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ISBN 978-3-319-74209-0 ISBN 978-3-319-74210-6 (eBook)
https://doi.org/10.1007/978-3-319-74210-6

Library of Congress Control Number: 2018935134

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Printed on acid-free paper

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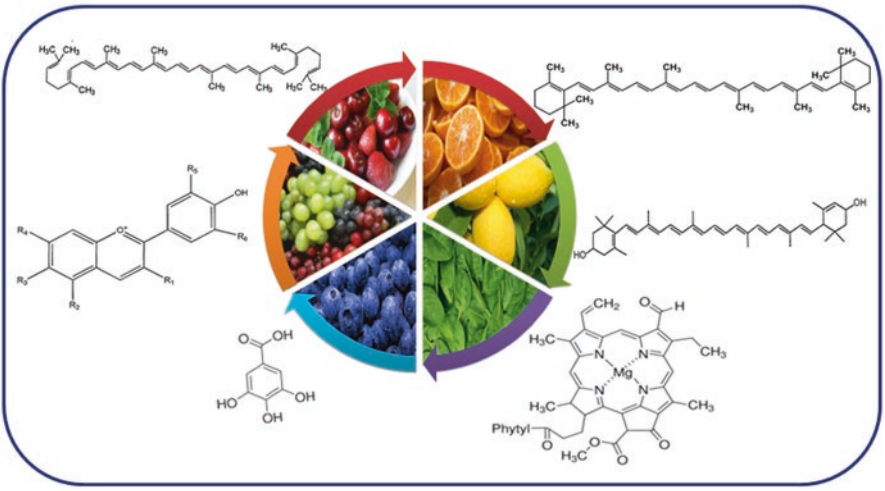
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Food is essential for each and every living organism on Earth. Especially, naturally available foods, i.e., fruits and plants, are being widely consumed throughout the world. Moreover, current research is mainly focused on the utilization of biomolecules present in fruits for biomedical applications. Hence, the isolation and identification of the natural products/biomolecules is a vital task to be played. The natural products or bioorganic phase from food sources as pure compounds provides many applications in the food and pharmaceutical industry. As extraction methods play an important role in isolation of the bioorganic phase, the different extraction processes for each bioorganic phase are discussed in detail.



In this book, Chaps. 1 and 2 deal with the importance of food science and provide an introduction about food science technology. Chapters 3, 4, and 5 discuss about the extraction process of bioactive compounds and the difference between conventional and nonconventional method and characterization. Chapter 6 by

Aparanjitha and Samratha explains about cardamom species in food and its commercial application. Chapters 7 and 8 focus on phytochemical, pharmacological, and total synthesis of bioactive compounds isolated from various food sources. In Chap. 9, the antidiabetic activity of fruits is summarized by Papitha et al. The importance of food science in nanotechnology is explained in Chaps. 10–15.
Thanks for reading.

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G. Madhumitha is presently working as assistant professor at the Department of Chemistry, School of Advanced Sciences in Vellore Institute of Technology, Vellore. She has been teaching unit process in organic synthesis, environmental studies, and engineering chemistry to UG students since the last 5 years. She did her B.Sc. degree in applied science from Coimbatore Institute of Technology, Coimbatore; M.Sc., M.Phil., and Ph.D. from Vellore Institute of Technology, Vellore; and M.B.A. from Bharathiar University, Coimbatore. She has published more than 30 research papers in international journals of repute. She has received the Young Scientist Award (FTYS-Scheme) from the Department of Science and Technology, New Delhi. In the last 5 years, she has received the Research Award from Vellore Institute of Technology. Currently, five research scholars are doing their Ph.D. work under her. Also, she is guiding B.Tech. and M.Sc. students. Recently, she has received the Abdul Kalam Scientific Excellence Award by Marina Lab, Chennai. She is also an editorial member in international and national peer-reviewed journals. She has contributed in more than ten book chapters in the field of natural products, food science, and nanomaterials. Her research area of interest includes natural products, bioactive materials, nanomaterials, and organic synthesis. She has been honored several awards from different organizations, e.g., best poster, best oral, research award, young researcher awards, etc.

Chapter 1
An Introduction and Overview of Food Science on Day Today Life

S. Mohana Roopan and Ganesh Elango

Abstract Food science is said to be one of the vast developing fields all over the world. This chapter completely deals about the brief introduction of food science, its origin, evaluation, storage techniques, packaging, etc., This food science can be evolved from different types of sources, like plants and animals which plays a major role in day today life. This chapter also comprises of important components present in the food science such as carbohydrates, proteins, vitamins, fats, oils, etc., and also this chapter deals about the importance of food technology in various applicational studies, for example, nanobiotechnology, agricultural fields, etc., overall this chapter comprises of importance about food science and its regulation which will facilitate the upcoming researchers to focus on food science.

Keywords Origin and evaluation · Major components · Nanotechnological and agricultural applications · Storage and packaging

1.1 Introduction

Food science is one of the rapidly growing fields in all over the world. In an easier way it is known to be a major scientific way to study about food and its regulation. Food science comprises of various applicational disciplines like health science, biochemistry, chemistry, biology, physics, genetics, nutritional science, statistics, etc., are utilized to deliver a safe and nutritious product to the consumers (Smithers 2016). From past decades processing of food were done using three common methods namely, fermentation, drying, and salting, these above mention processes were performed by a mankind before 2 million years (Wrangham 2009). Food science stated to be one of the vast areas of science which has various definitions as follows;

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_1

Integration of several basic sciences which together focus on the unique challenges associated with foods and the systems needed to deliver food products to the consumer, Application of basic sciences and engineering to study the physical, chemical, and biochemical nature of foods and the principles of food processing (Potter and Hotchkiss 1998). Overall food science comprises of the major process said to be processing of food. This food processing contains several fundamental aspects like nutritional value, safety aspects, the convenience of consumer, product acceptance and minimization of cost. This fundamental aspect plays a major role in various applicational disciplines (Knorr 1999).

Cultivation of crops and domestication of animals were an achievement for humans. The Bronze Age was the beginning for humans to prepare varieties of food which can be stored and stop exploiting animals for food (Hardy 1999). Food is a substance which provides nutrition to grow and maintain health. A healthy diet and regular physical activity is the foundation of good physical and mental health. Consuming healthy food is not very complicated only calories count and variety is important. Food science is the scientific discipline deals with chemical, biological, physical, microbiological and other important aspects of food.

