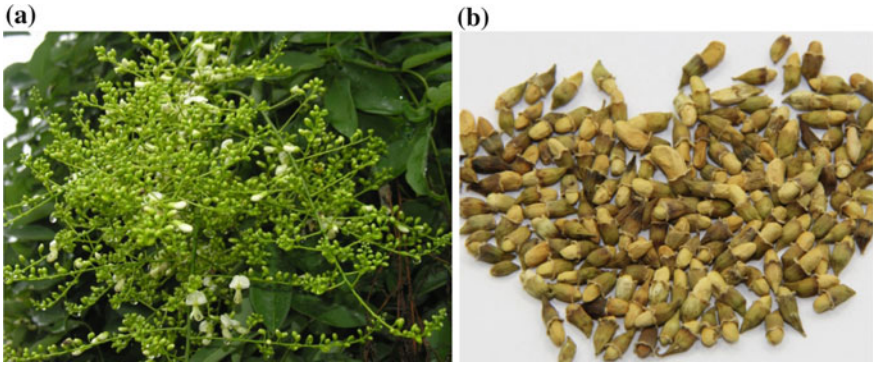

Fig. 79.1 The flowering plant (**a**) and crude drug (**b**) of Huaihua

79.2 Chemical Constituents [1]

S. japonica L, contains a variety of constituents including flavonoids, triterpene and triterpenoid saponins, steroids and other kinds of compounds. Among them, flavonoid and its glycosides are main effective compounds.

79.2.1 Flavonoids

Rutin (**1**), is the major flavonoid glycoside in the dried flower and flower bud of *S. japonica* L. Because of high amounts in the crude material and potent bioactivity, it is usually considered as a marker component for the quality evaluation of Huaihua and its related preparations. Other favonoids, including quercetin (**2**), kaempferol, isorhamnetin and isoflavonoid genistein (**3**) were also reported from this drug (Fig. 79.2).

The content of total flavonoids in Huaimi is far higher than those in Huaihua. According to the current Chinese Pharmacopoeia, the content of rutin should not be less than 15 % for Huaimi and not less than 6.0 % for Huaihua [2].

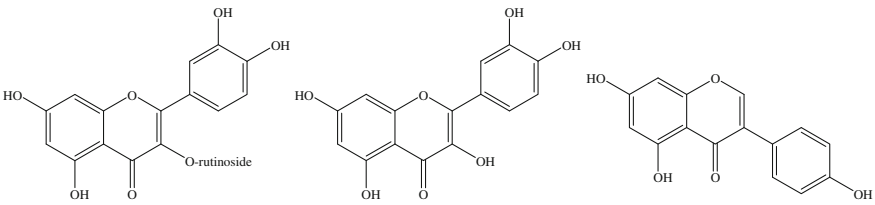

Fig. 79.2 Representative flavonoids and their glycosides from Huaihua

79.2.2 Triterpenoid Saponins

The content of total saponin is about 0.4 % in the dried buds of *S. japonica* L. After acid hydrolysis, betulin and sophoradiol as aglycones were separated, and glucose and glucuronic acid were detected by paper chromatography. The triterpenoid saponins, soyasaponin I, soyasaponin III, azukisaponin I, azukisaponin II, azukisaponin V, kaikasaponin I, kaikasaponin II and kaikasaponin III, are also isolated from the dried buds of this plant.

79.2.3 Steroids and Other Compounds

Sophorin B and C were found in the dried buds of *S. japonica* L., with the content of 1.25 and 0.35 %, respectively, however, the structures of both compounds were not elucidated. In addition, lauric acid, dodecanedioic acid, myristic acid, tetradecenoic acid, tetradecadienoic acid, palmitic acid, hexadecenoic acid, stearic acid and other fatty acids, glucose, glucose hexanetetrol acid and glucose propylgallate were found. Vitamin A was also measured.

79.3 Pharmacological Studies [2]

As an important herbal medicine for the treatment of different hemorrhagic diseases, Huaihua showed various pharmacological effects including antioxidant, antimicrobial, antihypertensive and hemostatic activities as well as an expansion of the coronary artery. All the three forms of Huaihua, (the crude material and its processed products; stir-baked and carbonized slices), have the hemostatic effect; moreover, the effect of the latter two is stronger than that of crude drug. Rutin, the main constituent in Huaihua, has an effect like vitamin P (that is, reducing the abnormal permeability and brittleness of capillaries), and can lower lipid on the fatty liver and inhibit aldose reductase. Quercetin, the aglycone of rutin, has similar bioactivities as mentioned above.

In addition, the Huaihua extract can protect the health of the skin because of its antioxidant and tyrosinase inhibition activity, and it is widely used in cosmetics.

79.4 TCM Applications and Dietary Usage

79.4.1 TCM Applications

The crude drug is cold in property, mildly bitter in flavor and attributive to liver and large intestine meridians. It can cool blood to stanch bleeding, clear the liver and

purge fire. It is used for bloody stool, hemorrhoid bleeding, blood dysentery, flooding and spotting, hematemesis, epitaxis, red eyes caused by liver-heat, headache, and dizziness.

For stir-baked Huaihua slices, its cold properties are weakened and the taste is bitter. It is used for patients with the physique of spleen cold in terms of TCM theroy. For carbonized Huaihua slices, its cold properties are very weak and the taste is bitter. It is used for the different hemorrhagic diseases.

79.4.2 Dietary Usage [3]

79.4.2.1 Huaihua Carp Soup

The crude material of the soup is composed of Huaihua (15 g), onion segment, purple garlic (20 g), carp (500 g), slices of ginger and a teaspoon of salt. The cleaned carp is cut into segments. The fresh flowers are blanched. The oil is put into the hot pot to fry the fish. The fried fish is cooked together with the flowers, salt and water, till the fish smells fragrant. This soup can be used for the treatment of psoriasis with hot and humid properties.

79.4.2.2 Huaihua Gruel

The crude material of the gruel is composed of Huaihua (30 g) and rice (60 g). The cleaned flower are blanched. The rice is washed, put into pot and boiled by strong fire after adding some water. Afterwards, the gruel continued to be cooked with a small fire till it is ready. The flower is put into the gruel and boiled before the cooking finished. The gruel is helpful for beauty and better hemostasis for excessive menorrhagia because of its blood heating qualities.

79.4.2.3 Diyu Huaihua Honey Tea

Diyu (root of *Sanguisorba officinalis* L., 60 g) is decocted with water twice (40 min per time), and the decoctions are combined and concerntrated. Huaihua (30 g) is added and then decocted with a strong fire for 10 min. Honey (30 g) is added before drinking. The tea is used for bleeding induced by the cervical cancer. Taken twice daily.

79.4.2.4 Shanzha Huaihua Heye Tea

Shanzha (fresh fruit of *Crataegus pinnatifida* Bge. var. *major* N.E.Br., 30 g), Huaihua (9 g), and Heye (fresh leaf of *Nelumbo nucifera* Gaertn. 15 g) are decocted

till the fresh hawthorn is almost frazzled, then it is crushed with a spoon, and re-boiled for 10 min. The decocted juice can lower lipids and is used for the treatment of a fatty liver.

79.5 Clinical Evidences

Few clinical observations regarding Huaihua or its preparations were reported, except for the following case. The effect of Compound Huaihua Jiangya granule on insulin resistance hypertension was observed in a pre-clinical investigation. Compound Huaihua Jiangya granules were given to the treated group for four weeks and it displayed significant effects on lipid-lowering and sugar-lowering effect compared with the control group [4].

79.6 Safety Evaluation and Toxicity Issue

Huaihua is a relatively safe herbal medicine and it seldom causes the side effects. However, it was also found in some reports that Huaihua can cause skin itching and a pimple-like rash, after eating. LD_{50} of rutin was 950 mg/kg doses to rats by intraperitoneal injection. LD_{50} of quercetin was 160 mg/kg doses to rats by oral adminstration.

The flower is very sweet and it is not suitable for the people with diabetes. In addition, it is hard to be digested. So, it should not be taken too much for the people with poor digestive system, especially the elderly.

References

1. Li et al (2002) Research on the constituents, pharmacological effects and process of *Sophorae Flos*. Chin J Inf TCM 9(6):77–82 (in Chinese)
2. Pharmacopoeia Committee of P. R. China (2010) Pharmacopoeia of the People's Republic of China. China Medical Science Publishers, Beijing
3. Yi (2009) The medicinal and edible pagodatree flower. Food Health (4):35 (in Chinese)
4. Xu et al (2005) The effect of compound huaihua jiangya granule on insulin resistance hypertension. Chin J Integr Med Cardio-/Cerebrovasc Dis 6:489 (in Chinese)

Part VI
Multiple-part Materials

Chapter 80
Cichorium glandulosum Bioss. Et Huet 菊苣 (Juju, Chicory)

Haji Akber Aisa and Xuelei Xin

80.1 Botanical Identity

Juju, a perennial herb in the family of Asteraceae is famous for its therapeutic and medicinal properties. It is used both in food, and traditional or modern medicine. Although there are 10–12 species of genus *Cichorium* in the world, only two of them, *Cichorium intybus* L. and *Cichorium glandulosum* Boiss. et Huet are familiar to us as medicine and edible food. *Cichorium intybus* L and *Cichorium glandulosum* Boiss. et Huet are major and legal sources recorded in The Pharmacopoeia of People's Republic of China [1], and many historical records of traditional Uyghur or Uighur medical works. Typical botanical traits of *Cichorium intybus* L are the tough, grooved, and somewhat hairy stems at a height of 30–100 cm. The leaves are stalked, lanceolate and unlobed. Flower heads are 2–4 cm (0.79–1.6 in.) wide. Flower petals are light blue, and sometimes white or pink [2]. *Cichorium glandulosum* Boiss. et Huet has very similar traits to *Cichorium intybus* L, except the stems are strigose [3].

The medicinal parts of the plant are the aerial part and root, and the edible parts are the root and leaf. The aerial part is taken in summer and autumn, and the root is harvested in late autumn. The main root of *Cichorium glandulosum* Boiss. et Huet is conical shaped with many fibrous roots and lateral roots. The main root is pale brown in color and has tiny, irregular wrinkles on the surface. This part of the root has a slightly bitter taste, and is about 10–20 cm long with a diameter of 0.5–1.5 cm. Sometimes, there are 2–3 forks at the top of *Cichorium intybus* L root. These roots are pale brown to dark brown, rough with deep longitudinal grain, and only few lateral roots and fibrous roots [1] (Fig. 80.1).

H.A. Aisa (✉) · X. Xin
Xinjiang Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Urumqi 830011, Xinjiang, China
e-mail: haji@ms.xjb.ac.cn

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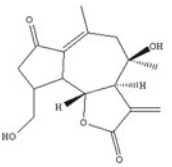
Fig. 80.1 Flowering plant (**a**) and dried roots (**b**) of *Cichorium glandulosum*

80.2 Chemical Constituents

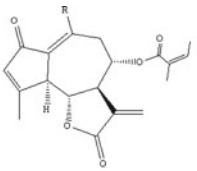
The study of the *Cichorium* genus mostly involves the study of *Cichorium intybus* L, while only a few papers reported covering *Cichorium glandulosum* Boiss. et Hue and other plants in this genus. Being a member of the asteraceae family, there are similarities to other plants in the asteraceae family, such as: terpenoids, flavones and coumarins et al. Up to now, coumarins, flavonoids, sesquiterpenoids, triterpenoids, steroids and organic acids were found in *Cichorium* genus, and here, some sesquiterpenoids and other new structure compounds were listed.

80.2.1 Sesquiterpenoids

Sesquiterpenoids are the main active components. Most sesquiterpenoids have the skeleton of guaiane sesquiterpenes, with few that are eudesmane sesquiterpene, referencing the structures of these below [4–14] (Fig. 80.2).

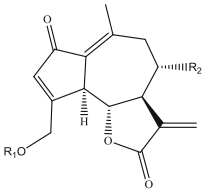


3, 4-dihydrolactucin[4], 1



Epi-8α-angeloxycichoralexin[5], 2, R=CH_3, αMe

8-O-methylsenecioylaustricin[5], 3, R=CH_3, βMe

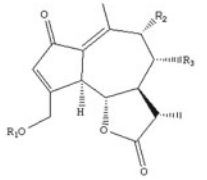


lactucin[6], 4, R_1=H, R_2=OH

8-deoxylactucin[6], 5, R_1=H, R_2=H

Lactucopicrin[6], 6, R_1=H, R_2=p-hydroxyphenlyacetoxy

crepidiaside A[7],7,R_1=Glc,R_2=H



jacquinelin[6], 8, R_1= H, R_2=H, R_3= H

crepidiaside B[6], 9, R_1= Glc, R_2=H, R_3=H

cichorioside D[6],10, R_1= Glc-Rha, R_2=H, R_3=H

cichorioside E[6], 11, R_1= Glc-Fru, R_2=H, R_3=H

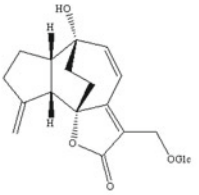
11β,13-dihydrolactucin[6],12,R_1=H,R_2=H,R_3= OH

cichorioside B[6], 13, R_1=Glc, R_2=H, R_3=OH

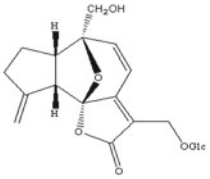
cichorioside F[6], 14, R_1= Fru, R_2=H, R_3=OH

cichorioside G[6], 15, R_1= H, R_2=H, R_3= OGlc

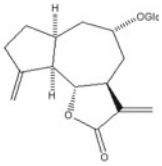
cichorioside H[6], 16, R_1= H, R_2=OGlc, R_3=H



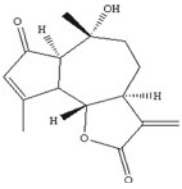
cichorioside J[6],17



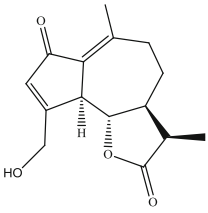
cichorioside K[6],18



Ixerisoside D[8], 19

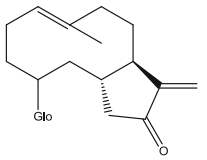


10α-hydroxycichopumilide[9], 20

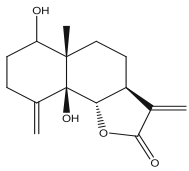


11-epijacquinelin[10], 21

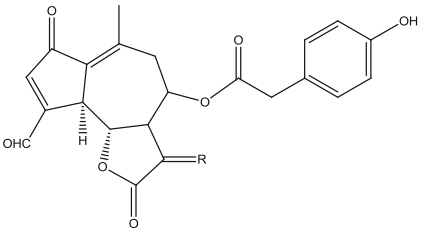
Fig. 80.2 Representative sesquiterpenoids isolated from *Cichorium* genus



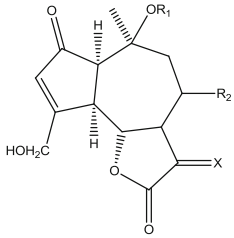
picriside B[7], 22,



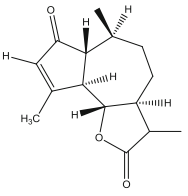
tanacetin[8] 23



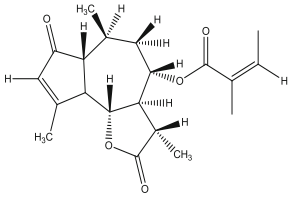
lactones lactupicrinal[8], 24, R=CH_2
11β,13-di-hydrolactupicrinal[10], 25
R=βH,αCH_3,



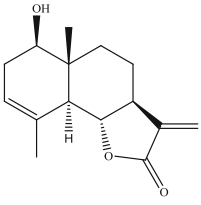
10β-methoxy-1α,11β,13 tetrahydrolactucin[11] 26, R_1=H, R_2=H,X=CH_2
hieracin II[1136],27, R1=CH_3, R_2=OH,X=H,Me
macrocliniside G[11] , 28,R_1=Glc,R_2=H,X=CH_2



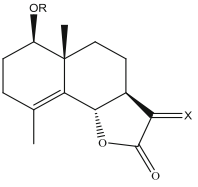
Cichoralexin[9], 29



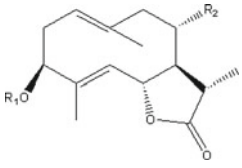
8α-angeloxycichoralexin[9], 30, R=CH_3



Santamarine[12] , 31



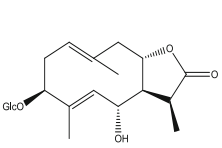
magnolialide[8], 32, R=H, X=CH_2
artesin[8], 33, R=H, X=H, α Me
11-epiartesin[12], 34 R=H, X=H, βMe
magnolialide-1-O-β-D-glucoside[8], 35, R=Glc,X=CH_2



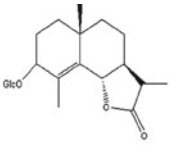
sonchuside A[6], 37, R_1=Glc, R_2=H
cichorioside C[6], 38, R_1=Glc, R_2=OH
hypochoeroside A[6], 39, R_1= H, R_2=OH
cichorioside L[6], 40, R_1= H, R_2= OGlc-Apl

11 β,13-dihydromagnolialide-1-O-β-D-glucoside[8] 36, R=Glc,X=H, α Me

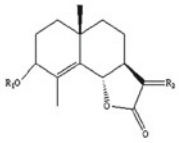
Fig. 80.2 (continued)



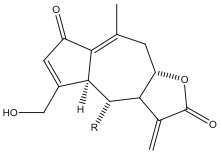
cichorioside M[6], 41



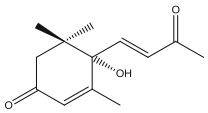
sonchuside C[8], 42



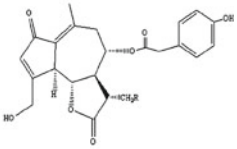
Cichoriolide [8], 43, R_1 =H, R_2=CH_2
CichoriosideA[8] , 434, R_1=Glc, R_2=CH_2,
eudesmanolide[8], 45,R_1 =H, R_2=H,α Me



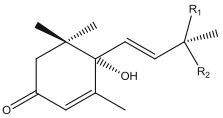
Intybulide[12], 46, R=OH



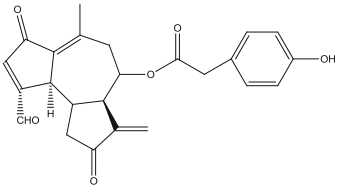
6S,7E-6-hydroxy-4,7-megastigmadien-
3,9-dione (S(+)- dehydrovomifoliol[13], 47



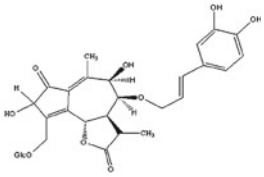
11β,13-dihydrolactucopicrin[6], 48, R=H
11β,13-dihydro-13-prolyl-lactucopicrin, [6]
49, R=prolyl



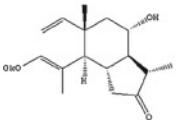
Roseoside, 50, R_1=CH_3, R_2=OGlc
6S, 7E, 9S-diastereomer[13], 51,
R_1=OGlc, R_2=CH_3



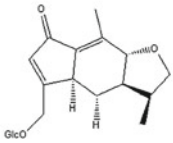
lactupicrin-15-al[8], 52



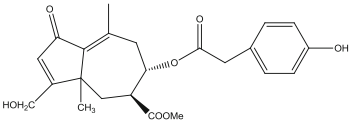
Cichotyboside[14],53



cichorioside N[6], 54



cichorioside I[6], 55

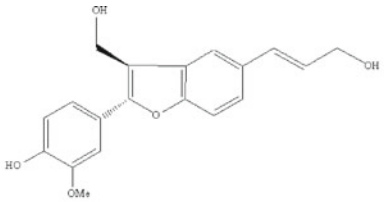


Lactupicrin methyl ester [8], 5 6

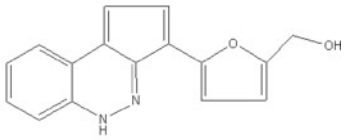
Fig. 80.2 (continued)

80.2.2 Some New Compounds Found Recently [7, 12, 15–19]

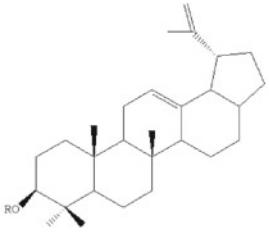
See Fig. 80.3.



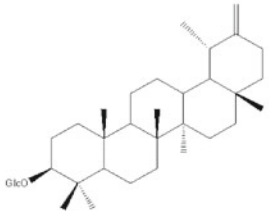
(7S, 8R)-3'-demethyl-dehydrodiconiferyl alcohol-3'-O-β-glucopyranoside, 57[15]



2-furanmethanol-(5→'11)-1,3-cyclo-pentadiene- [5,4-c]-1H-cinnoline[16], 58

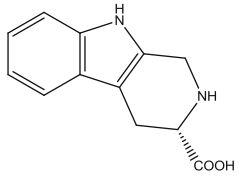


lup-12,20(29)-dien-3β-olyl hexadecanoate[17],59

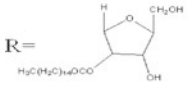


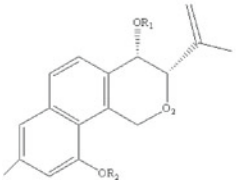
taraxasterol-3-O-β-D-glucoside[7], 61

lup-12,20(29)-dien-3β-ol-3β-L –arabino-furanosyl-2' –hexadecanoate[17], 60,



(3S)-1, 2, 3, 4-tetrahydro-β-carboline-3-carboxylic acid[18], 61





cichorin A[19], 63, R_1 =H, R_2= Me

cichorin B[12], 64, R_1 = R_2= Me

cichorin C[12], 65, R_1 = R_2= H

Fig. 80.3 New structures isolated from chicory

80.3 Pharmacological Studies

As an edible plant, *Cichorium intybus* L. is used in salads and a replacement for coffee in Europe. *Cichorium intybus* L. and *Cichorium glandulosum* Boiss. et Huet also have much bioactivity in traditional and modern medicine. Modern pharmacological studies have indicated they have the following bioactivities: hepatoprotective effect [14, 20], anti-diabetic and lipid lowering effects [21–23], antioxidant [23–25], anti-inflammation [25, 26], antifungal effect [27], antimalarial activity, antitumour activity [18, 28], etc.

80.4 TCM Applications and Dietary Usage

80.4.1 TCM Applications

Chicory is well known in Uyghur medicine, as medicinal plants have long been used in traditional Uyghur medicine. Chicory is labeled second class wet and cold; it has the ability to remove the obstacles, clean blood, relieve fever, reduce the function of abnormal sapra, as well as other conditions such as a cholagogic and diuretic agent to use for prevention and treatment of liver diseases, suppression and retention of urine, hypertension, and headache. There are four patent medicines that were collected in pharmaceutical standard-Uighur medicine part. Among those are granules of kasin which is made from chicory alone and is effective at prevention and treatment of urinary tract infections, liver function disorder, increasing urine, fever, psoriasis and cardiovascular diseases. In the other three Uighur medicine formulas, chicory is the principal drug widely used in the treatment of hepatic disorders such as hepatitis, fatty liver etc., also for treatment of hypertension, cholecystitis, rheumatism, prostatitis and adjustment of different abnormal Hilit disorders. The seed and root of *Cichorium glandulosum* Boiss.et Huet are used in the other folk recipes—Anti-inflammatory Syrup of Dinar, liver protection granules of Buzure, granules of Munziq [29].

80.4.2 Dietary Usages

80.4.2.1 Chicory Coffee

Chicory consumption has been associated with embargoes and cost cutting. The root of chicory could be roasted and as an alternative used in coffee, it is believed to have the effect on counteracting the stimulating effect of caffeine [30].

80.4.2.2 Chicory Salad

Chicory leaves are used in food as a kind of vegetable, and can be fried, boiled, steamed, braised. Salad is the commonest dish.

80.4.2.3 Chicory Tea

Chicory tea is a kind of tea which the main component is the shoot of chicory, it could be used alone or combined with the shoot of buckwheat, matrimony vine, asparagus and alfalfa, after cultivating, drying, roasting.

80.4.2.4 Chicory Used in Medicated Foods

Chicory coffee has repeatedly been assessed for resistance to thrombosis and inflammation due to its phenolics and caffeic acid content [31]. Chicory Capsule is consists of chicory, ramulusmori, tea polysaccharide, Juemingzi (seed of *Cassia obtusifolia*) and bee propolis; while the main functions are anti-diabetic, lipid lowering and hypouricemic effect etc. [32]. Inulin, which mainly comes from the root of chicory, is a mixture of oligo and polysaccharrides, it is also a kind of dietary fiber with health benefits including increased calcium and magnesium absorption, coordinating intestines and stomach etc. It could be used alone or in liquid products, semi-solid products and solid products [33].

80.5 Safety Evaluation and Toxicity Data

Few clinical reports on the toxicity or side effects are available that could be directly related to the use of chicory. In our study, toxicity of extraction from the air-dried aerial part of *Cichorium glandulosum* was examined in Kunming mice. A dose which is equal to 24.0 g *Cichorium glandulosum*/kg was given to mice, and repeated after 6 h for 3 days, no acute toxicity was observed in the mice following this treatment. So, a dose which is equal to 48.0 g *Cichorium glandulosum*/kg was orally administered to 2 groups of 10 mice. In the control animals, the vehicle of 0.5 % CMC was used. After the administration, animals were observed for 14 days, all mice were executed and dissected, no secretion was found in the mouth, eyes, nose and ears, no blood could be found in chest, abdominal, respiratory or digestive tract. No significant change had been found in volume, colour and character of viscera [34].

Subacute (4-week) oral toxicity was investigated by Johannsen FR, similar to lack of significant toxicity exhibited by other dietary carbohydrates (sorbitol, sucrose, glucose), oligofructoses (inulin/FOS) and carboxylated cellulose in repeated-dose rat studies, carboxymethyl inulin (CMI) did not found significant toxicity

at dosage of 0, 50, 150 and 1000 mg/kg/day too. No dermal sensitization was observed in groups of guinea pigs following CMI testing and no mutagenic activity was observed in TA1535, TA1537, TA98 and TA100-or in Escherichia coli WP2uvrA bacterial point mutation assays or in an in vitro Chinese hamster ovary cell chromosomal aberration assay [35].

No treatment-related toxic effects from chicory extract administered orally at 70, 350, or 1000 mg/kg/day was found by Schmidt BM inan Ames test and a 28 day subchronic toxicity study in SD rats. The NOAEL for the extract is 1000 mg/kg/day administered orally for 28 days [36].

Pirson F reported the side effect of chicory, rhino conjunctivitis, asthma and could be caused by it and a skin prick test results were positive to birch pollen and fresh/dry chicory, and negative for inulin [37].

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Chapter 81
Morus alba L. 桑 (Sang, White Mulberry)

Hua Wei

81.1 Botanical Identity

Morus alba L. (Sang in Chinese), a popular medicinal plant that belongs to the Mulberry family (Moraceae), has long been used in traditional systems of medicine. The genus *Morus* contains approximately sixteen members, about eleven species distributed widely in China. Among these, *M. alba* is the dominant one. Generally, all parts of *M. alba* are used as TCM, including leaves (Sangye), twigs (Sangzhi), root barks (Sangbaipi), and fruits (Sangshen). All of the medicinal parts are recorded in the Chinese Pharmacopoeia 2010 [1].

The plant is usually a monoecious shrub or a medium sized tree with a cylindrical stem and rough, brown, vertically fissured bark. Leaves are variable in size and shape, usually 5–7.5 cm long, often deeply lobed, margins serrate or crenate-serrate, apex acute or shortly acuminate, base cordate or truncate; three basal nerves, lateral nerves forked near the margins. Flowers are inconspicuous and greenish. Male spikes (catkins) are broad, cylindrical or ovoid, while female spikes are ovoid and stalked. Moreover, fruit (syncarp) consists of many drupes enclosed in a fleshy perianth, ovoid or subglobose in shape, up to 5 cm long, white to pinkish white in color, and become purple or black when ripe. Further, *M. alba* is native to China and it is widely cultivated and naturalized elsewhere [2].

M. alba parts are harvested in different times. Sangye is harvested after the first frost, Sangzhi is harvested in the late Sping and early Summer, Sangbaipi is har-

H. Wei (✉)
Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: weihua20@126.com

H. Wei
Key Laboratory of Plant Resources Conservation and Utilization, College of Biology and Environmemtal Science, Jishou University, Jishou 416000, China

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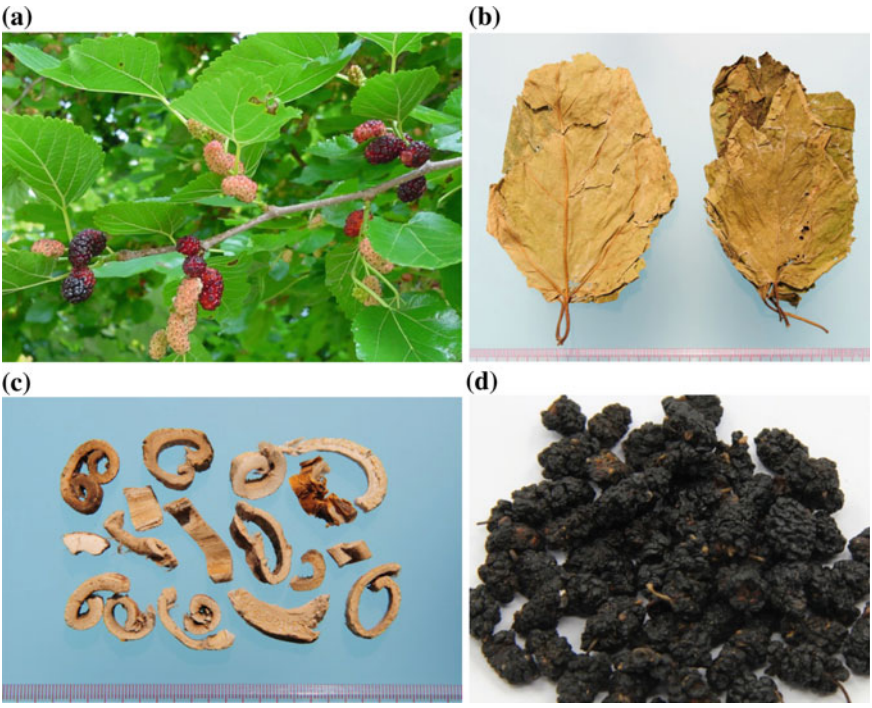


Fig. 81.1 Fruiting plant (**a**) and crude drugs (**b** Sangye, **c** Sangbaipi, **d** Sangshen) of *M. alba*

vested in the late Autumn and early Spring, and Sangshen is harvested from April to June when ripe. All the medicinal parts are sun-dried (Fig. 81.1).

81.2 Chemical Constituents

The main active constituents of *M. alba* include flavonoids, alkaloids, stilbenes, diels-alder type adducts, and polysaccharides, which are vary in different parts of *M. alba* [2, 3, 4]. Chemical structures for some of them are shown (Fig. 81.2).

81.2.1 Sangye (Leaves)

Main constituents of Sangye include rutin, quercetin, isoquercitrin, dihydrokaempferol, chlorogenic acid, morin, 1-deoxynojirimycin, fagomine, and folium mori polysaccharides [5].

Rutin, quercetin, and isoquercitrin are famous anti-oxidants. 1-deoxynojirimycin and fagomine are known for their inhibitory activities for α-glucosidase. Chlorogenic acid is known to have various activities including anti-oxidative, anti-cancer,

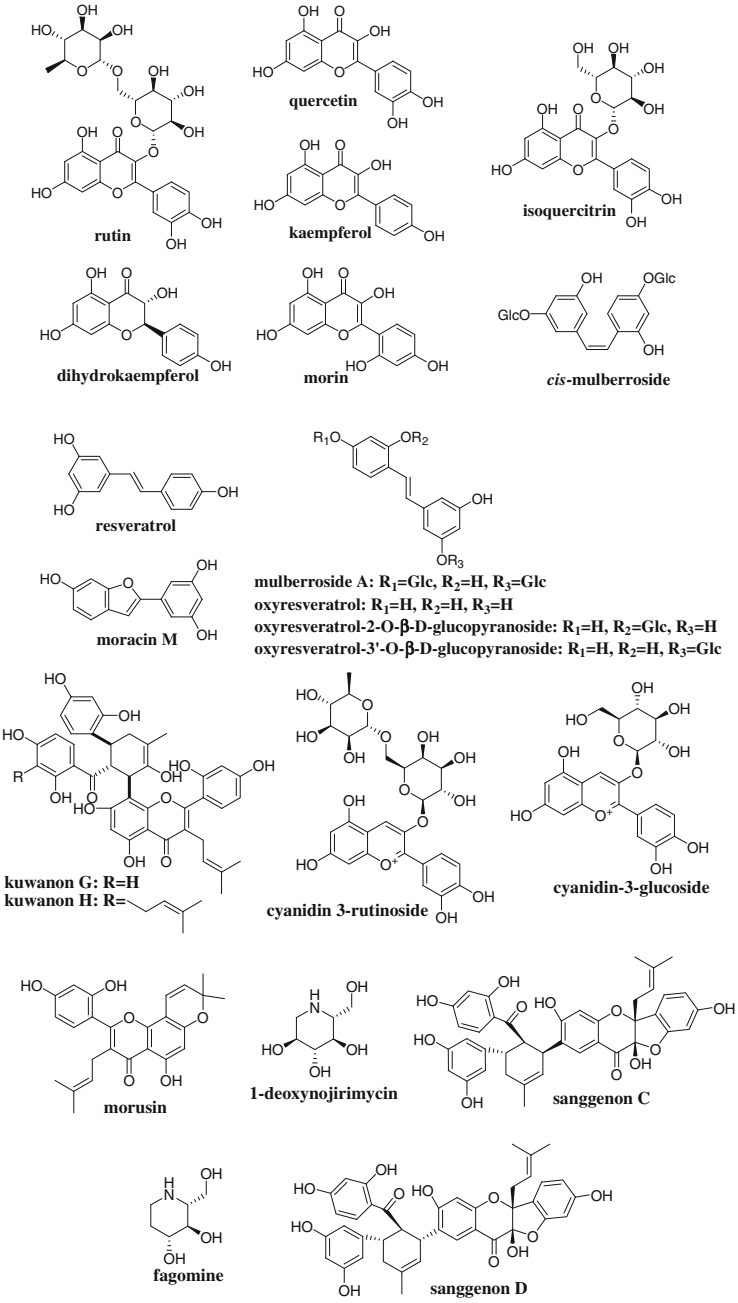


Fig. 81.2 Structures of some bioactive compounds in *M. alba*

anti-biosis, anti-viral, immunomodulating, hypoglycemic, etc. Morin have anti-infammation, anti-tumour, and anti-oxidization effects. Polysaccharides from Sangye have hypoglycemic, anti-oxidative, insulin sensitization-increasing, and immunopotentiating effects [6].

81.2.2 Sangzhi (Twigs)

Main constituents of Sangzhi include quercetin, kaempferol, mulberroside A, resveratrol, trans-resveratrol, oxyresveratrol, trans-oxyresveratrol, moracin M, 1-deoxynojirimycin, and ramulus Mori polysaccharides [7].

Kaempferol has anti-cancer, anti-inflammatory, anti-oxidant, anti-bacterial, and anti-viral activities. Resveratrol has shown its healthy benefits such as anti-oxidant, cancer prevention, blood thinning, and life span extension activities. Oxyresveratrol is an effective tyrosinase inhibitor, and has anti-tussive and anti-asthmatic, anti-oxidant, anti-inflammatory and analgesic effects. Moracin M is a natural phosphodiesterase-4 inhibitor, which has been identified to be a promising compound for treatment of asthma. Polysaccharides from Sangzhi have hypoglycemic and immunopotentiating effects.

81.2.3 Sangbaipi (Root Barks)

Main constituents of Sangbaipi include kuwanon G, kuwanon H, morusin, sanggenon C, sanggenon D, mulberroside A, oxyresveratrol-2-*O*-β-D-glucopyranoside, oxyresveratrol-3′-*O*-β-D-glucopyranoside, oxyresveratrol, cis-mulberroside A, oxyresveratrol-3′-*O*-β-D-glucopyranosyl-4-*O*-β-D-glucopyranosyl-(1 → 6)-*O*-β-D-glucopyranoside, oxyresveratrol-4-*O*-β-D-glucopyranosyl-3′-*O*-β-D-glucopyranosyl-(1 → 6)-*O*-β-D-glucopyranoside, and xeroboside [8, 9].

Both kuwanon G and morusin have significant antihypertensive, antimicrobial, antiviral, anti-cancer and anti-inflammatory effects. Sanggenon C inhibits tumor cell viability via induction of cell cycle arrest and cell death, NO production and iNOS expression by suppressing NF-κB activity and IκBα activation,and TNF-α-stimulated polymorphonuelear leukocyte adhesion to human synovial cell by suppressing the activation of NF-κB. Moreover, sanggenon C and G represent a new scaffold of positive GABAA receptor modulators. Sanggenon G would be expected to be a metastasis inhibitor of cancer cells. Most stilbenes in Sangbaipi have anti-oxidative effects, especially, mulberroside A, which is one of the main stilbene that also has a significant anti-tussive effect.

81.2.4 Sangshen (Fruits)

Main constituents of Sangshen are anthocyanins, morin, rutin, quercetin, isoquercitrin, dihydroquercetin, resveratrol, oxyresveratrol, 1-deoxynojirimycin, protocatechuic acid, and polysaccharides [10].

Anthocyanins in Sangshen have anti-oxidative, anti-inflammatory, and anti-cancer activities, besides it has cerebrovascular, liver and neuro protective effects. In addition, polysaccharides from Sangshen have anti-oxidative and hypoglycemic activities.

81.2.5 Quantitative Determination

In the Chinese Pharmacopoeia 2010, it is recorded that rutin in Sangye should not be less than 0.10 % [1]. According to the reports, several compounds like flavonoids, alkaloids and stilbenes were analyzed and determined in different parts of *M. alba*. For example, typical HPLC chromatograms are shown [11, 12] (Fig. 81.3).

81.3 Pharmacological Studies

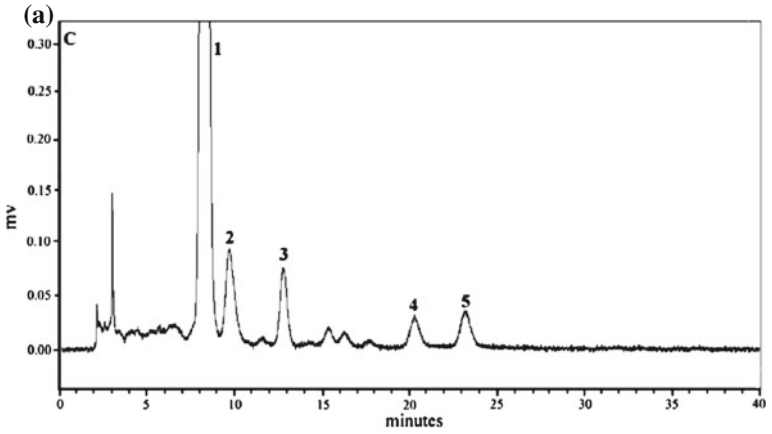
Many pharmacological studies have been reported for the different extracts and phytochemical constituents of *M. alba*. Biochemical compounds are isolated from different parts of *M. alba* which play a vital role in anti-obesity, anti-hyperlipidemic, anti-oxidant, skin tonic, anti-bacterial, anti-inflammatory, anti-allergic, vasoactive action, neuroprotective, anti-cancer, anxiolytic, anti-depressant actions, etc. [2, 6, 13].

Most of hypoglycemic actions attributed to some functional components like 1-deoxynojirimycin and fagomine, known to be one of the most potent α-glycosidase inhibitors. Several reports and studies proved that the anti-oxidant and anti-inflammatory actions are due to polyphenolic compounds like flavonoids and stilbenes. Other compounds may have multi-functions.

81.4 TCM Applications and Dietary Usage

81.4.1 TCM Applications

M. alba has been extensively used in conventional Chinese medicine. Almost all the parts of the plant are used as medicines. Sangye has wind and heat dispelling, lung clearing, dryness moisturizing, and eyesight improving properties. Sangzhi has

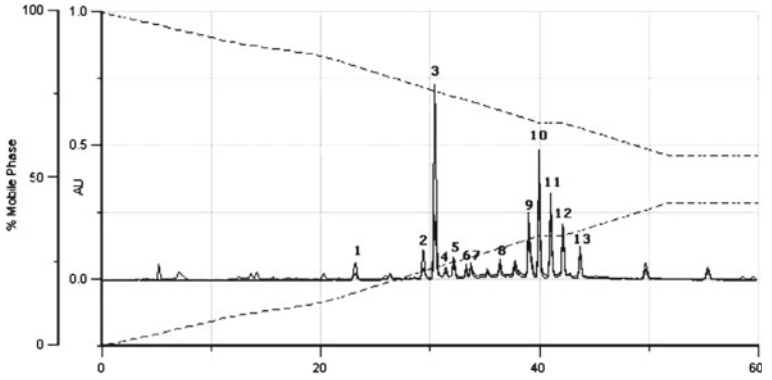


1, mulberroside A; **2**, cis-mulberroside A;

3, resveratrol-4,3′-di-O-β-D-glucopyranoside;

4, oxyresveratrol-2-O-β-D-glucopyranoside;

5, oxyresveratrol-3′-O-β-D-glucopyranoside.



1, 1-caféoylquinnic acid; **2**, caffeic acid; **3**, 5-caféoylquinnic acid; **4**, crypto-4-caffeoylquinnic acid; **5**, quercetin-3-O-rhamnoside-7-O-glucooside; **6**, quercetin-3,7-D-O-β-D-glucopyranoside; **7**, kaempferol-7-O-glucoside; **8**, rutin; **9**, quercetin-3-O-glucoside; **10**, quercetin-3-O-(6-malonyl)glucopyranoside; **11**, quercetin-3-O-glucoside-7-O-rhamnoside; **12**, kaempferol-3-O-rhamnopyranosyl-(1-6)-glucopyranoside; **13**, kaempferol-3-O-(6-malonyl)glucoside.

Fig. 81.3 HPLC Chromatograms of Sangbaipi (**a**) and Sangye (**b**)

anti-rheumatic, anti-spasmodic, diuretic, and repercussive effects. Sangbaipi has relieving effects on cough, wheezing, edema, and can promote urination. Sangshen has been used as a medicinal agent to nourish the blood, benefits the kidneys and treat weakness, fatigue, anemia and premature graying of hair [1, 3].

Common *M. alba* preparations clinically used include the following forms: (1) Sangzhi granule: It is a preparation of Sangzhi, and the major components are α-glycosidase inhibitors [14]. It is mainly used for nourishing blood and activating blood circulation, and for the treatment of thirst with desire for drinks, numbness and tingling in limbs, hyperglycemia, and diabetes. (2) Sangshen granule: It is a preparation of Sangshen. It is used for nourishing blood, tonifying kidney, and moisturizing dryness. It is for the treatment of soreness-tired of waist and knee, vertigo and insomnia, tinnitus, constipation, dryness of mouth, and premature whitening of hair. (3) Sangma oral solution: It is a preparation of Sangye and black sesame. It is used for nourishing liver and kidney, dispelling wind and improving eyesight, and for the treatment of deficiency of liver and kidney, dizziness, blurring of vision.

81.4.2 Dietary Usages

M. alba is a typical traditional Chinese Medicine plant, the leaves (Sangye), stems (Sangzhi), root barks (Sangbaipi), and fruits (Sangshen) are also used as food. The following preparation forms can be easily made in home ordinarily [3].

81.4.2.1 Sangye Tea

Herbal tea made of Sangye alone is the most common way to use Sangye.

Composition: Dried Sangye.