Human being depends on plant and animals for essential nutrients like carbohydrates, fat, protein, vitamins, minerals etc. Each and every component of nutrients has to be taken in the proper amount. The energy intake should be balanced with the corresponding energy expenditure. The poor intake or unbalanced diet is the main reason for reduced immunity.The balanced diet can prevent foodborne diseases and malnutrition. Fats, proteins, carbohydrates, vitamins, minerals intake should be managed according to the profession and activity. Physical fitness is the ability to perform daily physical tasks without fatigue; it involves muscular endurance, flexibility, body strength, body fat composition. The diet plan is most important while training for athletes. Each and every nutrient has its own significance. For example- The athletes require more calories with high protein and carbohydrates content due to the involvement in more physical activities. Food sciences analyze and study the change which occurs during the different process of production, storage, and packing. The quality of the prepared food depends on parameters like temperature and composition change during the preparation, pressure change during packing, the use of different gases during the production and packing. Plant and animals are the main sources of nutrients for human beings. Most of the nutrition can be obtained and fulfilled from plants directly. A country like India mainly depends on plants for food. Most of the crops like maize, wheat, rice results from plant seeds. Plants have different edible parts- roots, stem, flowers, leaves and most importantly fruits which are main sources of vitamins for humans. Poultry farm is a place where rear birds and animals are nourished with eggs, meat, milk. Animals are used directly for meat and indirectly for milk, eggs etc. Milk is one of the most important sources of calcium and protein. Plants generate food by the process of photosynthesis. It is a process which converts light energy into chemical energy by consuming carbon dioxide. Green plants are classified as photoautotrophs. Prototroph are organisms which are able to synthesize their food themselves using light as the source of energy. As a result of photosynthesis, sugars are obtained which can readily be

consumed by humans. Nowadays, many people find wine tasting a recreation. Preparation of wine involves the process of fermentation. The preparation of the wine is a scientific process and involves attention. The appearance, clarity, odor, taste, after-smell, finishing depends on the time of aging and the process. The clarity of the wine is viewed at the angle of 300–450 against the bright light. The viscosity of the wine is affected by sugar, alcoholic and glycerol content. The study of the wine requires analytical chemistry techniques for inspection. Nutrition supports illness and takes care of human health. Based on the availability of the food resources, the flavors and the diet varies from country to country. For example- the extensive production of coconut in the southern part of the India makes the coconut oil first choice for cooking. Coconut oil is one the healthiest oil available. It contains medium chain fatty acids which are saturated and makes it easy to digest. Agencies like International Association for Food Protection, World Resources Institute, World Food Programme, Food and Agriculture Organization, and International Food Information Council monitors the food security and safety. According to World Health Organization (WHO), children under the age of 5 years are more prone to foodborne diseases. Long-term intake of contaminated food can cause long-term health problems. Awareness is biggest problems for the countries fighting foodborne diseases.

1.1.1 Food Science Origin and Evolution

This food science can be practiced by thousands and thousands of years ago, maybe before history was recorded food science has been practiced (Wrangham 2009). The above-mentioned author stated about that the fire was invented before 2 million years ago to cook food and also he stated that the treatment of heat plays a major role for processing of food in several industries (Henry 1997; Floros et al. 2010).

Nowadays the transformation of food is completely reliable on reactions performed by enzymes, in another term it can be called as fermentation. These processes of fermentation were introduced several past decades. In ancient days several processes of molecular systems were involved by fermentation engineers and food enzymologist, Examples like flat bread are prepared from bread dates in 30, 000 BC, whereas these type of bread were still prepared in several countries in Egypt, North America, Europe, etc., (McGee 2007). Then Beer and wine product were also invented in ancient dates back to 7000 BC by the process of fermentation and contamination of spore yeasts (Mirsky 2007). Recently most of the peoples focusing on bread and cheese, but these products are explored back about 6000 BC by fermentation of food product said to be milk (Michel et al. 1993). These are some of the important ancient food regulations like, cooking, storage, processing and transformation which elaborate the heritage of food science in olden days (Dornbusch 2006; Farhat-Holzman 2014). In later 18th and 19th century the revolutions protested by industry modify the entire society which leads to loss of habitat and scarcity of food materials and also it leads to increase in the population through improved health,

medical facilities, and better sanitation. This population increase has to feed with food, whereas identified that the nineteenth century would suffer in hunger and starvation due to unpredictable increase in population growth.

To overcome these drawbacks (Henry 1997; Floros et al. 2010) came to an output of mass production of food for providing food to the rapidly growing population. But this mass production also has a drawback of storage and transportation. For this transportation and storage process, Louis Pasteur thermal treatment known as Pasteurization plays a role to increase the shelf life of foods and also decrease the bacterial contaminants of the food material which are packed and transported. These Pasteurization processes were majorly utilized in several industrial sectors of food processing.

In the recent era, the field of food science grows rapidly due to development of the technology of food science and various disciplines of engineering. Moreover, nutritional sciences were elaborately understood the major and minor components of food and food sources (Micro and macronutrients). Further, the analytical chemistry tends to identify the food adulteration. The modern science of food processing was stated by Henry 1997 which extends the automation of food processing, pasteurization, non-thermal development of food process, dehydration, concentration, etc. The modern food science professional could be a chemist, biochemist, physicist, molecular biologist, a chemical engineer, nutritionist, or even a mathematician, not to mention the many other science and engineering pursuits that form the meld that is food science. The evolution of food science, particularly over the past century, has been punctuated by the exciting intersection of the many basic science and engineering disciplines. Food science has transitioned from a very empirical pursuit to one that's dominated by a strong fundamental science base that has underpinned the research and development responsible for the myriad of successful food products and ingredients available today.

1.1.2 Food and Its Sources

Plants and animals are major sources of food, provides energy to do work. Animals are not only taken directly as meat but products like milk and eggs can also be obtained. The food derived from animals are not consistent, it depends on breeding. The productivity can be increased via hybridization but not necessarily.

1.1.3 Plant Sources

Meat, poultry, and fish can provide a high amount of protein with subsequently less fat, but it is not always true as skinless white-meat is low in calories and fat. Due to the high amount of protein in meat, it helps in building and repairing body tissues, protects the body from infection and strengthens the immune system. The meat is

high in vitamins and minerals like iron, zinc, selenium content. Iron is responsible for carrying oxygen in our body by forming a complex with hemoglobin. Creative levels are usually found to be low in vegetarians than people who consumed meat; it can increase brain functioning and level of oxygenated hemoglobin (Benton and Donohoe 2011; Fowsiya et al. 2016; Fowsiya and Madhumitha 2017).