Preparation: Add 1 teaspoon of Sangye powder to about 200–250 mL boiling water for 3–5 min. Drink it like an ordinary tea. It might taste sweet to bitter. This tea can be taken 2–3 times a day.

Function: The tea relieves colds, coughs, throat infections, inflammations of the eyes, liver and lung problems, supposed to prevent oxidation of cholesterol consequently keeping the arteries free of fat deposits and hence hardening of arteries.

81.4.2.2 Xiasangju Drink

Composition: Dried Sangye 15 g, dried Xiakucao (fruit cluster with flowers or whole plant of *Prunella vulgaris* L.) 10 g, dried Yejuhua (inflorescences of *Chrysanthemum indicum* L.) 24 g.

Preparation: Put Sangye, Xiakucao and Yejuhua in a pot, add about 500 mL of water. Heat with strong fire to boiling and then with mild fire for the 25 min. Then remove the residue and add the rock candy to desirable sweetness.

Function: Improving eyesight, and preventing of viral infection and throat-swelling diseases.

81.4.2.3 Sangshen Rock Candy Water

Composition: Fresh ripe Sangshen 60 g.

Preparation: Put Sangshen into a boiler, and add two bowl of water. Heat the water to boil and continue to concentrate to about one bowl of water. Then add the rock candy to desirable sweetness.

Function: Nourishing liver and kidney, moisturizing dryness. It is beneficial to neurasthenia, insomnia, and constipation.

81.4.2.4 Sangshen Honey Concentrated Decoction

Composition: Fresh ripe Sangshen.

Preparation: Boil pulped Sangshen juice with mild fire. Add Honey into the sticky decoction while it is hot. Take 1–2 spoon of the concentrated decoction with warm water twice daily.

Function: It is beneficial to pre-maturing gray hair, deficiency of blood and spleen, and premature senility.

81.4.2.5 Sangshen-Sangzhi Wine

Composition: Fresh Sangshen 500 g, fresh Sangzhi 1000 g, brown sugar 500 g, white wine 1000 g.

Preparation: Wash and slice Sangzhi, soak the Sangzhi together with Sangshen and brown sugar in white wine for a month. Drink 1–2 times daily, 20–30 mL each time.

Function: Nourishing liver and kidney, benefiting blood circulation, and alleviating rheumatism.

81.4.2.6 Sangzhi Dazao Porridge

Composition: Dried Sangzhi 30 g, dried 10 Dazao (dry fruit of *Ziziphus jujuba* Mill.), rice 50 g.

Preparation: Decoct Sangzhi in water. Boil rice and Dazao with the decoction solution to porridge. Take twice daily.

Function: Alleviating shoulder periarthritis.

81.4.2.7 Sangzhi Decoction

Composition: Dried Sangzhi 600 g.

Preparation: Sangzhi and 2000 mL water are put into a boiler. Strong fire is replaced by mild fire until 1000 mL water decoction left. The water decoction is used to fumigating and washing limbs for 15–25 min each time, twice daily.

Function: It is used for treatment of rheumatism, and arthralgia diseases.

81.4.2.8 Sangbaipi Tea

Composition: Sangbaipi 30 g.

Preparation: Put Sangbaipi into a pottery, add boiling water for 15 min. This tea can be taken at anytime for one dose a day.

Function: Treating acute nephritis, facial and limbs edema, and relieving asthma and cough.

81.5 Clinical Evidences

In recent years, mulberry leaves are widely used in clinical studies [3]. For example, Sangye is prescribed in China as a treatment for diabetes, hyperglycemia, hyperlipidemia, hypertension, pneumoconiosis, cough, fever, sore, elephantiasis, and inflamed eyes, sore throats, headaches, dizziness and vertigo. Sangzhi is uesd to treat arthralgia, rheumatic arthritis, spasm of limbs, numbness of hands and feet, foot edema, diabetes, hyperglycemia, and obesity. Sangbaipi is used to treat hyperglycemia, epilepsy, rheumatalgia, fever, headache, cough, bronchitis, bronchopneumonia, urinary incontinence, red dry and sore eyes. Sangshen is used to treat urinary incontinence, tinnitus, dizziness, thirst with desire for drinks, emaciation and thirst caused by internal heat, and constipation in the elderly patient.

81.6 Safety Evaluation and Toxicity Issue

M. alba has long been used in TCM, because of its good therapeutic activity and low toxicity. It was recorded in ancient books that Sangzhi is slightly poisonous, but no clinical adverse reaction is reported so far. Brown epidermis has to be removed before usage of Sangbaipi, and LD_{50} of Sangbaipi in mice was determined to be approximately 10 g/kg when administered by intraperitoneal injection [15]. Sangshen, which contains essential oil and trypsin inhibitor, may be slightly poisonous if consumed too much. The adverse reactions of Sangshen include nausea, vomiting, weakness, severe abdominal pain and diarrhea; serious adverse reactions include blood stool, blood pressure, and even shock. The recommended doses of

Sangye, Sangzhi, Sangbaipi, and Sangshen are 5–10, 9–15, 6–12, and 9–15 g, respectively, except for special purpose. Make sure to consult with a licensed practitioner before taking different medicinal parts of *M. alba*.

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Chapter 82
Nelumbo nucifera Gaertn. 荷 (He, Lotus)

Xiao-liang Zhao

82.1 Botanical Identity

N. nucifera Gaertn., belonging to the Waterlily family (Nymphaeaceae), is a kind of perennial aquatic herbage plant, which is one of the most important aquatic vegetables widely growing in China due to its pleasant flavor and high nutritional value, especially its seeds, rhizomes and leaves. It's easy to be cultivated and is distributed in wetlands throughout temperate and tropical Asia from Iran to Japan and from China to Queensland.

According to different purposes or morphological differences, the lotus is usually classified into three types: rhizome lotus, seed lotus and flower lotus. In China, rhizome lotus is mainly cultivated in Hubei, Jiangsu, Anhui, and Zhejiang provinces, seed lotus in Jiangxi, Fujian, and Hunan province, and flower lotus in Wuhan city, Hubei province, and Beijing [1] (Fig. 82.1).

82.2 Chemical Constituents

Alkaloids and flavonoids are two major kinds of active compounds found from *N. nucifera* Gaertn. [2].

X. Zhao (✉)
Experimental Research Center, China Academy of Chinese Medical Sciences, Beijing 100700, China
e-mail: zhaoxiaoliang1218@aliyun.com

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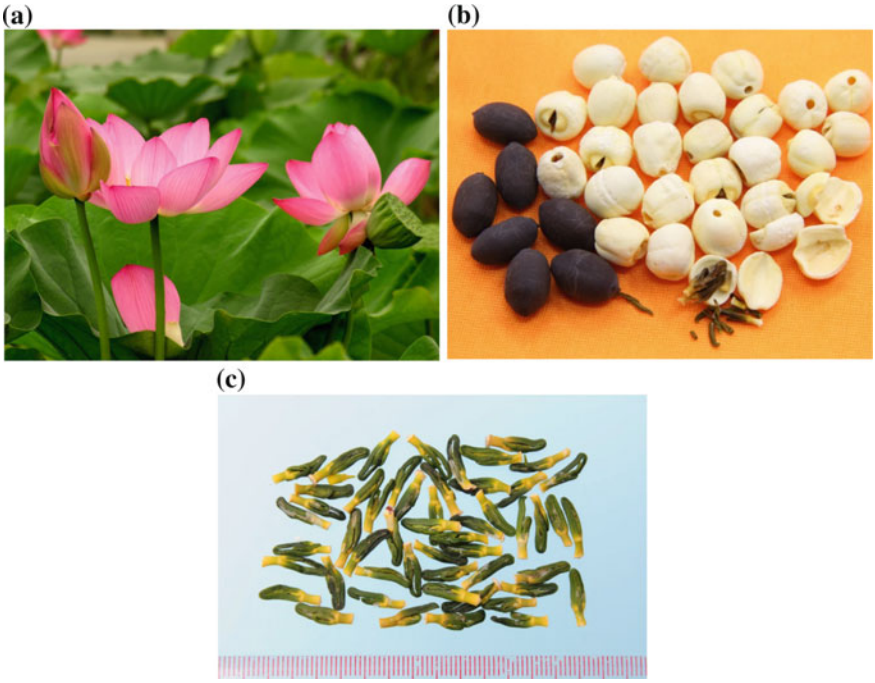

Fig. 82.1 The flowering plant (**a**) and crude drugs (**b** Lianzi, **c** Lianzixin) of lotus

82.2.1 Alkaloids

Lotus alkaloids dilate the blood vessels and reduce the blood pressure. The embryos possess small amounts of alkaloids, which are antispasmodic for the intestines and alleviate diarrhea. The embryos within lotus seeds possess an alkaloid isoquinoline, which is sedative, antispasmodic, and beneficial to heart. It dispels pathogenic heat from the heart and spontaneous bleeding due to heat. The major secondary metabolites present in *N. nucifera* Gaertn. are alkaloids such as roemerine (1), nornuciferine (2), armepavine (3), lotusine (4), pronuciferine (5), and anonaine (6) (Fig. 82.2).

82.2.2 Flavonoids

Several flavonoids have been identified in the plant of *N. nucifera* Gaertn. (Fig. 82.3). These include quercetin 3-*O*-*β*-D-glucuronide (1), luteolin (2), rhamnetin-3-*O*-*β*-D-glucopyranoside (3), leucocyanidin (4), leucodelphinidin (5).

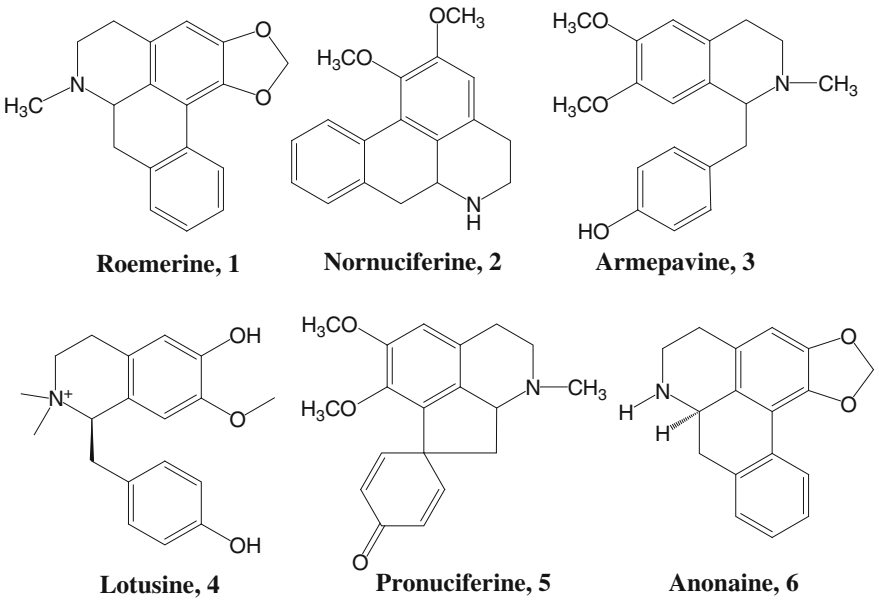

Fig. 82.2 Typical alkaloid isolated from lotus

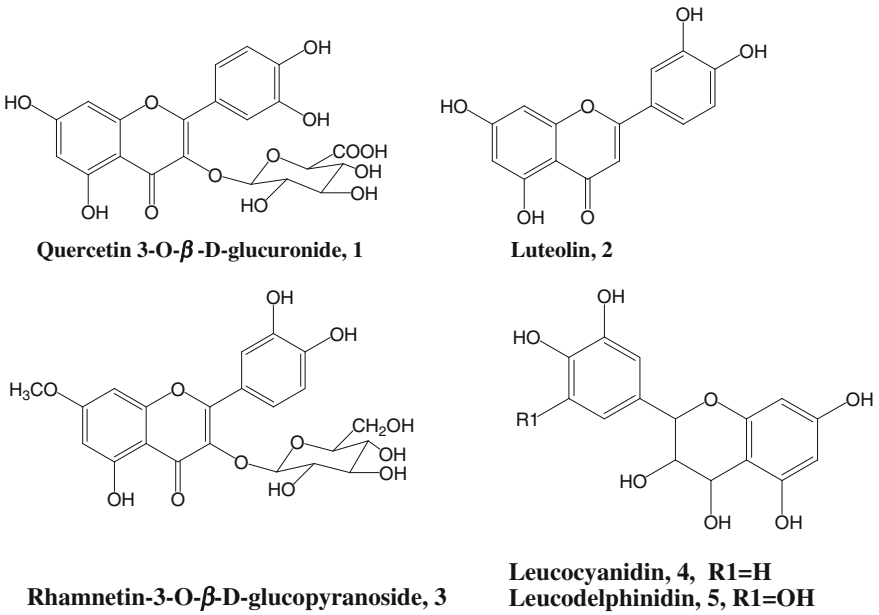

Fig. 82.3 Typical flavonoids isolated from lotus

82.3 Pharmacological Studies

Different parts of *N. nucifera* Gaertn., including the leaves, rhizomes, seeds and flowers, have therapeutic potential in traditional medicine for the treatment of various diseases. Pharmacological activities of different extracts of rhizomes, seeds, leaves and flowers, and the compounds isolated from these extracts, have been demonstrated through numerous in vitro and in vivo test models. The responsible bioactive compounds belong to several chemical groups; mostly they are alkaloids (like dauricine, lotusine, nuciferine, liensinine, roemerine, neferine, armepavine), flavonoids (like kaempferol, quercetin, leucocyanidin, leucodelphinidin, catechin, isoquercitrin, astragalin), glycosides (nelumboroside A, nelumboroside B, isorhamnetin glycoside, and isorhamnetinrutinoside), triterpenoids (like betulinic acid), vitamins, and minerals.

82.3.1 Anti-obese and Lipolytic Activity

It has been reported that the effects of leaf extract on digestive enzymes, lipid metabolism and theromogenesis together caused an anti-obese effect in mice with obesity induced by a high-fat diet. It also prevented increases in body weight, parametrical adipose tissue weight and liver triacylglycerol levels. A 50 % ethanol extract of *N. nucifera* Gaertn. leaves was reported to stimulate lipolysis in the white adipose tissue of mice. Chromatographic analysis of the extract showed that the phytochemicals responsible for lipolytic activity included quercetin-3-*O*-α-arabinopyranosyl-(1 $\rightarrow$ 2)-β-galactopyranoside, catechin, hyperoside, isoquercitrin and astragalin [3, 4].

82.3.2 Antioxidant Activity

The ethanol extract of the seed has been evaluated for its antioxidant activity using the DPPH free radical assay, and potent free radical scavenging effects were seen. Furthermore, the antioxidant activity of the hydroalcoholic extract of seed has been reported, and the hydroalcoholic extract exhibited strong free radical scavenging activity [5, 6].

Procyanidin and condensed tannin isolated from the seed pod of *N. nucifera* Gaertn. have the effects of anti-oxidation, lipoxygenase inhibition and free radical scavenging comparable to butylated hydroxytoluene (0.1 %) [7].

The potential antioxidant activity of the methanol extract from the lotus leaf was observed. A dose-dependent protective effect against reactive oxygen species (ROS)—induced cytotoxicity was observed, and the extract also exhibited concentration-dependent antioxidant activities against haemoglobin-induced linoleic acid peroxidation and Fenton reaction-mediated plasmid DNA oxidation [8].

The methanol extract of *N. nucifera* Gaertn. stamens showed strong antioxidant activity in the $ONOO^-$ system and marginal activity in the DPPH and total ROS systems. In a similar fashion, seven known flavonoids were isolated from lotus stamens, most of which also showed potent antioxidant activity [9].

The methanol and acetone extract of the *N. nucifera* Gaertn. rhizome also showed highest DPPH scavenging activity respectively, the methanol extract exhibited a higher antioxidant activity coefficient than ascorbic acid. The rhizome knot also exhibited radical scavenging activity, measured spectrophotometrically and by electron spin resonance [10].

82.3.3 Anti-inflammatory Activity

At a dose of 10 mg kg^{-1}, the seed extract of *N. nucifera* Gaertn. inhibited the production of pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) and increased anti-inflammatory cytokine IL-10 in BALB/c mice with systemic inflammation induced by an intraperitoneal injection of lipopolysaccharide (LPS). This result demonstrated that administration of the seed extract before systemic inflammation attenuates acute inflammation in vivo [11].

The rhizome extract at doses of 200 and 400 mg kg^{-1}, and betulinic acid at doses of 50 and 100 mg kg^{-1} (administered orally) showed significant anti-inflammatory activity; the effect was comparable to that of the standard drugs phenylbutazone and dexamethasone [12].

82.3.4 Antiviral Activity

The 95 % ethanol extract has been reported to show anti-HIV activity ($EC_{50} < 20$ μg mL^{-1}). Some anti-HIV principles, including (+)-1(R)-coclaurine, (−)-1(S)-norcoclaurine and quercetin 3-*O*-*β*-D-glucuronide, were found in *N. nucifera* Gaertn. leaves. Both (+)-1(R)-coclaurine and (−)-1(S)-norcoclaurine showed potent anti-HIV activity, with EC_{50} values of 0.8 and <0.8 μg mL^{-1}), respectively, and therapeutic index values above 125 and 25. Other potent anti-HIV bisbenzylisoquinoline alkaloids such as nuciferine, liensinine, negferine and isoliensinine have also been isolated from the leaves of *N. nucifera* Gaertn., with EC_{50} values below 0.8 μg mL^{-1} and therapeutic index values of 36, >9.9, >8.6, and >6.5, respectively [13].

82.3.5 Other Activities

These include antimicrobial, anti-arrhythmic, antipyretic, anti-ischaemic, anti-diabetic, hypoglycaemic, antidiarrhoeal, immunomodulatory, and other activities.

82.4 TCM Applications and Dietary Usage

All parts of *N. nucifera* Gaertn. have many medicinal uses. The leaf, rhizome, seed and flower are traditionally used for the treatment of pharyngopathy, pectoralgia, spermatorrhoea, leucoderma, small pox, dysentery, cough, haematemesis, epistaxis, haemoptysis, haematuria, metrorrhagia, hyperlipidaemia, fever, cholera, hepatopathy and hyperdipsia [14]. In popular medicine it is used in the treatment of tissue inflammation, cancer, skin diseases, leprosy and as an antidote [15, 16].

Lotus could be used on its own or by combining forms with other herbs based on TCM theory.

82.4.1 TCM Applications [17]

There are some well-known traditional formulas relying on lotus seeds or with lotus seeds as an important component. The medicinal dosage is 6–15 g when it is combined with other herbs that have similar applications and double that when used as the main ingredient.

A lotus seed formula is Qipi Tang (Lotus and Citrus Combination), which is also a therapy for weak digestion leading to diarrhea. The formula contains Lianzi (seed of *Nelumbo nucifera* Gaertn.), Renshen (root of *Panax ginseng* C.A. Mey.), Cangzhu (rhizome of *Atractylodes lancea* (Thunb.) DC.), Fuling (sclerotium of *Poria cocos* Wolf), Xiangsizi (seed of *Abrus precatorius* L.), Zexie (stem of *Alisma orientale*), Shuyu (root of *Dioscorea opposita*), Chenpi (fruit peel of *Citrus reticulata* Blanc), and Shanzha (fruit of *Crataegus pinnatifida* Bunge).

A formula using lotus seed for a different application is Qingxin Lianzi Yin, composed of Lianzi (seed of *Nelumbo nucifera* Gaertn.), Renshen (root of *Panax ginseng* C.A. Mey.), Huangqi (root of *Astragalus membranaceus* Bunge.), Maidong (root tuber of *Ophiopogon japonicas*), Cheqianzi (seed of *Plantago asiatica* L.), Gouqizi (fruit of *Lycium barbarum* L.), Fuling (sclerotium of *Poria cocos* Wolf), and Gancao (root of *Glycyrrhiza uralensis* Fisch.). It is used for urinary disorders, including urinary stones, kidney inflammation, and urinary tract infection; it is also used for disorders of the reproductive organs, such as prostatitis and leukorrhea.

Another astringent formula is Jinsuo Gujing Wan, composed of Lianxu (stamen of *Nelumbo nucifera* Gaertn.) and Lianzi (seed of *Nelumbo nucifera* Gaertn.), Longgu (*Fossilia Ossis* Mastrodi), Muli (shell of *Ostrea gigas*), Jili (fruit of *Tribulus terrestris* L.) and Qianshi (seed of *Euryale ferox* Salisb. ex DC). All the ingredients have some astringent properties. Its basic function is to restrain (like a lock) any further loss of essence due to disease or aging. It is often used for urinary disorders, especially frequent urination and turbid urine.

The leaf juice is used for the treatment of diarrhea. The dried leaf is used in summer heat, to invigorate the function of the spleen and to arrest bleeding by reducing heat in the blood. The leaf extract has diuretic and astringent properties, and is used to treat fever, sweating and as a styptic.

The flowers are used in the treatment of premature ejaculation, abdominal cramps and bloody discharges, and as a cardiac tonic. The flower stalk is used for the treatment of bleeding gastric ulcers, excessive menstruation and post-partum hemorrhage. The lotus honey is used as a tonic and for the treatment of eye infections.

The rhizome extract is used as a tonic. Powdered rhizome is prescribed as a demulcent for hemorrhoids and is beneficial in dysentery and chronic dyspepsia. External application in the form of a paste is useful in scabies and ring worm.

82.4.2 Dietary Usages

Different parts of *N. nucifera* Gaertn. have many dietary usages. In 1991, the lotus leaves were included in the both "health food and medicine" name list in China. Lotus leaves could be elaborated as tea or drinks by single form or combining forms with other herbs. "Lotus leaf anti-obesity tea" prevents the increase of body weight, parametrical adipose tissue weight. "Lotus leaf herbal tea" has effectiveness of clearing heat, removing heatstroke, cooling the blood.

The rhizomes are a food used extensively in China, sold whole or in cut pieces, fresh, frozen, or canned. They are consumed as a vegetable, usually fried or cooked in soups.