Killing animals for food can lead to an imbalance of ecosystem. According to Environment Protection Agency, killings animals for food is a major cause of water pollution. The parenting of these animals involves consumption of plant, crops, water, fossil fuels and soil. Many of the forests are cleared for cropping and generating food for animals which leads to a problem like soil erosion. Animals like cows, chicken, pig or fish consume much more resources than corresponding obtained meat. Milk contains proteins, amino acids, fat and other nutrients. It can easily fulfill the basic daily nutrition need for young ones. The content of fat and protein in milk depends on the breed of the cow or buffalo and its stage of lactation. Milk protein comprises of caseins, whey proteins, serum albumin and immunoglobulin (Givens and Shingfield 2004). The protein in cow's milk is higher in casein than whey protein (Haffman and Falvo 2004).

1.1.4 Food Safety

Easy going management during technical development in processing, packaging, distribution, and storage can lead to the growth of the pathogenic organism in food. The competition between food industries is increasing. Due to the competition, industries are practicing fraud and adulteration. Adulterants can be easily mixed with food and can be very difficult to detect to detect. The addition of adulterants can be profitable for companies but sometimes can be compromising for consumers and may result in health problems. These substances can lead to health and economic problems for global food industries. To detect these adulterants, techniques like near infrared, mid-infrared, Raman spectroscopy, electronic noises, and tongues are taken into account (Ellis et al. 2016). Addition of water to milk, selling skimmed milk as whole milk, the addition of an artificial sweetener and synthetic preservatives to food are some of the common practices which involve adulteration.

1.1.5 Balanced Diet and Healthy Guidelines

A balanced diet is a diet which comprises of a variety of food and provides an adequate amount of each nutrient to maintain health. As it is already discussed before, the nutrients intake depends on age, gender, profession and performed activities. The fruits, vegetables, whole grain, lean proteins, nuts are taken to fulfill daily calories needed. The energy consumed from food is calculated in terms of calories. Calories are a unit to measure the energy and are equal to 4.2 J. To function in

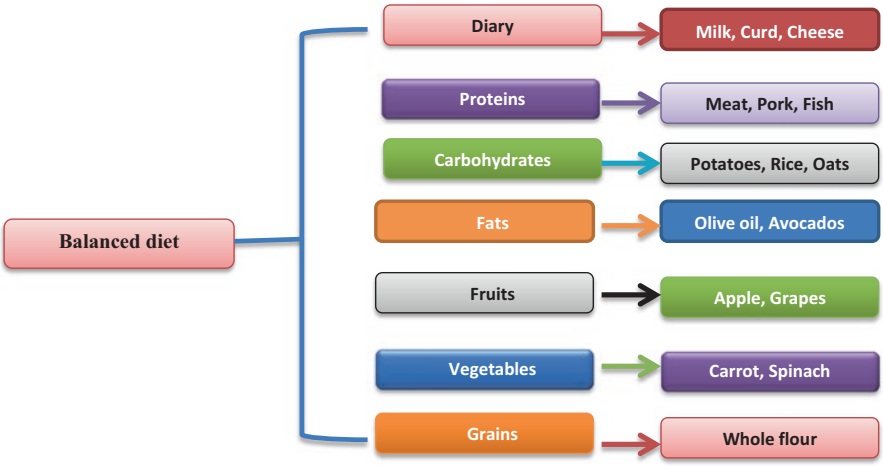

Fig. 1.1 Major constituents of balanced diet

proper way body tissues and organs requires an adequate amount of nutrition. Without good nutrition, the body is more prone to diseases, infections, and fatigue. Even if the person is fulfilling the required amount of calories and not taking a healthy diet, it can lead to obesity and diabetes.

1.1.6 Major Components of Balanced Diet and Their Importance

Major components in food cycle for maintaining balance diet were clearly illustrated in Fig. 1.1.

1.1.6.1 Carbohydrates

Carbohydrates are macronutrients as they are a major source of energy. It provides energy to the central nervous system. The carbohydrates are classified as simple and complex. As it can interpret by given names, simple carbohydrates are easy to consume whereas complex carbohydrates take some time to digest. Simple carbohydrates are monosaccharide's and usually, exist as fructose in fruits. These are present in soft drinks, candy etc. which are considered as empty calories and responsible for weight gain. Whereas complex carbohydrates are polysaccharides present in bread, corns, potatoes. A complex carbohydrate usually takes time to digest.

1.1.6.2 Proteins

Proteins are building blocks for the body. They are responsible for catalyzing metabolic reactions, DNA replications, repairing the muscle tissues in the body. Proteins are amino acids and are classified into two categories: essential and non-essential. The body requires minimum 0.8 grams of protein per 20 pounds of body weight (Livingston 1972). The deficiency of proteins can cause muscle loss, growth failure and decreased immunity. According to the studies conducted by Harvard University, even small consumption of red meat on regular basis can increase the risk of cardiovascular diseases (Bernstein et al. 2010; Pan et al. 2012; Bernstein et al. 2012).

1.1.6.3 Fats and Oils

Fat is one the most important macronutrients. The fat supplies immediate energy and is stored in excess of the body for immediate energy requirement. Fats and oils are classified on the bases number and type of bonds present between the carbon atoms. Oil is the fat with small unsaturated fatty acid and normally exists in liquid form at room temperature. Due to close packing of saturated fats, it exists as solid at room temperature. Vitamins A, E, K, and D are fat soluble and can only be digested or absorbs with fat.

Malnutrition is a serious condition due to the improper intake of nutrition. An overdose of certain specific nutrition like fat can lead to obesity. Malnutrition is the result of undernutrition. Poor intake of nutrients results to undernutrition. Weak muscles, tiredness, low mood, anxiety, sudden decreases in weight, infections are some of the common symptoms of malnutrition. Healthy and balanced diet is the best way to prevent malnutrition. People have right to decide how many children they have to give birth. This is the reason why people of countries like India are sometimes enabling to meet their daily nutrition need. Family planning an important role in controlling the population and fulfilling persons daily nutrition need. A women's body can exhaust by repeated pregnancies, a women should at least wait for two years before getting pregnant again. Healthy diet and balance of nutrients is the most advised by the doctors to have a healthy baby. Citizens of developing countries face problems in acquiring proper and adequate food which is unacceptable. Every person on this earth has right to eat healthy food, the wastage of the food should stop which can done by spreading awareness among people.