The seeds are roasted or candied for eating directly; made into a paste for producing sauces and cake fillings (in mid-Autumn it is customary to serve "moon cakes" which have a filling made of lotus seeds and walnuts); and cooked in soups, usually with chicken or beans. An example of the latter is a soup presented at banquets for newlyweds, made with red beans and lotus seeds. Red beans represent strength, while lotus seeds symbolize the newlyweds being blessed with a child each year. The soup is also presented at the New Year's festival [17]. For example:

Red Bean and Lotus Seed Soup

- 14 oz package red beans (also known as adzuki beans)
- 1.5 oz lotus seeds
- 1 piece dried tangerine peel, soaked in hot water 10 min until soft
- 0.75 cup brown sugar

In a large pot, combine 7 cups cold water, red beans, lotus seeds and tangerine peel. Bring to a boil over high heat, reduce heat and simmer, covered, with pot lid slightly ajar, for 1 and 1/4 h to 1 and 1/2 h or until beans become tender. When beans are tender and open, and lotus seeds soften, add sugar; stir. Turn off the heat, pour into a heated tureen and serve. Make 6 servings. Because the soup is sweet, it is also served as a desert. Another desert preparation is:

Cream Lotus Seed Soup

- 8 oz lotus seeds
- 8 oz can of crushed pineapple
- 4 tablespoons cornstarch
- 0.5 teaspoon salt
- 0.5 cup of sugar
- 8 maraschino cherries

Soak the lotus seeds in water overnight; combine drained lotus seeds and 3 cups water and bring to boil over medium heat for 15 min; remove from heat and drain. Smash the cooked lotus seeds in a blender and pour the resulting paste into a big bowl. Dissolve the cornstarch in four tablespoons of water, pour into a small cup and set aside. Bring 6 cups of water to a boil over medium heat in a non-stick pot, then add the sugar, salt, pineapple, and lotus paste. Return to a boil and mix in the cornstarch liquid. Stir constantly until smooth and thickened. Reduce the heat and simmer for 1 min. Remove from heat, pour into a large bowl, place pieces of the cherries on the top and serve hot. Make 6 servings.

Yet another example is this one with lotus and longan:

Sweet Lotus Seed Soup Dessert

- 9 oz lotus seeds
- 3.5 oz longan
- 3 oz rock sugar
- 0.5 tsp bicarbonate soda

Put dried lotus seeds into a basin. Put just enough cold water to cover the lotus seeds and add bicarbonate of soda. Set aside for 2–2.5 h. Drain, then wash thoroughly. Bring 5 cups of water to a boil. Add soaked lotus seeds and cook until the seeds turn soft. Add dried longan and rock sugar. Simmer until longan turns soft and sugar dissolves. Serve this dessert either hot or cold. In Asia, this mixture is flavored with pandan leaves (two leaves are added during the last few minutes of simmering the longan and sugar).

All the recipes given above are very low in fat, but high in carbohydrates.

82.5 Safety Evaluation and Toxicity Issue

As a plant with medicine and food characteristics, there was little clinical report on the toxicity and side effect directly with *N. nucifera* Gaertn. and related preparations.

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Chapter 83
Perilla frutescens (L.) Britt. 紫苏 (Zisu, Common Perilla and Purple Common Perilla)

Yang Zhao and Xin Zhou

83.1 Botanical Identity

Perillae Fructus (Zisuzi in Chinese, Fig. 83.1a), Perillae Folium (Zisuye in Chinese, Fig. 83.1b), and Perillae Caulis (Zisugeng in Chinese, Fig. 83.1c) are dried, mature fruits, leaves, and stems, respectively, of *Perilla frutescens* (L.) Britt., which belongs to the Mint Family [1]. It is a very attractive plant for the garden and attracts butterflies with a strong minty smell. Growing up to four feet tall when in bloom, the stems are square, reddish-purple and branching [2].

Generally, Perillae Fructus, the fruits, are harvested in autumn when they are mature. The fruits are then dried in shaded areas and used for medicinal purposes. Perillae Fructus are oval or spherical with a diameter of around 1.5 mm. The surface of the fruit is taupe brown or greige with slightly bulging dark purple cobwebbing. The epicarp is thin, brittle and squashy.

Perillae Folium, the leaves, are harvested when they are flourishing in summer. The leaves are then dried and impurities are removed. Most of the Perillae Folium are shrinking and crinkling. Unbroken ones are oval with length from 4 to 11 cm, width from 2.5 to 9 cm, when flattened. Petiole 2–7 cm, purple or purplish green, fragile, delicate fragrance, bitter taste.

Perillae Caulis, the stems, are collected after the fruits are mature in autumn and then dried or cut into slices. Perillae Caulis assume to be square shape with different lengths, diameter 0.5–1.5 cm, surface purple brown or darkviolet, light smell and taste.

Y. Zhao · X. Zhou (✉)
Key Laboratory for Information System of Mountainous Areas and Protection of Ecological Environment, Guizhou Normal University, Guiyang 550001, China
e-mail: alice9800@sina.com

Y. Zhao · X. Zhou
The Research Center for Quality Control of Natural Medicine, Guizhou Normal University, Guiyang 550001, China

Y. Liu et al. (eds.), *Dietary Chinese Herbs*, DOI 10.1007/978-3-211-99448-1_83

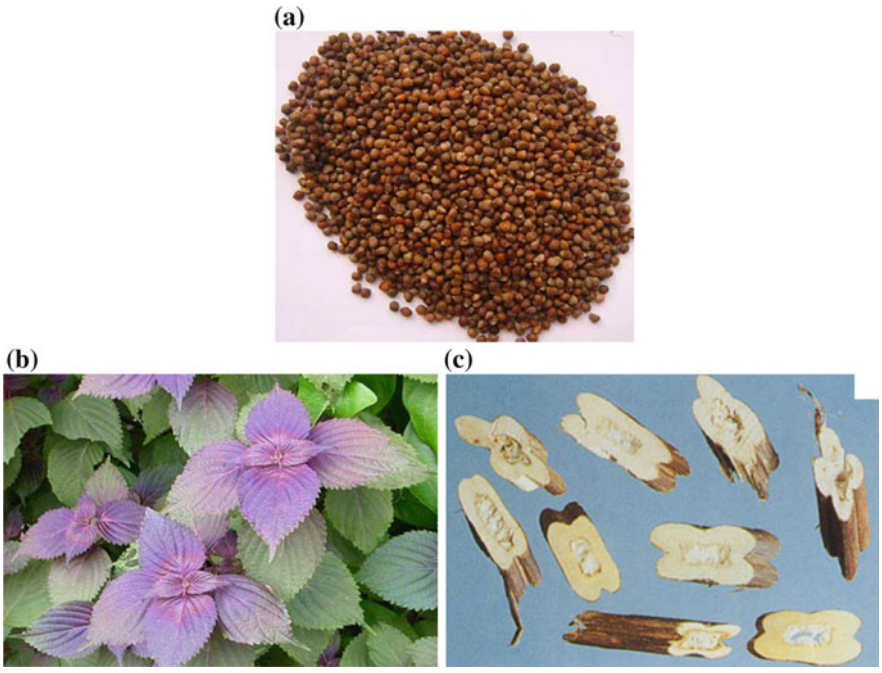

Fig. 83.1 Perillae Fructus (**a**), Perillae Folium (**b**), and Perillae Caulis (**c**)

P. frutescens have been traditionally cultivated in Asia for their seed oil and for their fragrant leaves that are used as medicine or as a garnish for fish. In China, *P. frutescens* is widely distributed. Much cultivation for oil was found around the Wei River valley in northern China in 1999. In Sichuan and Yunnan provinces in southwestern China, *P. frutescens* was also cultivated for oil. In southeastern China, *P. frutescens* was cultivated or grew spontaneously. In Korea, cultivation of *P. frutescens* for oil can be seen everywhere. Its weedy form was also frequently found along roadsides or in abandoned fields [3].

83.2 Chemical Constituents

Essential oils including aldehyde (**1**), limonene (**2**), and *β*-caryophyllene (**3**), flavonoids as well as phenolic acids such as rosmarinic acid (**4**), catechin (**5**), apigenin (**6**), luteolin (**7**), caffeic acid (**8**), and ferulic acid (**9**), shown in Fig. 83.2, were found to be the main chemical compounds in the leaves and seeds of *P. frutescens*.

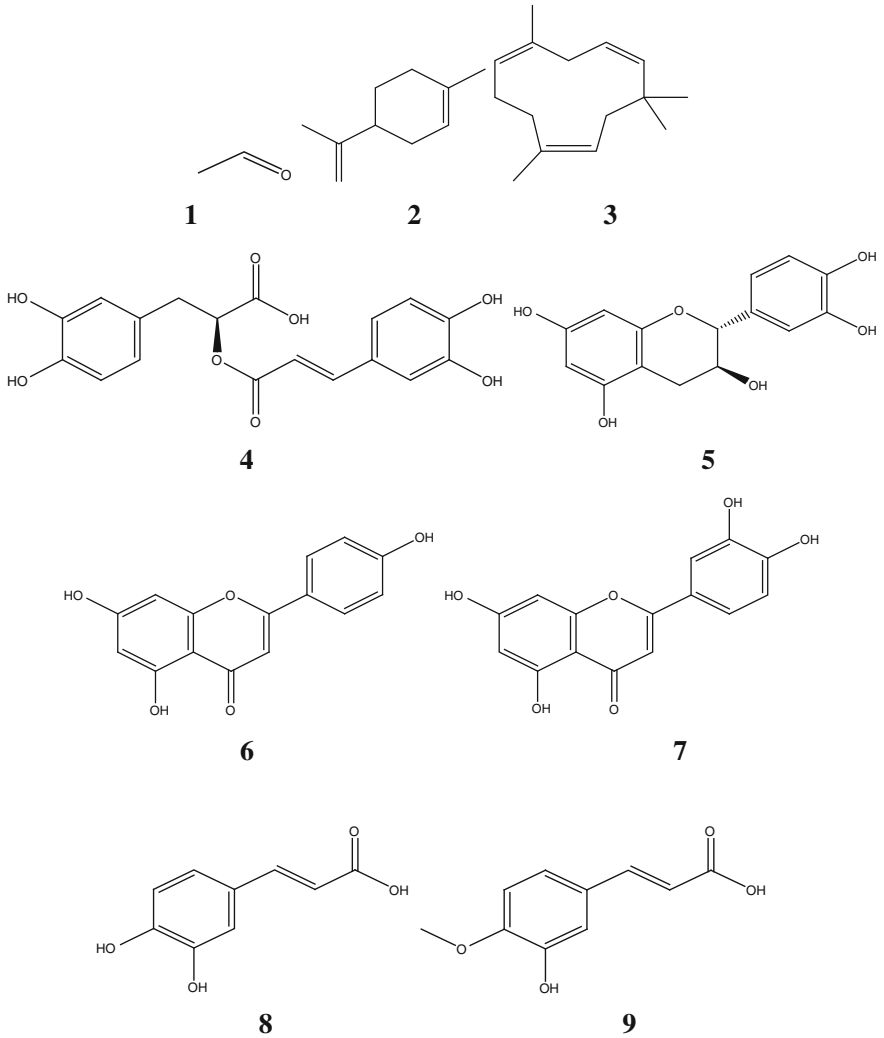

Fig. 83.2 Representative chemical compounds found in *P. frutescens*

83.2.1 Essential Oils

Liu et al.'s [4] research indicated that 87 volatile components were identified and determined, accounting for 99.38 % of the total area of the all the peaks in the chromatograms.

83.2.2 Flavonoids and Phenolic Acids

Ishikura [5] showed that sixteen flavonoid compounds including five anthocyanins, two flavones and nine flavone glycosides were found in mature dark-red leaves and seeds of the *Perilla* plant. In seeds, apigenin and luteolin were present in a ratio of about 1:1. Both flavones and flavone glycosides were found in the leaves. In addition, the leaves contained five kinds of anthocyanins including cyanidin 3,5-diglucoside and its esters with cinnamic acid derivatives. Among these flavonoids, the 3-*p*-coumarylglucoside-5-glucoside of cyanidin and the 7-caffeylglucosides of apigenin and luteolin were the major compounds in the leaves. Rosmarinic acid was isolated from the dried leaves of *P. frutescens* and was found to be the main chemical compound in 1985 by Aritomi et al. [6].

83.3 Pharmacological Studies

The medicinal uses of *P. frutescens* as antiasthmatic, antidote, antimicrobial, antipyretic, antiseptic, antispasmodic, antitussive, aromatic, carminative, diaphoretic, emollient, expectorant, stomachic, and tonic substances have been shown [7]. The plant constituents confirm these properties in alternative medicines and usefulness in curing various diseases and disorders, including many cancers [8–10]. The plant is useful in the treatment of asthma, common cold, cough and lung afflictions, nausea, vomiting, abdominal pain, constipation, food poisoning and cancers, and it can also be used to prevent influenza and to restore health and balance [11, 12]. The stems are a traditional Chinese remedy for morning sickness.

83.4 TCM Applications and Dietary Usage

83.4.1 TCM Applications

P. frutescens has been used as a traditional Chinese medicine for more than a thousand years. The leaves, stems, and fruits are applied for different diseases. Perillae Fructus is used mainly for relieving dyspnea and cough, for eliminating phlegm, and for relaxing the bowels; Perillae Folium is used to induce perspiration, to dispel cold, and to regulate stomach function; Perillae Caulis is used to regulate the flow of Qi and the function of the stomach, to alleviate pain, and to prevent miscarriage, Some monoterpenes from the leaves have been reported to possess bioactivity, such as promotion of intestinal propulsion, prolongation of hexobarbital induced sleep in mice, and inhibitory effects on xanthine oxidase and aldose reductase.

As one of the commonly used traditional Chinese medicines, *P. frutescens* is concluded as one the most important herbs in many compound preparations. Zhike Huatan Pill is composed of Zisuye (leaf of *Perilla frutescens*), Kuxingren (seed of *Prunus armeniaca* var. *ansu*), Qianhu (root of *Peucedanum praeruptorum*), Banxia (tuber of *Pinellia ternata*), Chenpi (pericarp of *Citrus reticulata*), Chuanbeimu (bulb of *Fritillaria cirrhosa*), Gancao (root of *Glycyrrhiza uralensis*), et al., and is mainly used to treat cough, excessive phlegm, and chest congestion. Juhong Pill is composed of Juhong (outer pericarp of *Citrus reticulata*), Chenpi (pericarp of *Citrus reticulata*), Banxia (tuber of *Pinellia ternata*), Fuling (sclerotium of *Poria cocos*), Gancao (root of *Glycyrrhiza uralensis*), Jiegeng (root of *Platycodon grandiflorum*), Zisuzi (fruit of *Perilla frutescens*), and Kuxingren (seed of *Prunus armeniaca* var. *ansu*) et al., and is commonly used to relieve cough and reduce sputum. Sizheng Pill consists of Guanghuoxiang (herb of *Pogostemon cablin*), Xiangru (herb of *Mosla chinensis*), Mugua (fruit of *Chaenomeles speciosa*), Houpo (bark of *Magnolia officinalis*), Zisuye (leaf of *Perilla frutescens*) et al., and is usually used to treat symptoms of influenza such as diarrhea and vomit.

83.4.2 Dietary Usage

P. frutescens is an edible plant. The leaves have a very pleasant sweet taste and are used as a spice for fish, rice, vegetables, and soups to give color and flavor to many pickled dishes. It is also chopped and combined with ginger root and salads in many Asian countries. The seeds from the plant also supply nutritious cooking oil. The essential oil of the plant is used as a food flavoring. The entire plant is very nutritious with vitamins and minerals [13]. Seedlings of the plant are added to salads, older leaves are used as a garnish or flavoring. The leaves contain about 3.1 % protein, 0.8 % fat, 4.1 % carbohydrate, and 1.1 % ash. The seeds can also be eaten cooked. Seeds from purple leafed forms of the plant are preferred for culinary uses. The seed contains about 21.5 % protein, 43.4 % fat, 11.3 % carbohydrate, and 4.4 % ash. The plant yields an essential oil which is used as food flavoring in candies and sauces [8].

83.5 Clinical Evidence

The earliest clinical application of *P. frutescens* was recorded in "Bencaojing Jizhu". As one of the famous Chinese medicines for the treatment of cough and asthma, *P. frutescens* is often used in combination with Chenpi (pericarp of *Citrus reticulata*), Fuling (sclerotium of *Poria cocos*), Gancao (root of *Glycyrrhiza uralensis*), et al., to treat Qi stagnation. Clinical application of Xiangsu Yiqi Pill, consisting of Xiangfu (rhizome of *Cyperus rotundus*), Zisugeng (stem of *P. frutescens*), Chenpi (pericarp of *Citrus reticulata*), Fuling (sclerotium of *Poria*

cocos), Gancao (root of *Glycyrrhiza uralensis*), et al. indicated that this compound preparation had significant curative effect on Qi depression and light-headedness. The recovery rate reached 100 % [14]. It has been used alone to prevent miscarriage, in combination with Juhong (outer pericarp of *Citrus reticulata*) and Sharen (fruit of *Amomum villosum*) for warming the middle energizer, in combination with Wuyao (root tuber of *Lindera aggregata*) for relieving pain, and in combination with Xiangfu (rhizome of C*yperus rotundus*) and Mahuang (herb of *Ephedra sinica*) for treating diaphoresis.

83.6 Safety Evaluation and Toxicity Data

Essential oil from *P. frutescens* exhibited strong contact toxicity against the booklice at a concentration of 0.16 μL/cm^2 and possessed fumigant toxicity at a concentration of 0.04 μL/L [15]. By i.g. only once, the essential oil of Hubei *P. frutescens* could poison the mice, even more to die successively. The LD50 of the oil in mice was 3.10 g/kg for i.g. [16].

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Chapter 84
Plantago asiatica L. 车前
(Cheqian, Asiatic Plantain)

Li Yang

84.1 Botanical Identity

Cheqian, a perennial herbal plant in the Plantago Family, is one of the most popular Chinese herbal medicines and is frequently used as an ingredient in dietary supplements. The medicinal part of the plant is the herb (Cheqiancao) or seed (Cheqianzi). Although there are 265 species of the genus Plantain in the world, only a few species with similar botanical characters are used as Cheqian. *Plantago asiatica* L. and *P. depressa* Willd. are the major and legal sources recorded in the Pharmacopoeia of the People's Republic of China and all historical records of Chinese herbal works [1, 2].

Cheqian is widely distributed in most areas of China, from north to south, such as Heilongjiang, Liaoning, Hebei, Jiangxi, Henan, Guangxi, Yunnan, Fujian, Qinghai, Jiangsu, Shanxi provinces, and so on. The fruit-spike is collected in the summer or autumn when the seed is ripe, and then dried in the sun. The seed is rubbed out and removed from foreign matter. When using the whole plant, the drug is collected in summer, removed from soil, and dried in the sun [3] (Fig. 84.1).

84.2 Chemical Constituents

Phenylethanoid glycosides, iridoid, flavonoids and its aglycones, polysaccharide, and triterpenoids are major kinds of active compounds found from *Plantago asiatica* L.

L. Yang (✉)
Shanghai University of Traditional Chinese Medicine, Shanghai, China
e-mail: cpuyl@126.com

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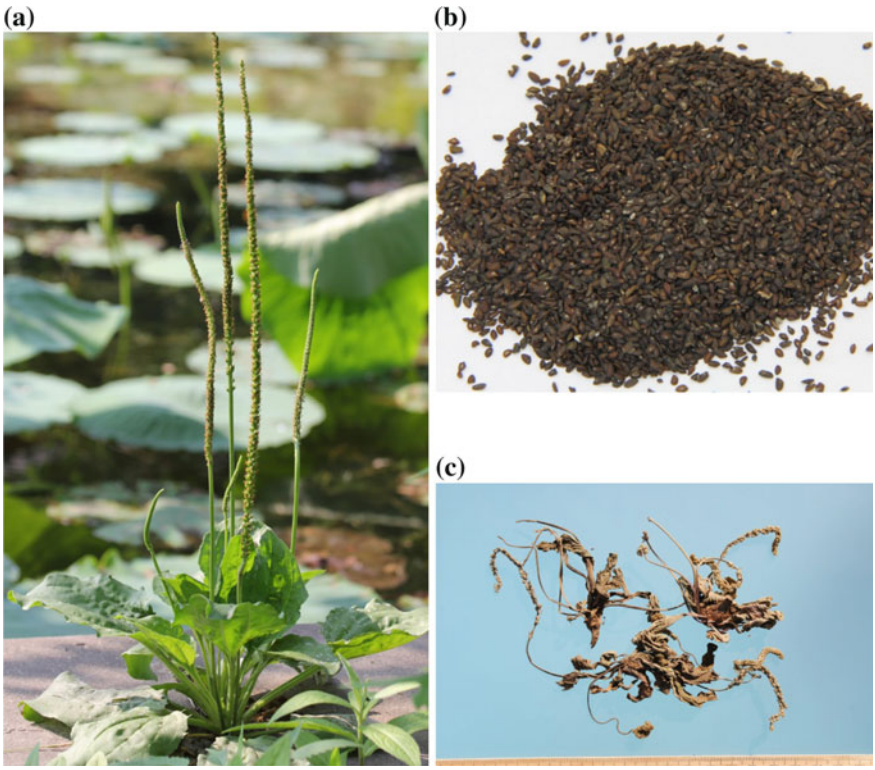

Fig. 84.1 The flowering plant (**a**) and crude drugs (**b** Cheqianzi, **c** Cheqiancao)

84.2.1 Phenylethanoid Glycosides

Acteoside (1), plantamajoside (2), isoacteoside (3), isoplantamajoside (4), desrhamnosylverbascoside, rehmannioside and many others are representative phenylethanoid glycosides isolated from Cheqian [4, 5]. Some of them are shown in Fig. 84.2a.

84.2.2 Iridoids

Geniposidic acid (4), aucubin (5), catalpol (6), 3,4-two hydroxyl aucubin and many others are representative iridoids isolated from Cheqian [6, 7]. Some of them are shown in Fig. 84.2b.

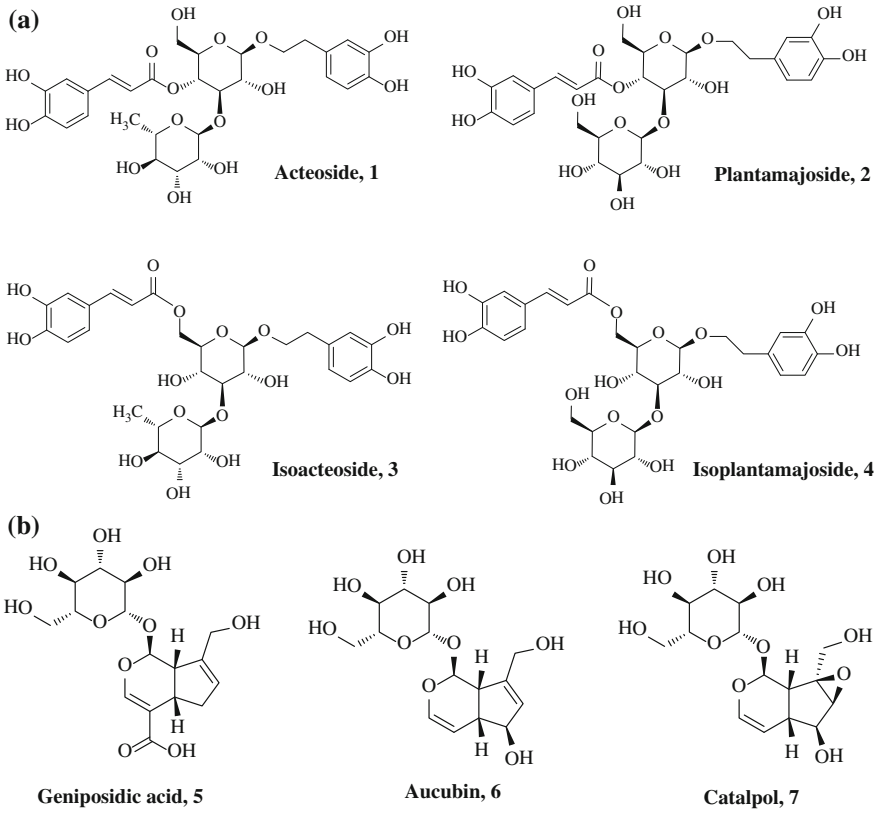

Fig. 84.2 Typical phenylethanoid glycosides (**a**) and iridoids (**b**) isolated from Cheqian

84.2.3 Flavonoid and Other Components

There are still flavonoids and its aglycones, polysaccharide, triterpenoids and other types of components found from Cheqian, such as homoplantagin, plantagoside, plantasan, and ursolic acid, etc. [8–10].

Among these compounds, acteoside and geniposidic acid are considered as the principal bioactive compounds in Cheqianzi, corresponding with traditional use of diuretics and antihypertention. However, plantamajoside is considered as the primary bioactive compound in Cheqiancao. Notably, there are the chemical markers which discriminate between Cheqianzi and Cheqiancao. Therefore, TLC identification and HPLC assay methods using acteoside and geniposidic acid as chemical markers were developed for the quality control of Cheqianzi, while TLC identification and HPLC assay methods using plantamajoside as a marker were established for the quality control of Cheqiancao [11, 12].

84.3 Pharmacological Studies

Cheqian is one of the most popular traditional medicines used by TCM. As recorded in Chinese Pharmacopoeia (2010 edition), the function of Cheqian could be expressed from many aspects as to clear heat, disinhibit urine and relieve stranguria, drain *Dampness* to check diarrhea, improve vision, and dispel phlegm. Modern pharmacological studies have proven that Cheqian can be used as a diuretic and antihypertensive, and a methanol extract of Cheqian was found to have dose-dependent glycation inhibitory activity and hepatoprotective effect. Cheqian essential oils have also shown hypocholesterolemic properties in mice through suppressing the expression of HMG-CoA reductase in vitro [13–16].

84.4 TCM Applications and Dietary Usage

84.4.1 TCM Applications

Cheqian is one of the most common herbal materials traditionally used as herbal medicines and diuretics, antipyretic and laxatives products. It exerts therapeutical and health-maintaining actions in the following aspects; as heat strangury with slow pain, edema distention and fullness, diarrhea caused by summerheat-dampness, swelling abscess, red painful swelling eyes, and phlegm-heat cough. Cheqian could be used by single form or combining forms with other herbs based on TCM theory.

Common Cheqian preparations are clinically used for: (1) diuretics or lithoexpulsium, like Bazheng mixture, Fenqing Wulin pill, Paishi granule, Qinglin granule and so on. They are usurally composed of 5–10 herbal components and Cheqian is mainly used for the treatment of edema distention and fullness, or swelling abscess. (2) Tonifying the kidney, like Wuzi Yanzong pill, Yishenling granule. Cheqian has been used clinically for nourishing the kidney and strengthening the essence. (3) Treatment of constipation and gastrointestinal functional disorder, Cheqian extract and preparations can be made from single Cheqian extract or active components, such as plantasan [17–19].

84.4.2 Dietary Usages

Because of the extensive documentation of Cheqian as one of the famous herbs and valuable dietary botanical materials, Cheqian can be used in many ways historically. Some of the ways to use Cheqian include making Cheqian tea or Cheqian soup. The following drinking or eating forms can be easily made at home.

84.4.2.1 Cheqian Tea

Composition: Cheqiancao (herb of *Plantago asiatica* L.) 50 g, honey 10 g.

Preparation: The whole plant of Cheqian is cleaned, dried in the sun and pounded into the juice, 100 ml should be obtained. Add honey. Drink the tea once or twice a month.

Function: Clearing phlegm, relieving coughs, and dispersing *Heat* and promoting eyesight. It is helpful for the treatment and prevention of ascites and edema distention.

84.4.2.2 Yeju Cheqian Tea

Composition: Yejuhua (capitulum of *Chrysanthemum indicum*) 15 g, Huangqin (root of *Scutellaria baicalennsis*) 9 g, Cheqianzi (seed of *Plantago asiatica* L.) 15 g.

Preparation: Put the slices or ground powder in a water pot or other glass container, add water and boil for 20 min. Remove the residue by filtration. Drink three times a day.

Function: It can be used in cases of red painful swelling eyes and helpful for the people suffering dizziness and hypertension.

84.4.2.3 Cheqian Drink

Composition: Cheqianzi (seed of *Plantago asiatica* L.).

Preparation: Pound proper amount of Cheqianzi into the juice and add honey. Boil the mixture a few minutes before drinking.

Function: It is used for the therapy for heat strangury and edema distention.

84.5 Clinical Evidences

There are thousands of clinical related reports or observational studies published on the effects of Cheqian and its related preparations for diseases of bacillary dysentery, chronic bronchitis, hypertension, and so on. Clinical reports showed that the preparation could effectively relieve hypertension in elderly patients in 50 cases. Cheqian is used with herbs such as Gualou (Fruit of *Trichosanthes kirilowii*), Zhebeimu (bulb of *Fritillaria thunbergii*), Pipaye (leaf of *Eriobotrya japonica*), etc. to treat a cough, and previous report showed 80 % of patients with a cough showed improvement after being treated with Cheqian decoction for a week. Cheqian is also used together with herbs that clear away heat and induce diuresis, such as Mutong (stem of *Akebia quinata*), Huashi (talcum), Bianxu (herb of *Polygonum aviculare*), etc., e.g. Bazheng powder to treat edema and strangury. After being treated with Cheqian tea, clinical symptoms of 80 % of the 30 pregnant women tested showed that their symptoms of gestational edema were eased or completely relieved [20, 21].

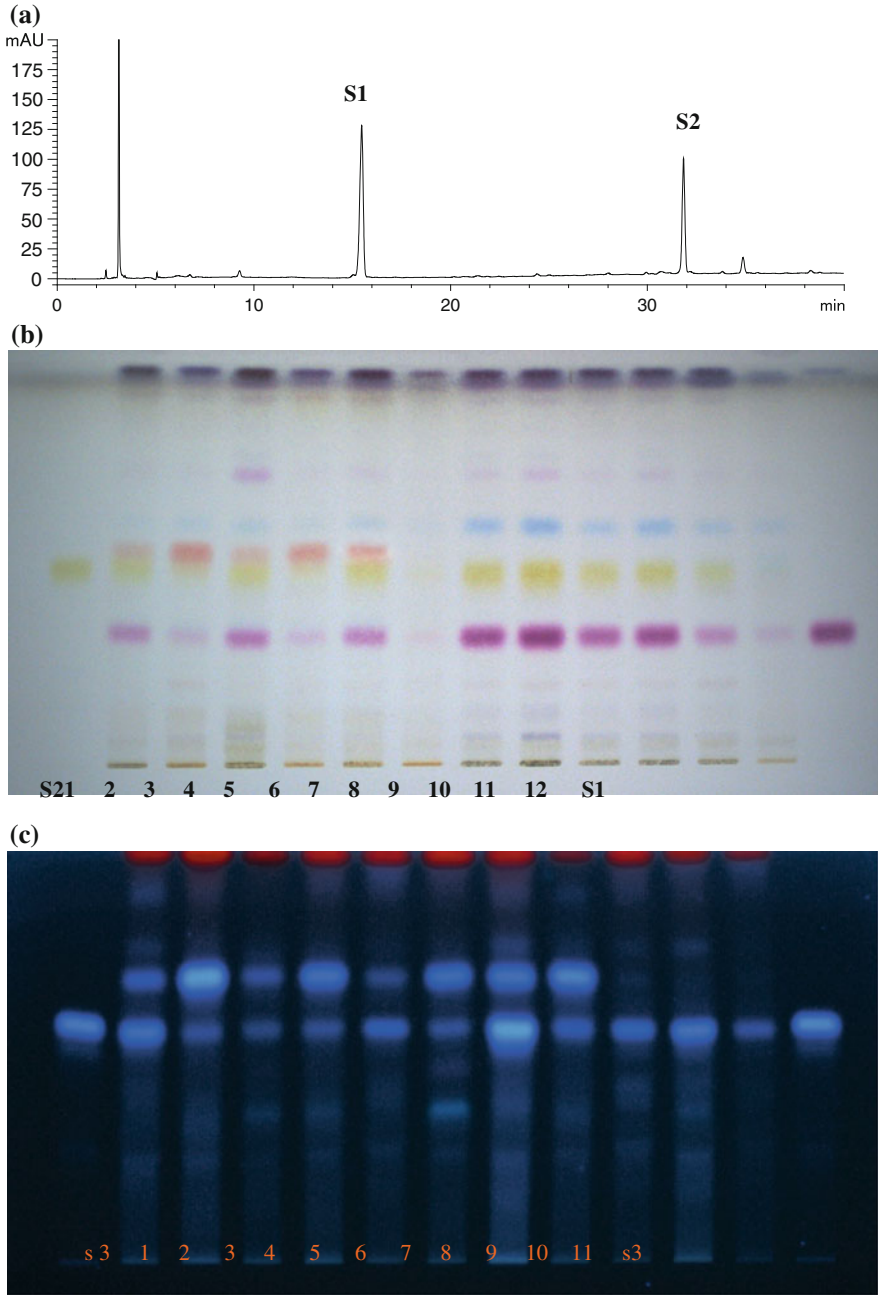

Fig. 84.3 Typical HPLC and TLC chromatograms of Cheqianzi (**a**, **b**) and Cheqiancao (**c**). *S1–S3* geniposidic acid, acteoside, and plantamajoside

84.6 Quality Evaluation and Assurance

Phenylethanoid glycosides and iridoids are two main types of active components of Cheqian. The typical HPLC and TLC chromatograms of crude Cheqian are shown in Fig. 84.3. From the figure we can see that acteoside, plantamajoside and geniposidic acid are the major components. Therefore, TLC identification and HPLC assay methods using acteoside and geniposidic acid as chemical markers were developed for quality control of Cheqianzi, while TLC identification and HPLC assay methods using plantamajoside as marker were established for quality control of Cheqiancao. Both the chemical markers and corresponding analytical methods have been adopted by the latest version of Chinese Pharmacopoeia (2010 edition) as quality criteria of Cheqianzi and Cheqiancao, respectively. As required in Chinese Pharmacopea 2010, it contains no less than 0.40 % of acteoside ($C_{29}H_{36}O_{15}$) and 0.50 % of geniposidic acid ($C_{16}H_{22}O_{10}$), with no less than 0.10 % of plantamajoside ($C_{29}H_{36}O_{16}$), calculated with the reference to the dried drugs Cheqianzi and Cheqiancao, respectively [1, 22].

84.7 Safety Evaluation and Toxicity Issue

There are few clinical reports on the toxicity and side effect directly related to Cheqian and related preparations. Additionally, animal tests have not shown clear toxicity for various organs through ip and oral administration. Cheqian is definitely a relatively safe herbal medicine often used as diuretics and antihypertention. However, when using the drug recreationally, without consulting a doctor, special care should be taken because it is obvious that Cheqian has strong biological activity and cannot be used as regular food. It's strongly suggested to ask your doctor if it's appropriate for you.

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Part VII
Fungi, Marine Algae, and Other Materials

Chapter 85
Ganoderma lucidum 灵芝
(Lingzhi, Ganoderma)

Caixia Dong and Quanbin Han

85.1 Botanical Identity

Ganoderma, also referred to as Lingzhi in Chinese, is the dried fruiting body of both *Ganoderma lucidum* (Leyss. Ex Fr.) Karst (Chizhi) and *G. sinense* Zhao, Xu et Zhang (Zizhi) belonging to the family of Polyporaceae. Lingzhi has been recorded in the Chinese Pharmacopeia (2010) [1] as one of the most popular Chinese herbal medicines, and is frequently used as an ingredient in dietary supplements. There are more than 200 species of *Ganoderma* in the world, of which 98 species have been found in China. *G. lucidum* and *G. sinense* are two of the most common species to be used for medicinal purposes, and they have been commercially cultivated for the preparation of health products since the 1970s.

Lingzhi is widely distributed in both tropical and temperate geographical regions, growing as a parasite or saprotroph on a wide variety of hardwoods. It grows to the height of 7–15 cm (*G. lucidum*) or 12–22 cm (*G. sinense*), and has a large, perennial, and woody basidiocarps. As shown in Fig. 85.1, the fruit body typically grows in a fan-like (*G. lucidum*) or umbrella-like form (*G. sinense*) on the trunks of living or dead trees. They have double-walled, truncate spores with yellow to brown ornamented inner layers.

Lingzhi are traditionally harvested all year round. After removing the impurities, sediment, and the bottom stalk of in culture, Lingzhi fruiting bodies are dried in shade or at 40–50 °C. The dried fruiting bodies can be stored and marketed as raw material. For further processing, the raw material can be sliced to 5–10 mm thickness or ground to a fine powder in order to form different commercial Lingzhi products.

C. Dong · Q. Han (✉)
School of Chinese Medicine, Hong Kong Baptist University, Kowloon, Hong Kong
e-mail: hqb0402@yahoo.com

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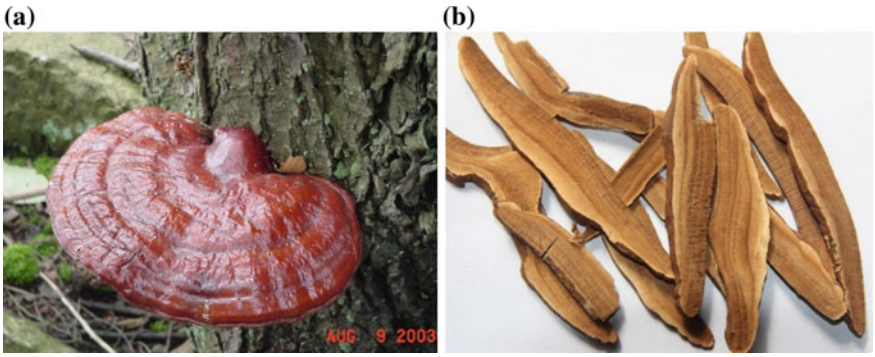

Fig. 85.1 Wild growing state (**a**) and slices of commercial Lingzhi (**b**)

85.2 Chemical Constituents

Numerous researches have revealed that Lingzhi contains approximately 400 different bioactive compounds, mainly triterpenoids, polysaccharides, nucleotides, steroids, fatty acids, proteins/peptides, amino acids, and trace elements. These studies have shown that Lingzhi contains properties which can enhance overall health and aid the body in relief of a multitude of diseases, such as hypertension, hepatitis, diabetes, neurasthenia, and cancer. Among the numerous components, triterpenoids and polysaccharides are two major classes of *Ganoderma* fruiting bodies.

85.2.1 Triterpenoids

G. lucidum is the only known source of a particular group of triterpenes, known as ganoderic acids, which have been found to have direct cancer cell cytotoxicity on a wide variety of cancer cell lines, and many of them have been suggested to counter angiogenesis and metastasis [2]. As a major class of bioactive compounds found in Lingzhi, triterpenoids are mainly contained in the spores and are responsible for Lingzhi's bitter taste. Previous studies have shown that triterpenoids exhibit a broad spectrum of anti-cancer effects, including anti-proliferative, anti-metastatic, and anti-angiogenic activities [3]. So far, about 29 triterpenoids [4] have been isolated from the spores and the major bioactive ones were shown in Fig. 85.2. Ganoderic acid T (**1**) is the most abundant triterpenic acid found in Lingzhi, and Ganoderic acid D (**2**) has shown significant anti-cancer effects in both in vitro and/or in vivo. Additionally, Ganoderiol F (**3**), a tetracyclic triterpene found in Lingzhi has also shown cytotoxicity on several kinds of tumor cells, including Lewis lung carcinoma, Meth-A, Sarcoma-180, and T47D cell lines. These triterpenoids are used as

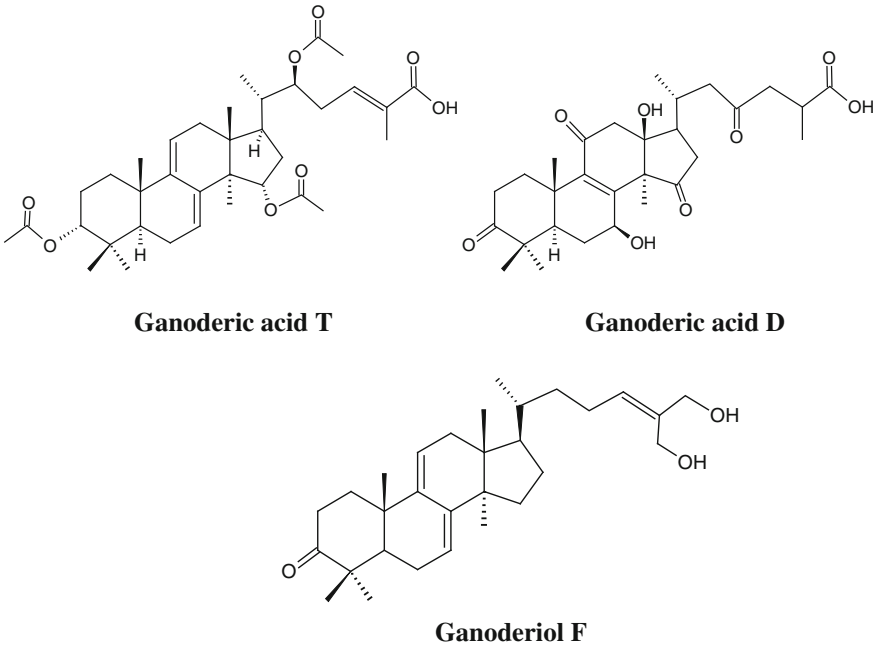

Fig. 85.2 Chemical structures of ganoderic acid T, D, and ganoderiol F from Lingzhi

chemical markers for quality evaluation of crude drug Lingzhi and related pharmaceuticals, as well as some natural health products containing Lingzhi.

85.2.2 Polysaccharides

Polysaccharides, a class of structurally-diverse biological macromolecules with wide-range physiochemical properties, were extracted from Lingzhi with water, based on the traditional use of Lingzhi (decoction), and followed by alcohol precipitation. Because of their various bioactivities, and very low to even no cytotoxicity, polysaccharides have attracted much attention of researchers. Up to now, many polysaccharides have been isolated from fruiting bodies, mycelium, spores, and culture medium of *G. lucidum*, including homo- or hetero-glucans, and heterosaccharides with different combinations of glucose, galactose, mannose, xylose, arabinose, as well as fructose. Among them, (1 → 3)-*β*-D-glucans branched at O-6 position as shown in Fig. 85.3, mainly existing in spores, and are considered to be the major active polysaccharides. Additionally, *β*-D-glucans consisting of (1 → 3)-, (1 → 4)-, and (1 → 6)-*β*-D linkages are reported to have a stronger anti-tumor potency and better absorption than other polysaccharides in *G. lucidum* [5].

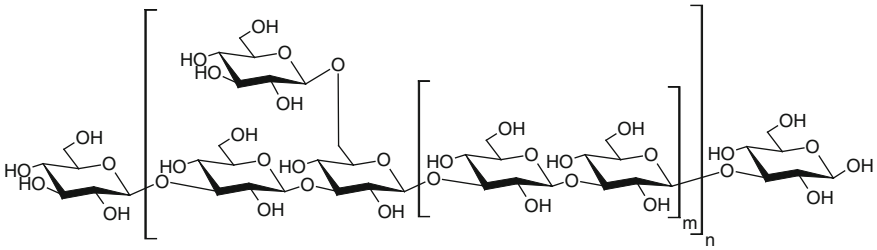

Fig. 85.3 structure of (1 → 3)-*β*-D-glucans branched at O-6 position

85.3 Pharmacological Studies

In Asian countries, Lingzhi has been widely used for centuries to promote general health and longevity. Modern pharmacological studies have reported that Lingzhi has a number of pharmacological effects including immune-modulating, anti-cancer, anti-oxidant, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, anti-diabetic, anti-aging, radical-scavenging, neuroprotective, hepatoprotective, and sleep promoting effects [6, 7]. Among them, Lingzhi's anti-cancer effect is the most extensively studied. Numerous researchers have demonstrated that triterpenes and polysaccharides are responsible for the major physiologically activity of Lingzhi. Further studies have revealed that ganoderic acids, which are composed of highly oxygenated triterpenes, exert antitumor activity by directly acting on a wide variety of neoplastic cells, such as murine Lewis lung carcinoma (LLC) and Meth-A, and many of them have been suggested to counter angiogenesis and metastasis [3]. In contrast to the actions of triterpenes, polysaccharides are reported to trigger an indirect antitumor mechanism, in which the host immune system is altered to target the tumor cells. It has been demonstrated that *β*-glucans have the ability to induce both innate and adaptive immune responses by targeting immune cells including macrophages, neutrophils, monocytes, natural killer cells, and dendritic cells [3].