1.1.6.4 Nanotechnology in Agriculture and Food

Nanotechnology gives new possibilities for the food and agricultural industries and several programs may be observed at one kind of meals manufacturing chain like agrochemicals shipping and nanomaterials for detection of animal and plant pathogens.

This list of applications derives from the currently posted "Stock of nanotechnology programs within the agricultural, feed and meals" aimed toward defining the contemporary state of artwork and the destiny traits of nanotechnology exploitation in food and agriculture. Particularly, it has emerged that 276 nanomaterials (NMs) are presently available on the market for ex; silver and titanium dioxide have the very best range of information inside the food components. As a long way as destiny traits are worried, evidently, a capability shift from inorganic materials like silver to organic materials like nano-encapsulates and nanocomposites might occur, suggesting that programs in novel meals feed components, biocides and insecticides were up to now only at an R&D. In this context, there are several packages that could be of interest for products of animal beginning, at some point of farming practices, at some stage in the processing of meat products and all through storage and advertising.

1.1.7 Food Safety and Packaging

How secure is the food that we eat?

Evolved international locations have ensured that the meals that visit the market are very well checked at diverse factors and ensure that there is no opportunity for dangerous substances present inside the food. Purchasers who buy processed foods genuinely demand all the information regarding it. Within the latest beyond troubles like mislabeling, fraud, authenticity and starting place have had a notable effect on the economic system, in addition to the purchasers who decide on processed foods. Food objects and uncooked ingredients are the most suitable for adulteration and fraud and that they have multiplied considerably. The two popular motives for meals adulteration are that its miles profitable and adulterants can be without difficulty blended making the system detection extra tedious. Criminal authorities have to ensure truthful alternate, meals safety and freedom of preference. In surroundings of a humungous technological technique, the evolution of purchaser life styles and among the backdrop of monetary troubles the miles very crucial to improve food protection and benefit the costumer self-belief within the food supply.

The non-compositional elements of meals are of large interest to many purchasers. This aspect of food is not associated with the unique composition of the meals i.e., proteins fats and the color present in them. In addition, they include the geographical beginning, rearing or production systems, processing, storage, and welfare. The exceptional system and protocols through which meals are demonstrated as conforming to its label description are known as food authentication.

Meals toxicology or chemical meals protection is a multidisciplinary and continuously evolving location of crucial importance to all stakeholders of the agrofood region. Food safety is of prime significance and is, in reality, an absolute necessity a good way to don't forget a probably edible commodity.

Food safety is a prime problem for enterprise, governments, and purchasers. Novel danger control schemes including the meals protection objective with extra efficient

regulation are proposed as major mechanisms to decorate food safety. Elements such as meals innovation in the international market and new food habits obtained via customers over the world are applicable challenges to food protection that need to be addressed by using Governments and industry. In this case, nowadays industries are keen to discover extra green renovation technology as a way to improve meals protection along the global food chain even as an assembly the purchaser demands greater natural and healthful meals. For the above reasons, food is now going through vital challenges concerning food protection and exceptional through the software of a mixed approach specifically primarily based on using meals protection rapid-reaction tools, the improvement of the novel and more natural food renovation technologies as well as the software of quantitative threat assessment strategies.

Food packaging can be a completely effective tool for controlling the increase of pathogenic organisms in meals. The number of the exceptional packaging technologies like the antimicrobial energetic packaging (AAP) will interact with the packaged food or the bundle headspace has obtained a whole lot of interest by way of the clinical network. Further, the author discusses the insights related to the present day regulatory repute and literary techniques of AAP that specialize in herbal and antimicrobial along with vital oils, plant extracts, or ethanol through various providers. Nowadays researchers end up with a successful attempt of AAP displaying the capacity advantages for the food enterprise (shelf-existence extension, prevention of recollects expenses, or recognition harm).

1.2 Conclusion

This chapter completely comprises of source of food science, major components of food science like carbohydrates, proteins, vitamins, fats, oils, etc., storage conditions of food at different climatic conditions, packaging and stability of food and various applications of food science nowadays like, role of food science in agricultural process and also major nanotechnological applications. Moreover, this chapter will facilitate most of the researchers to focus their work towards food science and its vast area of applications.

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Chapter 2
Importance of Food Science and Technology- Way to Future

Deena Titus, E. James Jebaseelan Samuel, and S. Mohana Roopan

Abstract Food science is the discipline of applied science dedicated to the study of food. It is not just limited to chemistry alone but is a combination of various disciplines like biology, biochemistry, engineering, molecular biology and genetics, nutritional and health science and microbiology which is aimed at providing a better understanding of food components and materials, their conversion to healthy and safe products and delivery to the consumers. The several ongoing technical advancements in order to enhance the supply of food and to increase the well-being of the growing population are discussed. This chapter summarizes the advances in agriculture and food technology from the prehistoric times to the present. Also explains the need for food processing and the different techniques used which guarantee the products quality. Future challenges and potential solutions are also discussed. Production to consumption food system is complex and our food which is diverse, tasty, nutritious, safe and less costly, has become easily accessible. Technological advancements should be accelerated in order to feed the growing population.

Keywords Food science · Disciplines · Technology · Food processing · Challenges · Population

2.1 Introduction

The cultural and social evolution of mankind has made the world progress from hunter- gatherer to goods and service provider. The increasing need for preservation of food and supply of adequate nutrition through consistent food supply

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_2

throughout the year led to the advancements in food industry which has immensely contributed to a healthier human civilization and the society to flourish and prosper (Lund 1989).

2.1.1 Food Science and Technology-Development

Primitive humans survived by feeding on wild fruits and vegetables, small insects, animals and fish. In the Pre-Neolithic age, man used fire for cooking and hunted animals. Cannibalism was prevailing at that time. Fire was a way to keep them away from wild animals, keep them warm, lighted their homes and also modified the food. Cooked food got more flavor, added nutritive value, made food chewable and digestible, killed harmful microorganisms, destroyed toxic chemicals (Stewart and Amerine 2012).

The original form of food processing was discovered almost 2 million years ago by our ancestors who discovered cooking (Wrangham 2009). Later, it was improved with drying, fermentation ad preservation of food materials with salt which helped the communities to survive. Humans thus learned to cook, transform, preserve and store food. This actually led to the food processing (Hall 1989; Floros 2008). Land cultivation and domestication of animals and plants developed over time as humans started eating meat. Hence, the animal and plant agriculture contributed to improved human condition.

Processing of food can be seen in the ancient times as well. Transformation of perishable, unpalatable or hard edible raw materials can be transformed to flavorful, stable, nutritious and safe foods like bread, wine etc., are such products (Floros et al. 2010).

Food system has become more accessible than ever before. The whole system includes production and harvesting of agriculture products, raw material storage, manufacturing of food, transportation and distribution, selling the product to the consumers, service and preparation of food at home.

As mentioned above, food science evolution took place hundreds of years ago but has increased momentum over the past few years due to developments in physics, chemistry, biology, microbiology, biotechnology, nutrition, molecular biology and other science and engineering disciplines (Smithers 2016). These disciplines have changed our lifestyle. Table 2.1 depicts the various disciplines and their roles encompassed in food science and technology. Integration of these disciplines have paved way to enhanced food safety and preserving the nutrition value in the food material.

2.2 Food Processing

The growing need to preserve the food from the time of harvest until the product reached the consumer led to the evolution of food processing. Raw material sourcing is also included in food processing as this can improve the nutritional qualities which contribute to the general wellness of the consumer.

Table 2.1 Role of various disciplines in food science and technology

Various discipline	Role of each discipline in food science and technology
Biology, cell biology	Plant and microbial physiology, quality of food, food safety and disease control
Biotechnology	Improved food retaining the nutritive value
Chemistry	Analysis
Computer science	Data analysis
Microbiology	Detection, identification and control of microorganisms, hygiene and food safety
Nutrition	Human physiology, nutrition, health, diet and disease
Physics	Environmental protection, wastage and pollution control
Sensory science	Chemosenses understanding like taste & odor
Toxicology	Assessment of food additives and components
Genomics	Better control of desired attributed, pathogen detection and identification
Material science	Packaging

The multiple objectives served by food processing include cooking and freezing which preserve the food, heating helps in attaining edibility and helps in removing toxic substances. Processing methods are performed under controlled conditions (Knorr 1999) in order to complete the process in an effective manner. The resultant products are delivered to the consumers through food manufacturers. Development of newer technologies improves the food safety. Such technologies give rise to new products with unique attributes.

Processing consists of a series of operations which include cooling, heating, mixing, washing, filtering, extracting, frying, irradiating, storing and packaging. The several purposes served by processing and packaging (Floros et al. 2010) are listed below:

Food Preservation This is the most common and oldest purpose which is much familiar to the consumers. The main purpose for this method is to extend the food or beverage's shelf life.

Food Safety Removal of health hazards related to microbes is done by food processing. Certain rules and regulations are maintained in processing operations which deal with food materials having pathogens which can create diseases. Pasteurization is one such example which eliminates the risk for consumer and extends the product's shelf life. Food safety is not just limited to risks due to microbial pathogens. Poor agricultural and manufacturing processes also address physical and chemical hazards. The interrelationship between food safety and food security is depicted in Fig. 2.1. Processing is one of the critical elements in food science as negligence to this can be fatal.

Product Quality Procedures for ensuring high quality food and beverage to the consumer end are continuing to progress. The attributes in quality include aroma, color, texture, taste and nutrient content. These characteristics tend to decline as the food materials are collected or harvested. This declination has to be reduced.

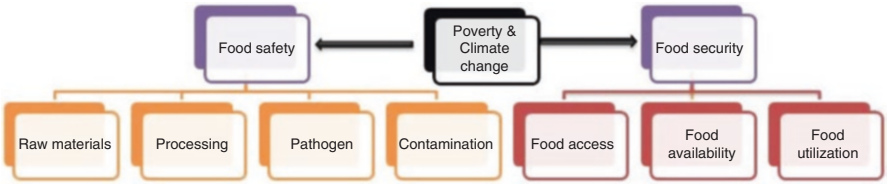

Fig. 2.1 Relationship between food safety and food security

Retaining the nutrient content in the food can be done by freezing or sometimes the food quality is increased after processing.

Availability Access to a wide range of food varieties at any instant of time is another aim of food processing. Retaining the quality from the time of harvest till its delivery to the consumer is improved. Extended freshness of fruits is achieved by controlling the atmosphere composition which surrounds the fruit is an example.

Accessibility Ready to eat food items are available which can be delivered to the consumer. Some processed foods are developed so as to be consumed after a small amount of preparation like frozen items which need a deep frying in order to be edible or even a microwave heating.

Sustainability Processing also ensures efficient utilization of resources which are necessary for providing food ingredients to food manufacturing. During the course of time of production till consumption, the raw materials are utilized to the maximum and the activities are integrated. Efforts are being made from the stage of production for the reduction in losses postharvest and also increased by product usage. In addition, the water and energy resources are used well and minimize the impacts on environment. Example: refrigeration increases the life of the product.

Fitness and Wellness At a basic level, food is observed as the source of nutrition towards meeting the minimum requirements for existence. Processing can improve the food's nutritional value. Food products are specially developed to increase the health and wellness of an individual. Certain ingredients can add desired attributes to the product which can meet the required need of the consumer. The texture, flavor and nutrient value should meet the expectations of the consumer.

2.3 Operations, Processes and Technology

Operations There are many mechanical operations used throughout the food system, most of them being large scale versions. The main purpose of using mechanical operations is to produce the required ingredients for any consumer food products. For example the extraction of oil from any oilseed requires a prior mechanical

operation before its efficient separation. Most of these operations involve series of steps including the manufacturing of by-products for an efficient use of the raw material, dry mixing to obtain a homogenous mixture of the ingredients before being taken to the final process of manufacturing.

Heating Thermal energy in the form of heating is the most widely used and effective method to preserve food or the ingredients. By maintaining the food at an appropriate temperature food spoilage due to any pathogenic bacteria can be greatly eliminated. This same principle is applied for cooking which not only helps in preserving the food but also aids in enhancing the flavor, texture and taste of the food. This thermal process assures shelf-stable food, like the pasteurized dairy products and fruit juices. Later, reported the essentiality of containers for cooking food. This initiated the beginning of integrating different disciplines of science to food science and technology. There are three types of thermal process namely blanching, pasteurization and canning (Floros et al. 2010). They help in reducing the enzyme activity on the flavor, texture and color of the food and also to reduce oxidation, softening of the plant tissue and inactivate antinutritional properties.

"Pasteurization" named after Pasteur who first demonstrated that a mild heating procedure could eliminate microorganism and thereby extend the shelf life of foods. Pasteurization is well-known for dairy preservation and most applied to liquids and to a lesser extent in solids. The process involves heating the food product at 140 to 212 °F for a short period which inactivates any pathogenic microorganisms. With knowledge of flow dynamics and heat transfer, the process has been made continuous using heat exchangers which allow the heating and cooling of the food product. These pasteurized foods are subsequently packed and refrigerated.