85.4 TCM Applications and Dietary Usage

85.4.1 TCM Applications

In traditional Chinese medicine, as well as Chinese legend and history, Lingzhi is described as a miraculous drug. Lingzhi is mainly used to treat tightness of the chest, boost the heart's *Qi*, and improve memory. Long-term administration may tonify Qi to tanquilize the mind, suppress cough and relieve panting [1]. Modern pharmacological research has mainly focused on Lingzhi's immunomodulating and anti-tumor effects. It exerts therapeutical actions in the following aspects: enhancing anti-tumor immunity, direct cytotoxicity against tumor cells, anti-angiogenesis,

anti-inflammation, and anti-oxidant actions. Clinically, Lingzhi is most often used as an alternative adjunct to conventional therapy in cancer treatment; especially to decrease the side effects resulting from chemical drugs, radiotherapy, and surgery.

Common Lingzhi preparations clinically used include the following forms: (1) Decoction: Thinly sliced or pulverized Lingzhi is added to boiling water and simmered for 2 h. The resulting liquid is fairly bitter in taste and dark, in which the red Lingzhi (*G. lucidum*) is more active and bitter than black Lingzhi (*G. sinense*). (2). Powder and capsule forms: There are many manufactures making this product. Some of them consist of the raw powder of Lingzhi or spores, such as Lingzhi broken spores powder. Dongfang Lingzhi Bao developed by Beijing Hengji Tang has been approved by State Food and Drug Administration for the treatment of cancer patients, which is a water extract preparation of fruiting bodies and broken spores. Additionally, other products such as Yunfeng, Tian'an, and Handu Lingzhi capsules, are used to enhance immunity, promote sleep, and improve memory. (3) Zhengqin Lingzhi Pills: This is the only one Lingzhi product available in market as OTC medicine for the treatment of insomnia, neurasthenia, and asthenic, which is manufactured by Hunan Zhengqin Pharmaceutical Group Co. LTD. (4) Lingzhi syrup: It is also sold as OTC medicine for the treatment of insomnia, neurasthenia, and asthenic. Finally, Lingzhi is also used as an ingredient in clinical decoctions or used to make an extract in liquid or powder form.

85.4.2 Dietary Usages

Due to its reputation of safety and efficacy, many dietary products containing Lingzhi are widely available, such as Lingzhi wine, Lingzhi tea, Lingzhi yoghourt, and Lingzhi soup. With a thorough investigation of Lingzhi, as well as development of new technology, highly processed Lingzhi products, such as Lingzhi extract, spore powder, and β-gluans are now commercially available. The following dietary forms can be easily made at home.

85.4.2.1 Lingzhi Tea

Lingzhi tea consumed as a functional product, made of Lingzhi alone or mixed with other herbs is the most common way to use Lingzhi. It has the function of modulating immunity to keep the body in balance. As the raw material of Lingzhi tea, Zizhi is thought to be better than Chizhi as it is less bitter. There is a recommended formula to make Lingzhi tea, i.e. Lingzhi, Dangui (*Orange osmanthus*), Jinyinhua (*Lonicera japonica* Thunb.), Shanzha (*Crataegus pinnatifida*) and Gouqi (*Lycium barbarum* L.). There are also many kinds of products of Lingzhi tea available in the market, such as Bairentang Lingzhi Tea composed of Lingzhi spore powder alone; Jingchuntang Lingzhi Tea composed of Lingzhi and honey; Zhirentang Lingzhi Tea composed of Chizhi, Huangqi (*Astragalus mongolicus*), Taizishen (*Pseudostellaria*

heterophylla), and Yunling (*Pachyma cocos*); Enhuatang Lingzhi Tea composed of Lingzhi spore powder, Lingzhi polysaccharides, and Lu'an Melon Seed Tea, etc. To make the herbal tea, it is recommended to use soft water, as it has a lower mineral content and is therefore less alkaline, which is important to reduce the decomposition of phenolic acids.

85.4.2.2 Lingzhi Wine [8]

Lingzhi alone or combined with other herbs can be used to prepare herbal wine for balancing the body and slowing down the aging process. To produce this wine, Lingzhi (5 g) is combined with Chinese spirit (500 g) and left sealed for 7 days. Drinking 20–40 ml twice daily in early morning and evening could enhance memory and strengthen the body. For the treatment of phthisis chronic cough through nourishing lung *Qi*, a Lingzhi wine [9, 10] composed of Lingzhi (75 g), ginseng (25 g), crystal sugar (250 g), and Chinese spirit (1500 ml) can be consumed. Lingzhi can also be used to make herbal wines in combination with many other herbs such as Huangqi, Shanyao (*Dioscorea opposite*), Wuweizi (*Schisandra chinensis*), and Roucongrong (*Cistanche deserticola* or *C. tubulosa*), Dazao (*Ziziphus jujuba* Mill.), depending on the specific functions needed. The daily intake amount is based on the content of Lingzhi, other herbs, and alcohol.

85.4.2.3 Lingzhi Used in Medicated Foods

In terms of the miraculous and versatile functions without toxicity, Lingzhi is also commonly used as the material of functional food in daily life. It can be used to make soups with meat, corn powder, rice, and/or with other herbs depending on different body status. The taste of Lingzhi-contained foods can be adjusted based on personal preferences.

One example of such soups is as follows: a medicated Lingzhi soup is cooked by boiling slices of Lingzhi (6 g), Heimuer (black fungus, 6 g), Baimuer (Tremella, 6 g), Mizao (6 honey dates) and lean pork (200 g) for 30 min. Consumption of this soup is said to nourish the lung and stomach, promote blood circulation, strengthen heart *Qi*, prevent and treat cancer, lower blood pressure, and prevent coronary heart disease.

85.5 Clinical Evidences

As a therapeutic medicine, Lingzhi is usually recommended as an alternative adjunct to conventional therapy in cancer treatment in terms of its potential to enhance anti-tumor response and stimulate host immunity, to improve the quality of life and prolong the survival time. There are thousands of clinical related reports or

observational studies published on the effects of Lingzhi and combinations. Ganopoly [11] is an aqueous polysaccharide fraction extracted from *G. lucidum* by patented biochemical technique and has been marketed as an OTC product for chronic diseases including cancer and hepatopathy in many Asian countries. A clinical research on immune functional evaluation of ganopoly on 34 advanced-stage cancer patients revealed that the treatment with 1800 mg ganopoly three times daily orally before meals for 12 weeks resulted in a significant ($P < 0.05$) increase in the mean plasma concentrations of IL-2, IL-6, IFN-γ, phytochemagglutinin response, and NK activity compared to baselines. The product ganopoly was also evaluated in patients with advanced lung cancer in a randomized double-blind, placebo-controlled, multicenter clinical trial. The results indicated that ganopoly may have an adjunct role in the treatment of patients with advanced lung cancer [12]. Lingzhi was generally well tolerated by most participants with only a scattered number of minor adverse events. No severe toxicity was observed across these studies.

85.6 Safety Evaluation and Toxicity Data

Lingzhi, a famous herbal medicine that has been used in TCM for thousands of years, is being used as an adjunctive to chemotherapy to help boost the immune system. Few clinical reports on the toxicity or side effects of the use of Lingzhi are available. Although laboratory research is being carried out to determine its immunostimulatory properties, no essential data on toxicity were observed in animal models in addition to few reports on cells [13].

In conclusion, Lingzhi is definitely a relative safe herbal medicine. It is often taken alone or together with other herbs in many forms for the treatment of asthenic, neurasthenia, insomnia, and prevention of cancers and coronary heart diseases.

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Chapter 86
Laminaria japonica Aresch. and *Ecklonia Kurome* Okam. 昆布 (Kunbu, Kelp)

Xiaoliang Zhao, Guangling Jiao, Jiandong Wu, Junzeng Zhang and Guangli Yu

86.1 Botanical Identity

Laminaria, *Ecklonia* and some large brown algae of Phaeophyeae are sharing common names "Kelp" and "Kunbu", which are abundant in North Atlantic and Pacific area. To avoid confusion, in this chapter, kelp only represents *Laminaria japonica* Aresch. (Haidai) and *Ecklonia kurome* Okamura (Kunbu). Kelp is not only a popular healthy food, but also an important traditional Chinese medicine (TCM). As a herb, kelp origin, principally includes thallus from *L. japonica* Aresch. of Chordaceae or *E. kurome* Okamura of Alariaceae. *L. japonica* Aresch., was first introduced into China from Japan in late 1920s, and it is now largely distributing along the eastern seaboard of five provinces from the Northern Province of Shandong, Liaoning to southern province Fujian. *L. japonica* is mainly cultured in Rongcheng of Shandong province, *E. kurome* Okamura is mainly distributing in Yushan Island of Zhejiang province and Pingtan of Fujian province of China. Yearly, up to 400,000 tons of fresh kelp, and 35,000 tons of alginate is produced in China making it the largest kelp manufacturer in the world [1].

X. Zhao · J. Wu · G. Yu (✉)
Key Laboratory of Marine Drugs, Ministry of Education, Shandong Provincial Key Laboratory of Glycoscience and Glycotechnology, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, Shandong, China
e-mail: glyu@ouc.edu.cn

G. Jiao · J. Zhang
Aquatic and Crop Resource Development, National Research Council of Canada, 1411 Oxford Street, Halifax, NS B3H 3Z1, Canada

G. Jiao
Coastal Zones Research Institute Inc., 232B, avenue de l'Église, Shippagan, NB E8S 1J2, Canada

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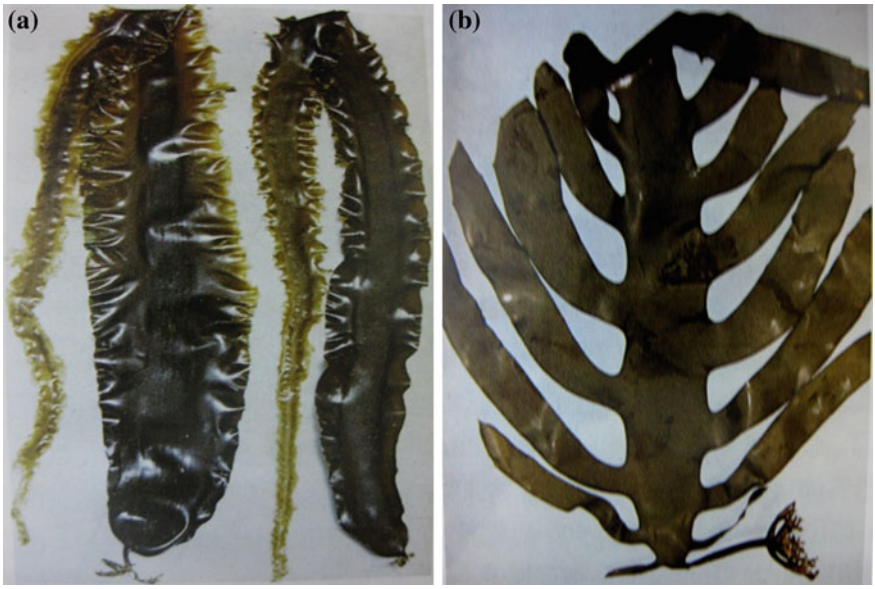


Fig. 86.1 Algae body of *Laminaria japonica* Aresch. (**a**) and *Ecklonia kurome* Okam. (**b**) [1]

L. japonica usually grows on natural rocks 2–3 m deep in shallow sea. Its frond is brown, leathery, single strap-like, flaky, unbranched, 2–5 m high and 20–30 cm wide. The sporophyte of *L. japonica* is complex and leathery. Its parenchymatousthallus is divided into a blade, a stipe and a holdfast. The blade is single stape-like or cleft deeply into palms without ribs, while the stipe is cylindrical or subcylindrical attaching to the substratum by profusely branched rhizoids with many fingers like a haptera. The blade and the stipe roughly have the same structure, consisting of three tissues: epidermis, incrustation and pith. In some species, blades and stipes both have mucus cavity (shown in Fig. 86.1a) [1].

Comparison with *L. japonica*, the algae body of *E. kurome* is smaller, usually 20–100 cm high, and can also be divided into distinct holdfast, stems and blade. Its blade is 3–5 cm in diameter and 4–12 cm long, and has thicker center, pinnate or compound pinnate lobes generally with coarsely toothed edges (shown in Fig. 86.1b) [1].

86.2 Chemical Constituents

Kelp is eaten as Kombu (昆布) in Japan and Haidai (海带) in China, respectively, also in some South and East America countries as sea vegetables or traditional herbs, because they have been known to be rich in nutrients, including

carbohydrates, proteins, fatty acids, vitamins, minerals, dietary fiber, and other bioactive components, such as phlorotannins. For example, *L. japonica* was found to contain 17.1–32.0 % alginic acid, 19.4–45.3 % ash, 0.1–0.7 % iodine [2], 7.50 % crude protein, 1.0 % lipids and 36.0 % dietary fiber [3].

86.2.1 Carbohydrates

Like other brown algae, the cell walls of kelp generally contains carbohydrates including three bioactive components: alginate (**1**), a water soluble polymer composed of guluronic acid (G) and mannuronic acid (M) and their Na^+, K^+, Mg^{2+}, and Ca^{2+} salts, which provides structural support for the algae; Fucose-containing polysaccharides mainly composed of fucose with small of galactose, glucuronic acid and mannose etc. which is usually named as fucoidan (**2**); and laminarin (**3**), a linear or β-1,6-branched β-1,3-glucan (shown in Fig. 86.2) [4].

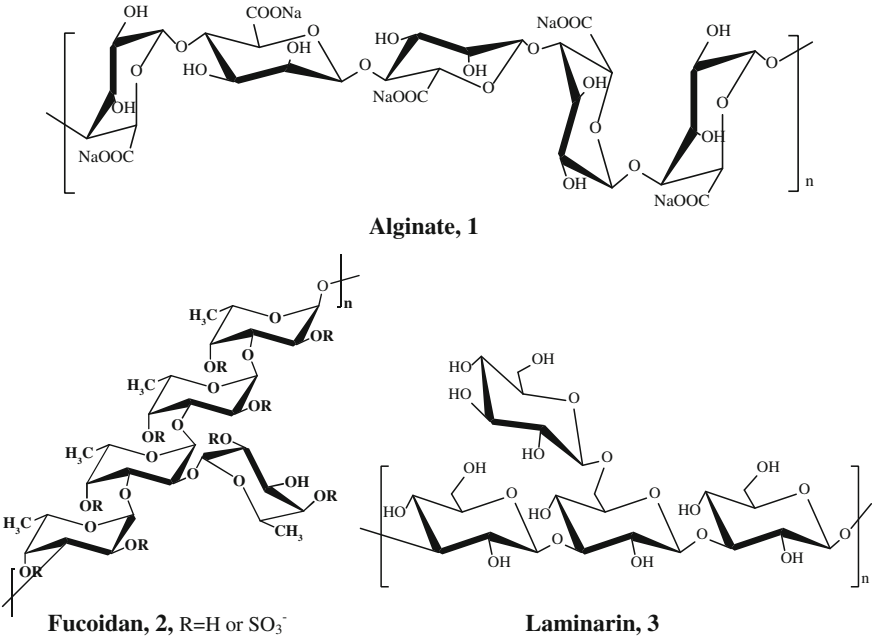


Fig. 86.2 The structures of three polysaccharides from kelp [5]

86.2.2 Fatty Acids

Kelp primarily contains monounsaturated fatty acids and polyunsaturated fatty acids. As reported by Dawczynski et al. [3], the contents and compositions of fatty acids determined in eight kinds of *L. japonica* from China were 36.0 % of palmitic acid (16:1), 12.8 % of oleic acid (18:1) and 16.2 % of eicosenoic acids (20:5). They also found that *E. kurome* contains 0.13 % of daturic acid (17:1), 0.12 % of oleic acid (18:1), 0.094 % of pentadecoic acid (15:1), 0.061 % of eicosenoic acids (20:5) and others of the dry weight algae body [1].

86.2.3 Vitamins

Kelp contains most types of vitamins except vitamin D and K. Nevertheless, vitamin A, C and E are very abundant in *L. japonica* [6].

86.2.4 Mineral Elements

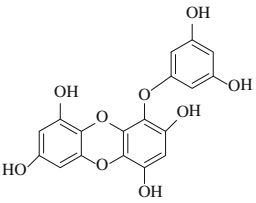
Most of kelps are rich in salts; accounting to 16–36 % of dry weight, including the mineral macronutrients potassium, sodium, calcium, magnesium, chlorine, sulfur and phosphorus, and the micronutrients iodine, iron, zinc, copper, selenium, molybdenum, fluoride, manganese, boron, nickel and cobalt [1, 2].

86.2.5 Phlorotannins

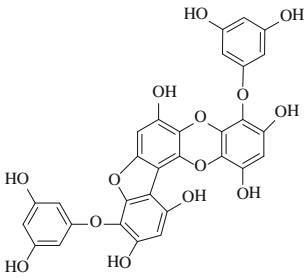
Phlorotannins are a class of bioactive components from *E. kurome* Okamura, which contains m-trihydroxybenzen, eckol (**4**), phlorofucofuroeckol A (**5**), 8,8′-bieckol (**6**), dieckol (**7**), phloroglucinol tetramer and 6,6′-bieckol (**8**) [1]. Recently, Yotsu-Yamashita M and his partner isolated and determined two novel phlorotannins 974-A (**9**) and 974-B (**10**) from *E. kurome* with radical scavenging activities (shown in Fig. 86.3) [7].

86.2.6 Other Constituents

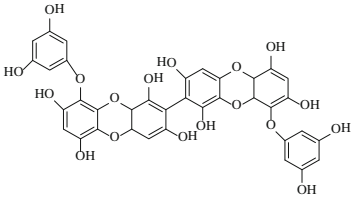
Iodine is the largest proportion of micronutritions in kelp, especially in cultivated fresh seaweed, which generally yields 3–5 %, and even up to 7–10 % [1, 3]. In addition, fucoxanthin, a characteristic orange colored bioactive carotenoid has been



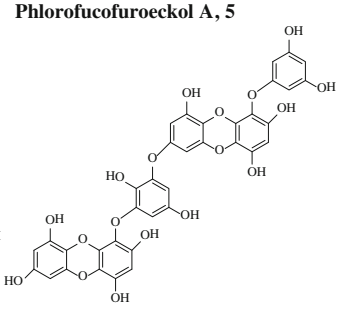
Eckol, 4



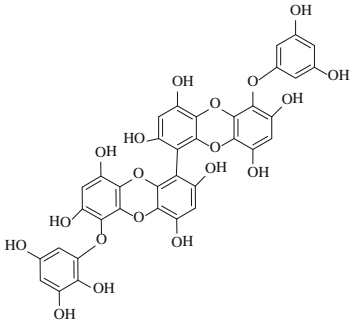
Phlorofucofuroeckol A, 5



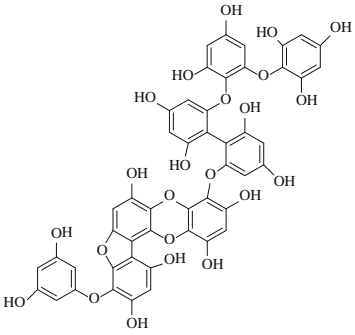
8,8'-Bieckol,6



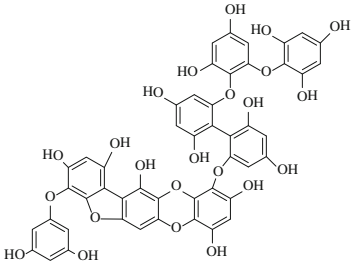
Dieckol, 7



6,6'-Bieckol, 8



974-A, 9



974-B, 10

Fig. 86.3 The structures of phlorotannins from *E. kurome* [1, 7]

extracted from *L. japonica*, *E. kurome* and others edible brown seaweeds [8]. In addition, mannitol, sterols, terpenes, and other small molecule substance are also reported as important components in kelp.

86.3 Pharmacological Studies

Kelp is farmed as commercial seaweed not only for food, but also as the resources for abundant bioactive compounds. For example, kelp is effective to adjust the function of thyroid gland due to the high amount of iodine. Moreover, kelp is abundant in alginate, fucoidan and β-1,3/1,6-glucan, which has anti-coagulant, anti-tumor, anti-virus, anti-oxidant and immunostimulating activities.

86.3.1 Anti-coagulant Activities

Anti-coagulant activity of polysaccharides from kelp is similar with other algal polysaccharides relies on their high content of sulfate groups, which indicates that sulfated kelp polymer is more effective. Interestingly, three low molecular weight fucoidan from *L. japonica* have been exhibited to obviously inhibit coagulant in activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT) assays [9]. Zha et al. [10] found that polysaccharides from *L. japonica* showed good potential of enhancing antioxidant enzyme activities in serum of atherosclerosis mice. Moreover, polysaccharides from *E. kurome* were found to have good anti-coagulant activity both in vivo and in vitro; its anti-coagulant activity of each 1 mg is equivalent to 7 U heparin [1]. In the last decade, series of sulfated alginate products, such as PSS and PGMS, have been developed abilities to inhibit aggregation of erythrocytes and blood platelets, which makes great success in Chinese medicine market [1].