Blanching is a process mainly applied for canned, frozen or dried food products. In this method the food is heated below 212 °F for less than 2 to 3 min. In canning the food product is heated at temperatures above 230 °F for several minutes, to get rid of all pathogenic microorganisms. In this there are two methods of heating namely (i) canning, in which the food is heated after being sealed in a contained and (ii) asepting processing, where the food is first sterilized and then sealed in a container.

Refrigeration and Freezing Contrast to heating, this method involved preserving the food at low temperature. Although the complete elimination of microorganism in this method cannot be expected, it ensures reduction in microbial growth and allows extending shelf life. Refrigeration helps in maintaining the freshness of food products, reducing enzyme reaction rate and provide high quality products that can last longer (Heldman and Hartel 1997). Though food products undergo thermal treatment, many require refrigeration to reduce the bacterial growth.

Freezing is the most powerful use of refrigeration where the temperature is reduced below the freezing temperature of water (−0.4 to −14 °F). Though most nutrients are not affected by freezing it does cause an impact on some of the quality attributes of food products like texture and flavor. Therefore the control of temperature and

time to freeze and its maintenance during storage and distribution of the food products are necessary to ensure best quality products (Erickson and Hung 1997). Though the size of ice crystals can be controlled, it cannot be applied to all products. With smaller ice crystals, for smaller pieces of fruits or vegetables, a uniform distribution is achieved while in larger ice crystals this is not observed. Nevertheless, in many foods the quality of frozen or refrigerated foods is in par with fresh counterparts (Mallet 1993).

Dehydration or drying is mainly used to arrest or reduce the growth of microorganisms and chemical reactions. This method offers the feasibility to reduce the volume and weight of the food product. In addition it allows the conversion of liquids to powders, for instance, instant coffee or soup mix.

Several dryer types, equipments and methods for dehydration are used for the food variety. Sun dried foods are still in use today using tray or any platform. Recently this includes conveyor, bed, drum, vacuum and spray dryers. Lyophilization or freeze drying and microwave are in use too. Drying is always developing which offers quality products. Sometimes the dehydration techniques are combined (two or more) or with other processing techniques which optimizes the cost and food quality.

Acidification The acid level in beverages and food vary significantly. Lower acid level in food makes it more prone to microbial growth and thus gets easily spoilt. A deliberate adjustment in the acid level in food can be a method of preservation as it is done in pickles. This method is based in the idea that higher levels of acid inhibit growth of pathogens thereby extending the products shelf life. Adding acid to the food or by fermentation, this can be achieved along with other techniques like additives or heat for the complete protection of the product.

Fermentation Another method of preserving is done with the use of microorganisms. Example of this include curd, cheese etc. This is considered as an old way of preserving perishable food when refrigeration was not there. Even though few microorganisms lead to spoilage of food and some can cause food poisoning, certain specific microorganisms can bring about desirable changes in food and this can be used to overpower others which are unsafe. This will make the food environment less likely prone to pathogens as they create an environment which is not suitable for their growth. Dairy products, pickled food, baking bread, wine (Michel et al. 1993) are all examples of fermented food products.

Smoking Applying smoke to food added flavor and also prevented food from getting perished. The smoke flavor as a result of this in meat, poultry, fish, sausage, cheese etc., is in use nowadays. Extended shelf life is another benefit of the process. Smoking adds to food safety as smoke kills bacteria. Smoke accompanied by mild heating controls spoilage and pathogens. Smoking also results in drying of the product surface which again helps prevent contamination. Smoke imparts quality to the food, creates an aroma, smoky flavor. The visual appearance makes it more appealing to the consumers. It also helps in preserving the food.

2.4 Challenges

The rise in demand for food materials to feed the rising population has increased drastically which pose a serious concern. The major challenges (Fig. 2.2) in the present scenario are:

Population Food production has to be increased more than double its present production to feed the predicted population. Lack of proper handling, processing, packaging and distribution methods in underdeveloped and developing countries is another challenge to be met (FAO 2009). Developments in the area of production of food, its distribution and food science and technology are important to overcome this barrier. Besides, conservation of energy and resource is also critically important. To meet the food requirements, there should be an increase in the agriculture production, without negotiating on the natural resources, efficient food manufacturing systems, utilizing less energy, generating less waste and a product with a good shelf life. Acceleration in scientific and technological advancements is demanded in the case of both food manufacturing and agriculture sectors.

Climate change Raise in atmospheric temperature, increased level of carbon dioxide and changes in precipitation is referred to as climate change (FAO 2009) and this can affect the food production and agriculture causing draught and extreme temperature in many areas. Heat stresses negatively affect crop productivity and hence the crop yield and global food production (de Gorter et al. 2013), Change in climate is a challenge which requires an effective action. The food price rises due to the climate change, thus becoming unaffordable and relies on import of food (FAO 2009). Measures should be taken to control global warming by reducing greenhouse gas emissions in order to combat the climate change; this could actually improve the sustainability of food production.

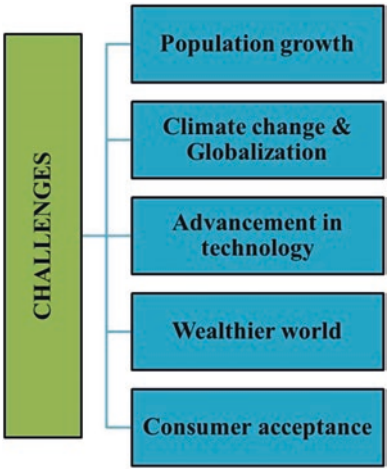

Fig. 2.2 Major challenges faced by Food science

Water shortage Water shortage has become an important issue as a result of its increased use in industries, agriculture and domestic needs. The heavy usage is a part of maintaining food security and fight against poverty. A large quantity of water is getting wasted by pollution and improper management (FAO 2009). Over one fifth of the population survives with water scarcity, another quarter percentile on water shortage and two thirds on inadequate water supply (Tian et al. 2016). Hence, proper management of water and accessibility to fresh water supply is needed to meet agricultural needs and production of food.

Urbanization and fertile land Reduction in arable land is a result of growing population. Demand for food needs extra land for cultivation of crops. The challenge is not just the production but also to make this food accessible and available for the population. Biofuel is another aspect that requires land, reduces the use of fossil fuel and emission of greenhouse gases (Elbehri et al. 2013). The employment of biofuel also affects the food security as this can have its effect on energy and price of the commodity (FAO 2009; de Gorter et al. 2013).