86.3.2 Anti-oxidant Activities

Sulfated polysaccharides extracted from *Laminaria* spp. possess excellent anti-oxidant activities, which vary among their molecular weight and degree of sulfation [11]. Wang et al. isolated three sulfated polysaccharide fractions, two galactans and one fucoidan, from *L. japonica* and had their anti-oxidant activities investigated on various in vitro systems, including superoxide and hydroxyl radical scavenging activity, chelating ability, and reducing power. The correlation between the sulfate content and scavenging superoxide radical ability was found to be positive and can be used as an effective indicator to anti-oxidant activity [12]. In addition to this,

Yotsu-Yamashita et al. [7] found that phlorotannins from *E. kurome* also have good anti-oxidant activity in DPPH and intracellular reactive oxygen species assay.

86.3.3 Anti-tumor Activities

Laminarin (β-1,3/1,6-glucan) and fucoidan (sulfated fucan) can affect tumor cells directly or indirectly. Laminarin has the ability to kill tumor cells directly, besides it inhibits the growth of neovascular (new blood vessels). Previous studies have shown that sulfated polysaccharides isolated from *Laminaria* spp. and their hydrolyzed products can be used as apoptosis-inducing agents and anti-cancer drugs, because they inhibit more than 50 % Heps tumor cells but not affect the growth of normal cells [13]. Two fucoidans extracted from the holdfast of cultivated *L. japonica* by Ozawa et al. [14] were proved to have anti-tumor activity against Adenocarcinoma 755-transplanted mice by i.p. and p.o. administration. Moreover, polysaccharides from *E. kurome* also showed good anti-tumor activity for hepatoma cells HepG2 and gastric carcinoma cells SGC-7901; their 50 % inhibiting concentration (IC_{50}) are 592.2 and 649.8 μg/mL, respectively [15]. In the study done by Zhang and his colleagues, fucoxanthin from dietary *L. japonica* has been determined its anti-growth and apoptosis-induction activities against EJ-1 human bladder cancer. Their results indicated that fucoxanthin may act as a chemopreventive and/or chemotherapeutic carotenoid in bladder cancer cells by modulating cell viability [16]. Furthermore, many other extractions of kelp also have showed antitumor activity through the different mode of action in vivo and in vitro.

86.3.4 Anti-virus Activities

A large number of sulfated polysaccharides from brown seaweeds and other polyanionic substances can inhibit various virus infections in vitro containing important human pathogens, such as the human immunodeficiency virus, herpes simplex virus, human cytomegalovirus, dengue virus and respiratory syncytial virus [17]. Fucoidan extracted from *L. japonica* has been studied on anti-virus ability on poliovirus III, adenovirus III, ECHO6 virus, Coxsackie B3 virus, and Coxsackie A16. Furthermore, a sulfated polymannuroguluronate with an average molecular weight of 8.0 kDa, also isolated from this species, has been reported to be in Phase II clinical trials in China against acquired immunodeficiency syndrome (AIDS) [18, 19].

86.3.5 Anti-inflammatory and Immune-Stimulant Activities

Fucoidans isolated from *Laminaria* spp. have been reported to possess immune modulate activities including anti-inflammatory as they regulate and enhance immune function in many ways [20]. As reported by Mizuno, fucoidan was found to exhibit suppressive effects on interleukin-8 mRNA expression in $Caco_2$ through tumor necrosis factor-alpha (TNF-α) production from RAW264.7 cells stimulated with lipopolysaccharide [21]. Also, laminarin has been reported to modulate the immune response as well [6].

86.3.6 Other Activities

Many reports stated other bioactivities of polysaccharides from *Laminaria* spp. and *E. kurome* such as hypolipidemic and hypoglycemic activities, radiation protection, anti-diabetic and anti-fatigue activities. Additionally, an interesting research showed that laminarin has an effect on the preservation of plants [22]. Collectively, kelp has been studied widely for its potential pharmaceutical advantages.

86.4 TCM Applications and Dietary Usage

86.4.1 TCM Applications

As a traditional Chinese medicine, kelp has been used in disease treatment for decades, such as prevent dysphagia, cough, vaginal discharge, emission, wet beriberi, malignant sore, goiter, swollen neck lymph nodes, liver and spleen enlargement and ascites, leaching disease, chronic bronchitis, testicular pain, arteriosclerosis, senile cataract, etc. [1]. The dried raw materials of Kelp and its extracts have been widely applied in clinic in China.

1. Propylene glycol alginate sulfate sodium salt (PSS) is a highly valued heparinoid drug, which is prepared from kelp following hydrolysis, esterification and sulfation [23]. PSS has been principally used for the prevention and treatment of ischemic cerebrovascular disease such as cerebral thrombosis, cerebral embolism and transient cerebral transient ischemic attack, besides cardiovascular diseases such as hypertension, hyperlipidemia, coronary heart disease, and angina pectoris. In addition, PSS has been described to treat disseminated intravascular coagulation, chronic glomerulonephritis and hemorrhagic fever [1].
2. Sulfated propylene glycol ester of mannuronate (PMS) is another heparinoid marine drug, which is developed from kelp alginate following hydrolysis, fractionation, esterification and sulfation. PMS has been used to treat

hyperlipidemia by reducing blood cholesterol and triglycerides levels and increasing plasma high density lipoprotein level [24].
3. Mannitol, which is mainly extracted from kelp for decades in China, can be used clinically to treat cerebral edema and glaucoma, extensive burn, burn caused edema, renal failure, and ascites [25].
4. Iodine prepared from kelp can be used in iodine-glycerol production, which is a mixture of potassium iodide-iodine, water and glycerol. In dental clinic, iodine-glycerol is a common agent for oral mucosal ulcers, gingivitis and pericoronitis treatment [25].
5. Haikunshenxi capsule is the mainly composed of fucoidan, which is separated from kelp. It has a great benefit in curing chronic renal failure in China [24].

86.4.2 Dietary Usages

Most people in Asian and western countries share different diet habit. A preference for seaweeds, particularly brown seaweeds (kelp), seems to be confined to the Asian population. As mentioned above, kelp is known as the "longevity food" and it is rich in polysaccharides, trace elements, vitamins and other nutrient substances. Thus, it becomes a great valuable traditional Chinese healthy food that is suitable for the elderly people, especially. Several studies have shown that kelp has possessed remarkable properties making them a wonderful component of dietary supplements. Besides family cooking as salad, soup, fries and other process, a variety of new types of food made with kelp has been developed, such as fermented kelp beverage, kelp health tea, kelp chili sauce, kelp sausage and kelp fiber noodles. Some examples are listing here as follows:

1. Kelp beverage: Xu et al. [26] developed a compound beverage of *E. Kurom* with *E. Kurom* juice and lotus leaf juice in the proportion of 2:3, together with 0.3 % maltodextrin as debitterizing. The fermentation drink of kelp was produced from *L. Japonica* as the raw material by lactic acid fermentation, whose optimal formula is 50 % of natural kelp fermented juice, 0.08 % of citric acid and 2 % of sugar [27].
2. Kelp health tea: Gu et al. [28] has described the processing technology and operation key points of a low-cost but multi-functional natural health drink made from black rice, kelp, and green tea. Citric acid and water solution (2 %) has been applied to remove the fishy flavor of kelp. According to the national food safety standards, kelp has been soaked and washed with water 12–24 h to get rid of extra arsenic salt before further processing. Besides the nutritional values of this seaweed, the addition of kelp extract can be part of stabilizers and thickeners for drink production.
3. Kelp frozen yogurt: Kelp and skim milk powder have been used as raw materials in Fu's study for fermented seaweed and black sesame frozen yogurt [29]. The ratio of kelp to water, the addition amount of sugar and skim milk powder

were taken as 3 factors, respectively, when designed the experiments. The results suggested that when the ratio of kelp to water was 1:20, with 6 % of sucrose, 13 % of skim milk powder and 5 % of inoculating lactic acid bacteria, after fermentation at 42 °C for 24 h, with addition of agar, sugar and black sesame, the final yogurt jelly had unique milky-white color, homogeneous tender, moderate sweetness and rich nutrients.

4. Kelp sausage: A new kind of vegetable-rich sausage product has been developed by Dong's group, which consists of carrot, kelp and pork [30]. This sausage contains great portion of protein, dietary fiber, mineral matter and multi-vitamins, as well as it meets the requirements of modern diet and has a great market value.
5. Kelp chili sauce: Yuan et al. has introduced the preparation of kelp chili sauce with 30 % chili, 10 % salt, 6 % garlic, 5 % kelp, 2 % sugar, 1 % modified starch and 0.7 % xanthan gum to make it delicious and nutritious, besides stimulating appetite and helping in digestion and absorption [31].

86.5 Clinical Evidences

Due to kelp's amazing medical benefits, it has been used as a traditional Chinese medicine since centuries, and it has been listed in the Pharmacopoeia of the People's Republic of China. In addition to PSS, PMS and FPS as mentioned above, kelp has also been used widely in the clinical applications.

86.5.1 Treatment of Infusion Phlebitis

Phlebitis is a common adverse reaction during infusion. Due to relieving swelling and pain effects of kelp, Wang has developed a new treatment using kelp combined with specific electromagnetic irradiation (TDP), and compared with the traditional magnesium sulfate therapy on 184 cases of infusion phlebitis patients which were divided randomly into observation group and control group, respectively [32]. After irradiated under specific electromagnetic wavelength for 20–30 min, the phlebitis area was covered by fresh or rehydrate kelp in observation group. Other than the poor effect of magnesium sulfate control, TDP irradiation increased the absorption efficacy of the mannitol, alginate, iodine and other trace elements from the kelp which reduced the treatment period and satisfied the patients.

86.5.2 Treatment of Ophthalmic Diseases

Kelp eye drops containing vitamin B and C have been reported to treat commotio retinae, vitreous opacities and senile cataract significantly [1]. Studies have shown that the kelp-based iodine could inhibit connective tissue proliferation, enhance inflammatory exudation absorption and accelerate blood circulation. This slowly absorbed and excreted iodine is believed to work more effectively the longer it remains in body than other iodine products.

86.5.3 Other Clinical Applications

Kelp has also been concerned by scholars for its wide original and notable benefits for many other treatments in clinic. Reviews have packed up the documents about the clinical application of kelp, such as thyroid diseases, hypertension, mammary gland hyperplasia, chronic pelvic inflammatory disease, cancer, icteric viral hepatitis, astriction, etc. [33].

86.6 Safety Evaluation and Toxicity Data

As a traditional Chinese vegetable, especially more common in coastal areas, wild and cultured kelp and their extracts have been proved notoxicity and no mutagenic effects in the mice experiments [34]. In intragastric administration doses of 21,500, 10,000, 4640 and 2150 mg/kg, no animal death was observed for five days. Cumulative toxicity test showed no toxic accumulation of *Laminaria* extracts in animals observed within 20 days. Further Ames experiments showed that it did not induce gene mutation to four histidine-deficient *Salmonella typhimurium* strains, which suggested it as a safe food additive and medicinal material. In an experiment where female mice fed normal diet to 2.4 g/kg · day dose and given kelp capsules intragastrically for 18 days, the experimental group showed no significant difference compared with the control group in the indicators of pregnancy rate, implantation rate, embryonic development, fetal body weight, body length, tail length, and bone development [1].

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Chapter 87
Poria cocos (Schw.) Wolf 茯苓 (Fuling, Indian Bread)

Xiao-jun Gou, Gang He and Xiao-qiang Guo

87.1 Botanical Identity

Fuling, *Poria cocos* (Schw.) Wolf, is a saprophytic fungus that grows in diverse species of Pinus. It is a well-known traditional Chinese medicine (TCM) widely used in China and East Asian countries for its diuretic, sedative and tonic effects. It is commonly used as a constituent of many preparations in Asian medicine [1–5].

Fuling has been cultivated on Pinus lamb in large scale in China for the production of sclerotia. Sclerotium globose is irregularly shaped and varies in size, up to 20–30 cm in diameter or larger. Fleshy sclerotium is relatively loose and soft, however, once dried it becomes hard. The outer surface or skin is pale to dark brown over a tuber-shaped. The inner-granular part is composed of a large number of mycelium, the outer layers of which are slightly pink and inner layers of which are white. Sporophore lies on sclerotium, 3–8 mm thick, white, turning brownish when dried. Tube polygon (or anomalistic) is 2–3 mm long and 0.5–2 mm in diameter. Examined under microscope, the basidium is a short claviform. The basidiospore is oblong or columnar [1, 2].

Fuling is the dried sclerotium of the fungus *Poria cocos* (Schw.) Wolf. It is collected mostly from July to September, cleaned, air-dried under the sun until wrinkles appear and the moisture inside is evaporated. It is then further dried under shade. Based on the size of cuttings, it is referred to as "Fuling Kuai" or "Fuling Pian" in the market (Fig. 87.1) [1, 2].

X. Gou (✉) · G. He · X. Guo
Key Laboratory of Medicinal and Edible Plants Resources Development of Sichuan Education Department, Chengdu University, Chengdu 610106, Sichuan, China
e-mail: jmee@cdu.edu.cn

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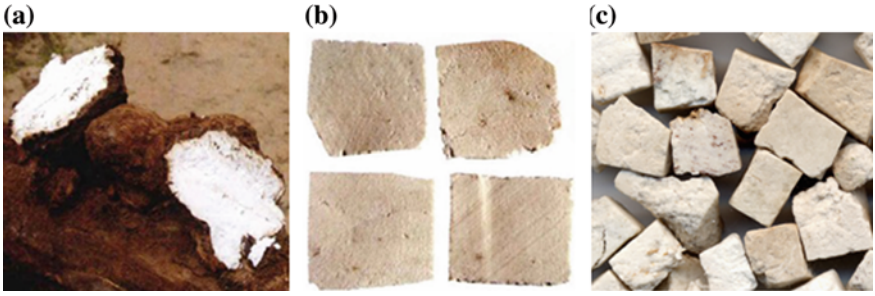

Fig. 87.1 **a** Fuling grown on wood log. **b** Fuling Pian. **c** Fuling Kuai (Reproduced from a colored identification atlas of Chinese materia medica and plants as specified in the pharmacopeia of the people's republic of China)

87.2 Chemical Constituents

Polysaccharides and triterpenes are two major classes of bioactive secondary metabolites found in *Poria cocos* (Schw.) Wolf. Other minor compounds have also been discovered, including steroids, amino acids, choline, histidine and potassium salts [3, 4].

87.2.1 Polysaccharides

Polysaccharides from Fuling, which are the major active components, mainly contain pachyman and heteropolysaccharides. Water-soluble pachyman is with a β-D-(1,3)-,(1,6)-glucan structure, which is only composed of glucose. Heteropolysaccharides, on the other hand, are linear β-D-1,3-glucans with some β-1,6 branches. Monosaccharides of heteropolysaccharides include D-glucose, D-galactose, D-mannose, D-fucose, and D-xylose. Of these D-glucose is the predominant monosaccharide. Heteropolysaccharides of the *Poria cocos* (Schw.) Wolf mycelia obtained from fermentation via submerged cultivation biotechnology, contain mainly D-glucose, D-galactose, and D-mannose, which have the characteristic structure features of α-D-1,3-glucan [6–9].

87.2.2 Triterpenes

In the past decades, several research groups in China and Japan have isolated large numbers of compounds from *Poria cocos* (Schw.) Wolf, including various triterpenes. The isolated triterpenes from Fuling are considered to be derivatives of the lanostane skeleton; however, some differences have been observed (Figs. 87.2, 87.3, 87.4 and 87.5) [3, 4, 9–12].

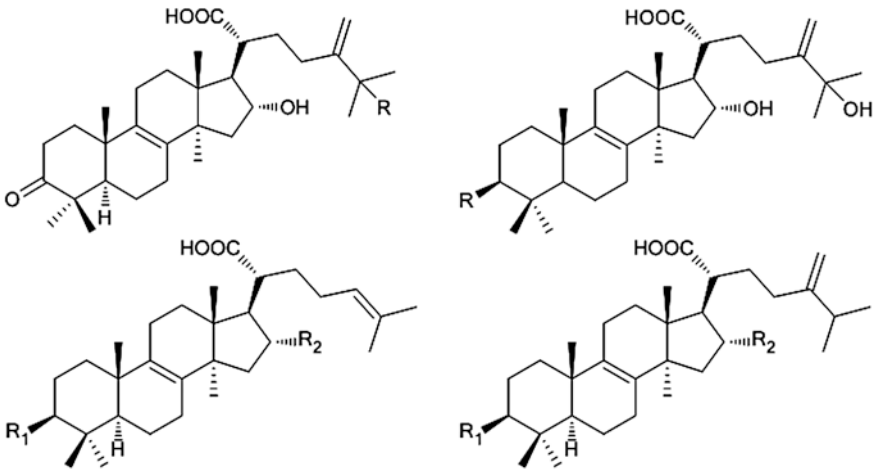

Fig. 87.2 Structures of lanosta-8-ene type triterpenes from Fuling

87.3 Pharmacological Studies

As described previously, Fuling is one of the most popular herbs used in TCM. Modern pharmacological studies have indicated that Fuling has the following bioactivities; anti-tumor, anti-oxidant, anti-inflammatory, antibacterial, anti-diabetic, and nematicidal activities, as well as immunosuppressive or anti-rejection effect, etc.

Fuling polysaccharides have anticancer activity. Daily administrations of Fuling polysaccharides (100 and 200 mg/kg b. w.) for 7 weeks were effective in fully inhibiting tumor cell growth, as detected in groups. Liver tumor weight was effectively reduced by the administration of Fuling polysaccharides in a dose dependent manner in rats of both the groups [13]. Huang et al. obtained three polysaccharides fractions from Fuling, all of which exhibited strong antitumor activities against Sarcoma180 solid tumor implanted in BALB/c mice in vivo and against HL-60 tumor cell in vitro [14]. Wang et al. investigated the water-insoluble native β-(1→3)-D-glucan from Fuling showed no antitumor activity either in vivo or in vitro, whereas its sulfation and carboxymethylation derivatives 20 × 8 (mg/kg × days) dose exhibited good water solubility and manifest against Sarcoma 180 and gastric carcinoma tumor cell in vivo and in vitro [15–18].

Fuling polysaccharides have an anti-inflammatory activity. Fuling polysaccharide stimulates macrophages to produce NO through the induction of iNOS gene expression. Lee et al. demonstrated that treatment with Fuling polysaccharides significantly induces NO production and iNOS transcription through the activation of NF-kB/Rel in the mouse macrophage line RAW 264.7 [19]. Fuling polysaccharide was effective against original-type anti-GBM nephritis in rats and that the antinephritic mechanisms of pachyman may be partly due to the inhibitory action of

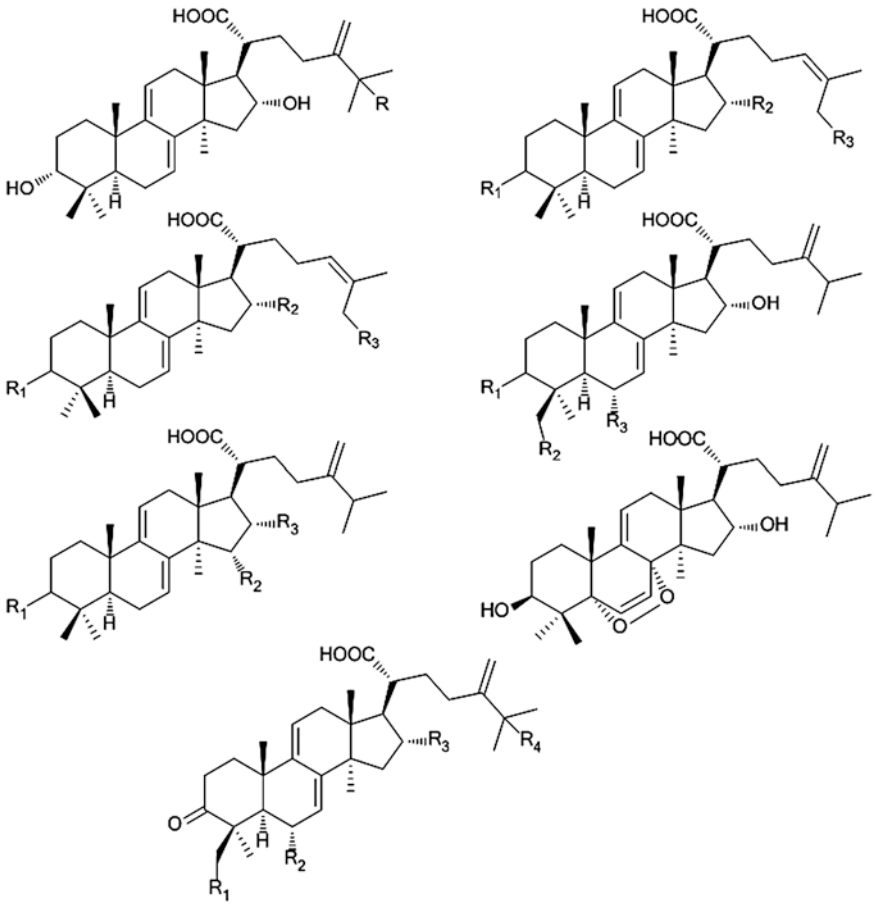

Fig. 87.3 Structures of lanosta-6,9-diene type triterpenes from Fuling

this agent on C3 deposition in the glomeruli. Tomohisa Hattori et al. investigated when Fuling polysaccharide given to original-type anti-GBM nephritic rats for 10 days from the day of anti-GBM serum injection. Results showed that Fuling polysaccharide prevented urinary protein excretion and the elevation of serum cholesterol content, which also reduced the degree of histopathological changes such as, hyper-cellularity and adhesion as compared to the control group. Sun investigated the significantly higher concentration of Fuling polysaccharide to reach the plateau of growth inhibition of treated U937 cells, as well as lower cytokines secretion after stimulation, showing that immune response in male collegiate wrestlers to the polysaccharide [20].