2.5 Issues Related to Food

Malnutrition refers to a strange physical condition mainly due to insufficient and unbalanced nutrients. Consumption of less protein and calorie rich food or over consumption of energy food can result in malnutrition. Unavailability of food and poverty are some reasons for this. Measures are being taken to fight against poverty and malnutrition but still a large population is still malnourished.

Obesity One of the reasons for obesity can be due to malnutrition. This unhealthy gain in weight can create lot of trouble as this can impair the health. Obesity can lead to life threatening diseases. People have to be educated to know about the implications and the need for a healthy balanced diet which can indirectly reduce food loss and increase its accessibility for others also at an affordable price.

Food regulation and laws are different in different countries. A broad and consistent regulatory system with sufficient budget is required to meet the challenges posed in food quality and maintaining the standards (Chiesal et al. 2012).

Waste Management From the production time till consumption, a large amount of material gets lost. The extent of losses keeps varying in developing countries. Lack of knowledge and infrastructure in terms of protection against damage and wastage due to rodents and microorganism are a major factor concerning these losses (Godfray et al. 2010). Throughout the stages of production, harvest and storage, these losses can occur. Commercialized food manufacturing operations efficiently convert the raw materials to products when compared to home preparation. The resultant wastes are used as animal feed and can also be converted to food ingredients, bio-products, biofuel (Hang 2004) and animal feed (Hudson 1971).

Fig. 2.3 Food safety-elements

The overall food safety is dependent on various factors and needs support from every end as shown in Fig. 2.3.

2.6 Acceptance – Consumer End

Acceptance of new food items will be determined by the attitude of the consumer and on the new technology implemented in processing. Consumer acceptance is one among the difficult yet critical task when a novel technology is being used to find a solution. Unless the idea gains public support it cannot be called as a good idea.

The success rate of using a technology depends on the early addressing of the consumer acceptance and their attitude towards that technology. At the development stage itself, the technology used and the one need to address the technology Proper knowledge on the technological aspect, risk factors associated with it, social media influences, personal experiences are some of the factors on which the consumers rely on (Tian et al. 2016).

2.7 Nanotechnology

The area of nanotechnology is attaining lot of attention in the past few years. The unique change in properties of the particle in nanoscale makes it viable for its use in various fields. Making at least one dimension approximately 1–100 nm brings about remarkable changes in the properties of the material when compared to its macroscale (Joseph and Morrison 2006; Duncan 2011; Fathi et al. 2012). Food system is expected to have beneficial impacts from nanotechnology from the production stage till its delivery which includes management of resources and nutrition (Fig. 2.4). Nanoemulsions and nanoencapsulations have been developed for protecting bioactive ingredients thus making an increase in bioavailability (Fathi et al. 2012).

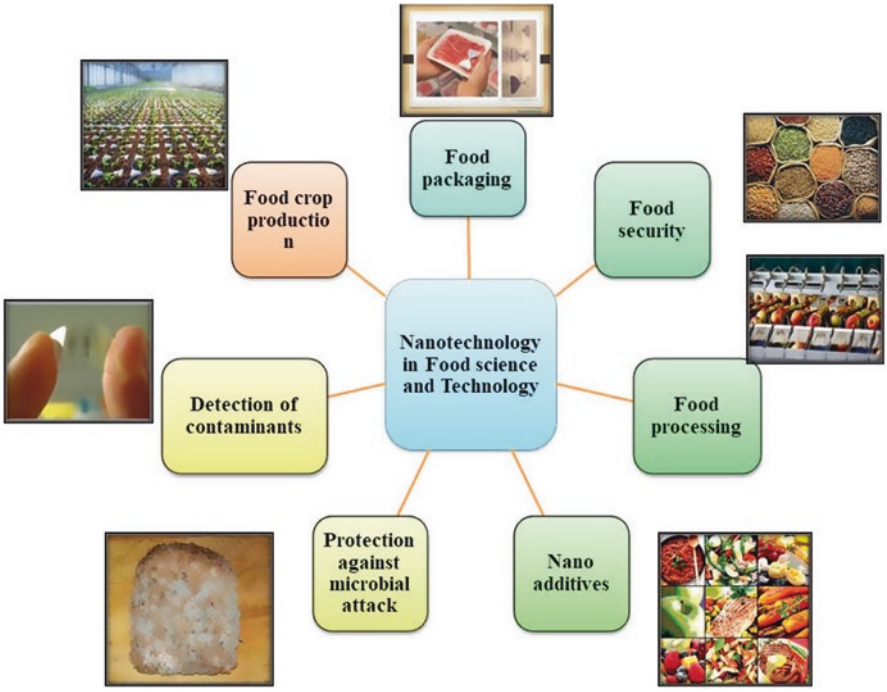

Fig. 2.4 Relationship between food safety and food security

Anti-caking agents, sensors for detecting contaminants (Liu et al. 2008; Nugen and Baeumner 2008; Inbaraj and Chen 2015; Palchetti and Mascini 2008; He and Hwang 2016; Hernández-Hernández et al. 2017), packaging materials (Imran et al. 2010; Pereira de Abreu et al. 2012; Mihindukulasuriya and Lim 2014; Sharma et al. 2017; Singh et al. 2017; Fowsiya et al. 2016) are some examples of the utilization of nanoscience. Due to issues like consumer acceptance and regulatory measures, many of the technologies are delayed in getting implemented.

2.8 Conclusion

The complex food system is changing continuously. Processing of food has developed over the time making food easily accessible, more nutritious, safe and affordable. With the aid of various disciplines in food science and technology, raw materials are being converted to edible foods. Reduced diseases, improved safety and quality, variety, less cost, less wastage are some of the advancements in the field. But the growing need of food with specific attributes due to population hike is of concern. Biotechnology field has made progress to meet the increasing demand by improving crop production. Maintaining human health and wellness is of much importance. Newer technologies and detecting mechanisms can be anticipated in future with the evolving progress in nanotechnology. Minimizing risks and maximizing the benefits should be the main objective. Experts in Food science and technology should work hand in hand to get the maximum output. Investments in education and research are needed. The approach should be balanced and persistent to safeguard both nature and human health.

Acknowledgment Authors would like to thank Vellore Institute of Technology for the kind support and motivation.