Triterpenes isolated from Fuling are shown to have potentially beneficial effects on certain diseases such as rheumatoid arthritis, psoriasis, autoimmune uveitis, septic shock, and possibly bronchial asthma. These triterpenes also exhibited potent

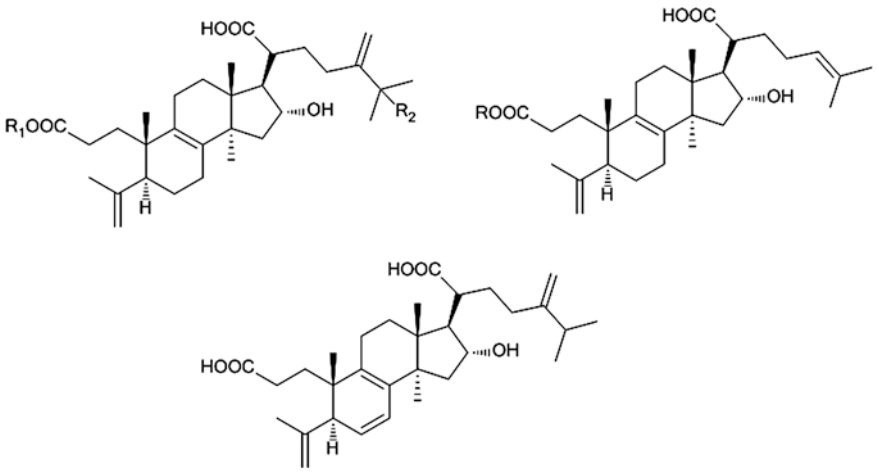

Fig. 87.4 Structures of 3,4-seco-lanostan-8-ene type triterpenes from Fuling

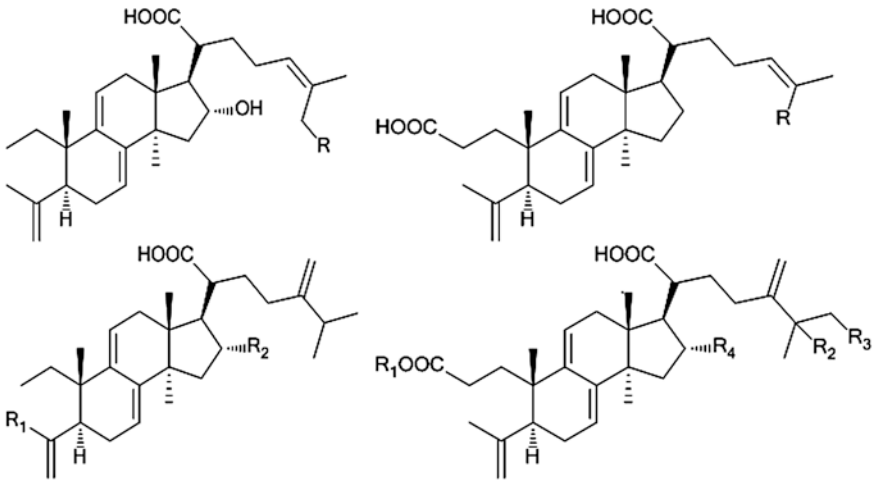

Fig. 87.5 Structures of 3,4-seco-lanostan-7,9-diene type triterpenes from Fuling

cytotoxicity against human cancer cells, insulin sensitizing effect related to anti-hyperglycemic activity and anti-inflammatory potential by regulating the activator protein-1 signaling pathway. Cai et al. obtained eight triterpenes compounds from the dried Fuling, 29-hydroxydehydrotumulosic acid (1) and 29-hydroxydehydropachymic acid (2), dehydropachymic acid (3), dehydrotumulosic acid (4), 29-hydroxypolyporenic acid C (5), polyporenic acid C (6), tumulosic acid (7), and pachymic acid (8), these triterpenes isolated compounds reduced nitric oxide (NO) production by lipopolysaccharide (LPS)—induced RAW 264.7 cells. With compounds 5 and 6, the IC50 values of which were 16.8 ± 2.7 and 18.2 ± 3.3 μM,

respectively, exhibited the greatest inhibition activity. Luciferase assays on activator protein 1-dependent gene expression, and Western blot analysis conducted on cells pre-treated with compounds 5 and 6 revealed that the inhibited NO release was attributed to the reduced expression of iNOs enzymes [21].

87.4 TCM Applications and Dietary Usage

87.4.1 TCM Applications

Fuling is one of the most common herbs traditionally used in herbal medicines and health-maintaining products, and has been demonstrated to have spleen-invigorative, stomach-tonifying, sedative, tranquilizing, diuretic, and damp-clearing effects. It is used alone, or in combination with other herbs based on TCM theory.

For example, a common Fuling preparation that is clinically used, Guizhi Fuling Pill or Capsule [1] is composed of five herbal items: Guizhi (twig of *Cinnamomum cassia* Presl), Fuling, Mudanpi (root bark of *Paeonia suffruticosa* Andr.), Baishao (root of *Paeonia lactiflora* Pall.), Taoren (seeds of *Prunus persica* (L.) Batsch.). There are hundreds of manufacturers making this product legally based on the same formula in China. It is mainly used for promoting blood circulation and removing blood stasis. It is also used for female breast cystic hyperplasia and prostatic hyperplasia caused by blood stasis syndrome.

87.4.2 Dietary Usages

As one of the most famous TCM herbs and valuable dietary fungus materials, Fuling has been used in many ways historically. These include Fuling Jiabing, Fuling wine, Fuling cream and Fuling chestnut porridge. The dietary forms can be easily made at home.

87.4.2.1 Fuling Ja Bing

Fuling Ja Bing, also known as Fuling Bing or Tuckahoe Pie, is a traditional snack food of Beijing and is an integral part of the city's culture, originated from being a snack served to the royal family in the Qing Dynasty [3]. It is a pancake-like snack made from wheat flour, sugar, and Fuling, rolled around nuts, honey, and other ingredients. A variety of ingredients can be rolled into the pancakes to make different Fuling Fuling. The pancakes can be carved into beautiful patterns.

87.4.2.2 Fuling Wine

Poria cocos (Schw.) Wolf itself or combined with other herbs can be used to prepare herbal wine for the deficiency of Qi and blood, back pain, fatigue, impotence, spermatorrhea, premature white hair, palpitation and insomnia and loss of appetite. Herbal ingredients for this wine include Fuling (60 g), Dazao (fruit of *Ziziphus jujuba*, 20 pieces), Danggui (root of *Angelica sinensis*, 12 g), Gouqizi (fruit of *Lycium barbarum* L., 12 g), and white spirits (1500 mL). All of the herbal materials above are chopped, soaked with white spirits, sealed for 15 days and shaken once every 3 days. Suggested to take 10–15 mL twice a day for the above mentioned deficiency symptoms.

87.5 Clinical Evidences

As a therapeutic medicine, Fuling is mostly used in combination with *Cinnamomum cassia* Presl. For example, Guizhi Fuling Pill and Guizhi Fuling Capsule are two major preparations made with Fuling. Numerous clinical reports and observational studies have shown the positive effects of Fuling and related preparations, for example it has been found to; promote blood circulation, removing blood stasis, diuresis, invigorate the spleen, resolving phlegm, calming the heart, tranquilizing the mind, and possibly anticancer applications.

87.6 Safety Evaluation and Toxicity Data

Of the few clinical reports available on Fuling, none report toxicity or side effects. With regard to the potential cytotoxicity of *Poria cocos* (Schw.) Wolf, no report was found in literature. This fungus is usually administered in China at high doses (up to 45 g), with no indication or report of adverse effects.

As narrated above, Fuling is a relatively safe herbal medicine often used for polyuria, spermatorrhoea, or urogenital prolapse. It is strongly advised to consult with your doctor before use of Fuling, as it has a strong biological activity and cannot be consumed as regular food.

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Chapter 88
Sargassum fusiforme (Harv.) Setch. 羊栖菜 (Yangqicai, Hijiki)

Yanze Liu

88.1 Botanical Identity

Sargassum fusiforme (Harvey) Setchell (syn. *Hizikia fusiformis*), also known as Yangqicai in Chinese and Hijiki in Japanese, is a brown marine plant which can be found growing in abundance on rocky coastlines around Japan, Korea, and China. Yangqicai was first recorded in Shennong Bencao Jing dated in 200 AD as a traditional Chinese medicine with the name of Haizao (seaweed) to treat Yingliu (tumor-like induration), edema, and dysuria etc. [1]. Yangqicai is also used as a traditional food due to its rich dietary fiber and essential minerals such as calcium, iron, and magnesium etc. As a health food, it has and continues to become more popular amongst the Chinese, Korean, and Japanese cultures (with the name of long-life vegetable), as well as in the UK and North America, especially in natural food stores and Asian-American grocery stores.

Living *S. fusiforme* [2] ranges from green to brown in color when found in the wild. The algae body is hypertrophy and juicy, generally with a height of 30–50 cm, and up to 2–3 m for cultural one. There are four parts that form the algae body including rhizoids, stems, leaves, and airbags. The variation of frond shape is large; depending on the north-south geographical environment. Northern populations have intensive branches and leaves, flat and wide airbags with multi-tooth, while southern strains have long and thin branches and leaves, and linear or rod shaped airbags. The fishermen and professional divers can harvest the Yangqicai with a sickle at the time of the low tide in the spring from March to May. After collection, it is boiled and dried. The dried Yangqicai turns black and is then sold in stores.

Y. Liu (✉)
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, 100193 Beijing, China
e-mail: yzliu@implad.ac.cn

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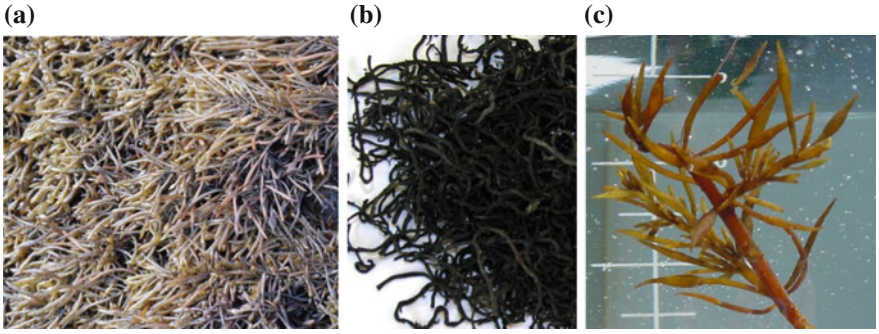

Fig. 88.1 Fresh (**a**), desiccated (**b**), and recovered (**c**) Yangqicai by soaking in water

To cook dried Yangqicai it is necessary to soak it in warm water until fully expanded. It's fairly difficult to recognize the Yangqicai plant in its black and dry form, however after soaking and fully expanding it will become much easier. Figure 88.1 illustrated the forms before soaking in warm water and after.

88.2 Chemical Constituents

Polysaccharides are noted early on and extensively investigated, including the extraction technology, structure analysis, and biological activities etc. Plant sterols, minerals, fatty acids, and vitamins are also studied chemically and biologically.

88.2.1 Polysaccharides

Approximately 20–70 % of total carbonhydrates (polysaccharide) exist in dry weight of Yangqicai. Most of the researchers focused on the polysaccharides including bioactivities, extraction and purification technology, content determination, and structure analysis. The basic protocol to extract and purify the polysaccharide is water-alcohol method, i.e. to extract ground Yangqicai with boiling water and then precipitate with alcohol after concentration. The precipitate containing polysaccharides are then purified through repeated water-alcohol precipitate process and then removal of proteins and minerals. The reliable content of polysaccharide reached 53.46 % of dry weight [3]. However, the yield of total polysaccharides extracted by various improved technologies was just 10.0–24.35 % [4–6]. Structural analysis showed that the composition of Yangqicai polysaccharide was mannose

(46.4 %), glucuronic acid (50.5 %), and minor galactose. Proposed basic structure is β-D-GlcA(1 → [2)-α-D-Man(1 → 4)-β-D-GlcA(1 →]$_{n1}$ → 4)-β-D-Gal(1 → [4)-β-D-GlcA(1 → 2)-α-D-Man(1 →]$_{n2}$ → 4)-β-D-GlcA(1 → 2)-α-D-Man [7].

88.2.2 Plant Sterols

The plant sterols reported so far included fucosterol (1), 24*R*, 28*R* and 24*S*, 28*S*-epoxy-24-ethylcholesterol (2), 24-hydroperoxy-24-vinylcholesterol (3), 29-hydroperoxy-stigmasta-5, 24 (28)-dien-3β-ol (4), (24*S*)-5, 28-stigmastadien-3β, 24-diol (5), and (24*R*)-5, 28-stigmastadien-3β, 24-diol (6) [8], and saringosterol (7) [9].

88.2.3 Fatty Acids

There was a low total fatty acid content of 2.2 g/kg in Yangqicai. The ratio of unsaturated fatty acid and saturated acid was about 60:40. 65 % of saturated fatty acid was palmitic acid [10], which was very interesting with the later discovery of anti-HIV activity by this compound [11]. The main fatty acids isolated from Yangqicai are illustrated in Fig. 88.2.

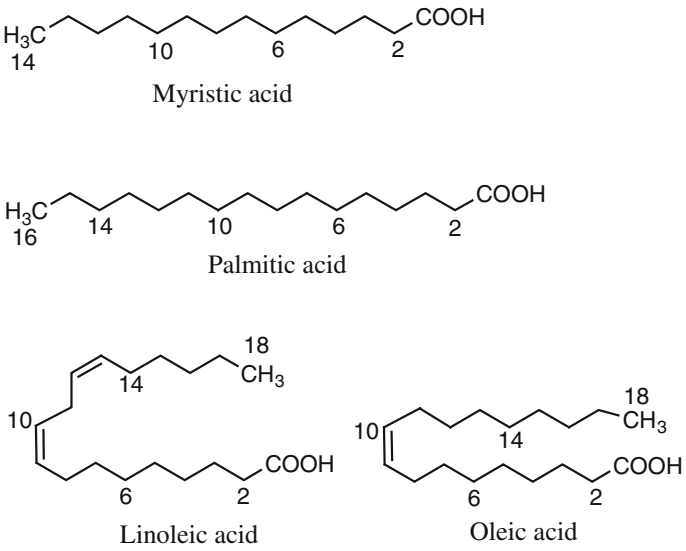

Fig. 88.2 Representative fatty acids isolated from Yangqicai

88.2.4 Other Nutritious Components

Except for total carbonhydrates (~57.8 %) and fatty acids (~2.2 %), Yangqicai contains about 14.8 % of crude proteins, 6.4 % of crude fibers, and 23.9 % of ash. Seventeen amino acids including eight essential amino acids were detected from hydrolysate of crude protein. Vitamin C (0.0217 %) and E (0.0014 %) were main vitamins detected. For minerals and trace elements (mg/kg), I (241.4), Fe (89.0), Zn (19.0), and Li (49.6) are major trace elements besides general minerals Ca (1.3 %) and K (3.1 %) [10]. Very high contents of Sr (0.028–0.086 %), Fe (0.28–0.86 %), and Si (0.28–0.86 %) need to be further confirmed [12].

88.3 Pharmacological Studies

Inspired by the traditional experience and literature record, most of the pharmacological researches focused on its antitumor activity, which could be linked to the function of treat Yingliu (tumor-like induration). From screening, more activities such as antitumor, antivirus, immunomodulation, hypoglycemic, and antihyperlipidemic effects etc. were investigated.

88.3.1 Antitumor Activity

One of the publications reported that the antitumor activities of Yangqicai polysaccharide (SFPS) were observed in vivo by testing the tumor weight of S_{180} mice and survival time of H_{22} mice. MTT and colony-forming methods were applied to study the antitumor activities in vitro, and the influences on cell cycle and apoptosis of SFPS were observed by FCM. The results showed that SFPS produces potent antitumor activities to SGC-7901 and COLO-205 by inducing the apoptosis of tumor cells [13]. Further studies revealed that the apoptosis was associated with the increase of intracellular calcium concentration, where the intracellular calcium store releases the calcium during its action [14]. More researches on the mechanism also proved that SFPS exerts antitumor activities through markedly enhancing the immune function of normal and S-180 sarcoma transplanted mice [15, 16].

88.3.2 Antivirus Activity

MTT method was used to evaluate the antiviral effects and mechanism of SFPS on herpes simplex virus type l (HSV-1) and coxsackie virus (CVB_3) using four different methods. The results showed that the SFPS not only killed the above viruses

directly but also restrained them from getting into cells or absorbing on the surface of the cells, while the cytotoxicity of all extracts and SFPS on Vero cells were undetectable (CC_{50} > 5 000 mg/L), and the purer, the stronger of the activity [17].

During screening for anti-HIV agent, the water decoction of Yangqicai showed significant anti-HIV activity by comparing with other herbs and positive control. But, when testing the polysaccharide part which was obtained through 70 % acetone extract and precipitated with alcohol after concentration, no activity was observed. Interestingly, the activity was found from the oily part which was obtained from the precipitate after concentration of 70 % acetone extract solution. Further purification guided by bio-assay, palmitic acid and related fatty acids were isolated and palmitic acid showed the strongest activity on HIV-1 to inhibit the fusion process of HIV-1 entering CD4 [18].

88.3.3 Immunomodulating Activity

Immunomodulating activity is one of the main mechanisms of polysaccharide and herbal medicines against various cancers. SFPS markedly increased the weight index of thymus and spleen in normal and tumor-bearing mice. The activity of NK cells and the function of macrophages in mice were significantly enhanced by SFPS at doses of 20 and 40 mg/kg, suggesting that enhancing the immune function of mice was one of its mechanisms to inhibiting the growth of sarcoma in mice [15, 16].

88.3.4 Antihyperlipidemic Effect

In order to investigate the antioxidant effects and mechanism of Yangqicai in hyperlipidemia rats, forty healthy female Wistar rats were used to establish hyperlipidemia models by feeding fat-rich forage, and then the raw material powder of Yangqicai was applied for two weeks. Simvastatin was used as positive control. The levels of serum lipid including the triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were detected by oxidase assay. The results indicated that the levels of serum TG, TC, and LDL decreased while HDL significantly increased in both the test and positive control group than those in model group rats ($P < 0.05$). Mechanism studies revealed that the effect was caused through antioxidant effect of active component from Yangqicai on lipid metabolism by increasing the activities of SOD and GSH-PX [19].

88.3.5 Other Effects

Experiments showed that SFPS can significantly lower the levels of blood sugar, serum and pancreatic tissue lipid peroxide in alloxan-caused diabetic mice, while no affect to normal fasting mice. SFPS can also significantly improve the tolerance of sugar [20]. Yangqicai decoction showed hepatoprotective activity for experimental high-fatty rats against fatty liver [21]. Anticoagulant of fucoidan, a kind of SFPS, was also observed to be effective in an in vitro test [22].

In order to understand whether the SFPS has anti-fatigue effect on mice, the body weight, swimming time with load, activity of blood SOD, content of blood MDA, liver glycogen, muscle lactic acid, and the content of urea nitrogen in blood were measured after 15 days administration with different doses (50 and 150 mg/ml d) of SFPS. The results showed that there was no significant difference on the body weights between control and test group ($p > 0.05$). However, the swimming time, activity of SOD and concentration of liver glycogen were enhanced while the concentration of MDA, muscle lactic acid, and urea nitrogen in blood were decreased, indicating that the SFPS had an anti-fatigue effect on mice [23].

88.4 TCM Applications and Dietary Usage

88.4.1 TCM Applications

As mentioned previously, Yangqicai (Haizao, seaweed) has been used as Chinese materia medica thousand years ago. In the theory of TCM, the property of taste Xian (salty) and the function of Xiaotan Ruanjian which means desolving "sputum" and softening induration, and Lishui Xiaozhong which means diuresis and reducing swelling was used to treat Yingliu (tumor-like induration), edema, and dysuria etc. The amount of 10–15 g raw material was recommended in decoction, pill or powder for therapeutic purpose. As a fundamental principle of TCM theory, Yangqicai cannot be used together with Gancao (Radix Glycyrrhizae) [1].

88.4.2 Dietary Usages

Yangqicai contains a high content of calcium, iodine, magnesium, carbohydrate, protein, and dietary fiber. It is said to aid in skin and hair health and prevent anemia. The high iodine content also makes it ideal for fighting goiter. Besides the therapeutic purpose, Yangqicai is very enjoyed as part of Asian cuisine for its beautiful name "long-life vegetable" and desirable taste. A lot of people enjoy adding Yangqicai to soups or mix with other vegetables to make cold dishes. For any dishes, the dried plants must be soaked thoroughly to soften the desiccated tissues before cooking.

Yangqicai can also be processed to be dry powder, sauces, extract, drink, tea bag or instant tea, and then further to bread, cookie, and so on. For most of cases, it's necessary to remove the smell for the final product.

88.5 Clinical Evidences

There are a few uncertain clinical reports on crude Yangqicai or processed products. 50 cases of children with high blood lead were given Yangqicai Capsules, and the control group was given the placebo (starch) for a month. The result showed that the amount of urinary lead excretion was significantly increased, compared with pre-test. The amount of urinary lead excretion after 10 and 20 days of administration in the experimental group was significantly increased by comparing with the control group. Furthermore, the urinary calcium and zinc excretion showed no significant difference, indicating that the Yangqicai Capsules can promote lead excretion on children with high blood lead [24]. Some reports also reported that the Polysaccharide Sulfate Injection (i.v) chemically modified from SFPS was clinically effective for the treatment of ischemic cerebrovascular disease and some other diseases [25], but the side effect to cause priapism was also reported [26].

88.6 Safety Evaluation and Toxicity Data

There is no clinical or dietary toxicity reported thus far. For animal acute test of SFPS extract for mice, the maximum tolerated dose is equivalent 1440 times of clinical daily use with 60 kg of body weight, while no LD_{50} detected, which means the toxicity is very small or nontoxic [27].

There is a potential risk should be reminded that the content of arsenic is higher than regular standard either as food or medicine. Recent studies have shown that Yangqicai contains a higher quantity of potentially toxic arsenic up to 64 ppm [28].

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Latin Index

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