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Chapter 3
Extraction of Bio Organics Phase from Various Food Sources

J. Fowsiya and G. Madhumitha

Abstract The natural products or bioorganic phase from food sources as pure compounds provides many applications in the food industry and pharmaceutical industry. The fruits and vegetables are the main sources for many bioorganic phases such as phenolic compounds, flavonoids, alkaloids etc., The focus of this book chapter is on the extraction and preliminary detection of active ingredients in food sources. The common problems and key challenges in the extraction process of food sources is discussed. As extraction methods play an important role in isolation of bioorganic phase, the different extraction process for each bioorganic phase is discussed.

Keywords Bio-organic phase · Food source · Alkaloids · Flavonoids · Phenolic compounds

3.1 Introduction

The phytochemicals or natural products is a term which strictly speaking about the chemicals found in the living organism usually called as secondary metabolites and it is not necessary for the survey of a living organism (Sasidharan et al. 2011). The Phytochemistry or chemistry of plants is one the subdivision organic chemistry has gained more significance in the isolation and identification of phytochemical substance of living organism. With the development of new phytochemicals extraction and techniques, it is more concerned with a various structural diversity, biosynthesis methods, biological applications etc., (Manivel et al. 2008; Madhumitha et al. 2012; Manivel et al. 2009). The field of phytochemistry needed more specific separation, extraction and purification techniques to isolate and identify constituents of plants (Priyanka and Srivastav 2013; Srivastav 2014; Anu and Ankita 2014;

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_3

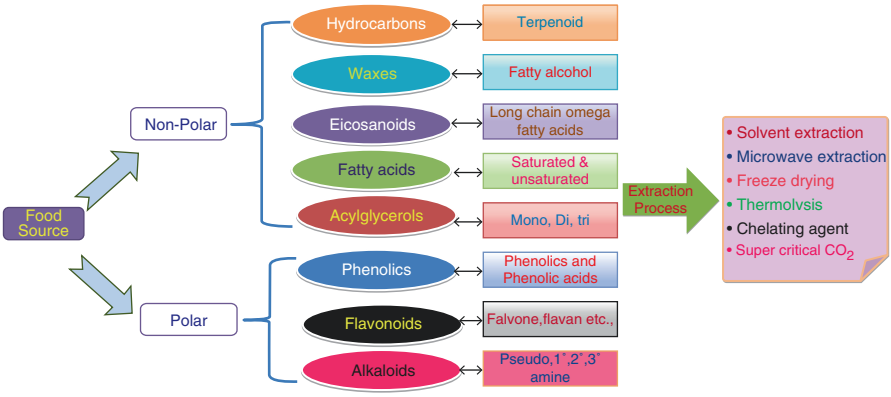


Fig. 3.1 Different bioorganic phase and its extraction process

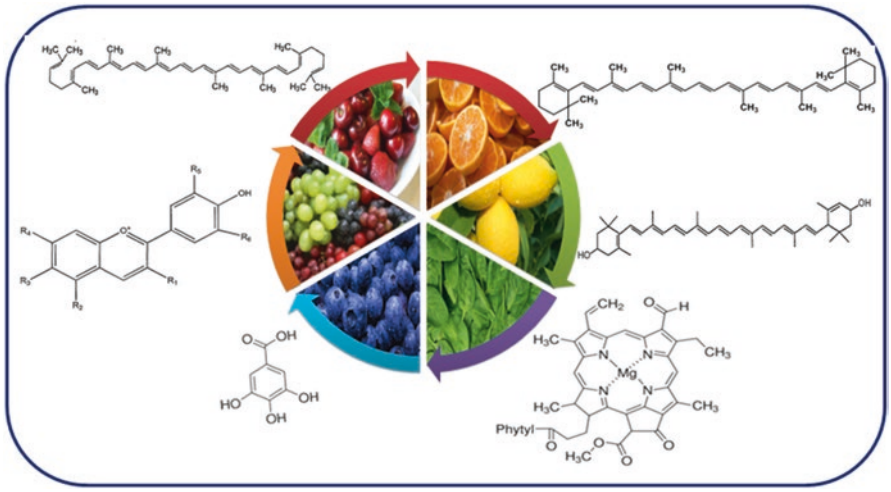


Fig. 3.2 Different bioorganic phase from food source

Tasneef et al. 2013; Amita and Shalini 2014; Azwanida 2015). Thus, understanding the advanced methods in phytochemistry are directly associated with successful development of well-known techniques and also continues new methods to solve problems (Fig. 3.1). The extraction of phytochemicals from a food source is more essential processes and they play a significant role in quality optimization of foods, beverages, production of high-value compounds and recovery of wastes from food processing (Prakash et al. 2012). The phytochemicals of food sources including fruits, vegetables have become very important bio-resource of drugs, nutraceuticals and food supplements (Roopan et al. 2016). The phytochemicals such as phenolic compounds, flavonoids, alkaloids, terpenoids and steroids have distinct chemical properties and structural diversity (Drewnowski and Carmen 2000) (Fig. 3.2).

Therefore, extraction and separation techniques must be more specific to isolate the bio-organic phase from a food source. The term extraction is a way to separate the desired bio-organic phase or phytochemical when it brought into contact with the soluble and insoluble substance. In other words, the extraction process defined as two immiscible phase to isolate phytochemicals from one phase into the other phase. The general extraction process includes the conventional and non-conventional method such as infusion, fluid extraction, microwave extraction etc., (Anoma and Thamilini 2016). The purpose of the standardized extraction process involves separation of individual phytochemicals from the mixture of the crude extract. The standardized extraction process depends on the alkaline nature, acidic nature, ability and ease of formation of salt and acids and solubility of phytochemicals. The following section describes various extraction processes used for isolate the phytochemicals from a food source (Dong et al. 2017).

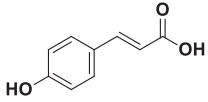
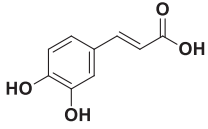
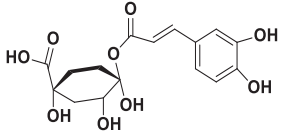
3.1.1 Extraction Process for Phenolic and Phenolic Acid Compounds from Food Sources

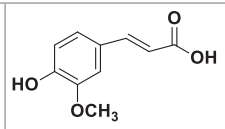
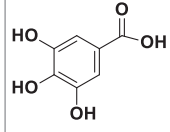
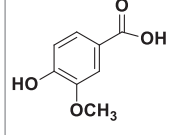
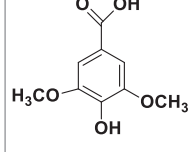
The free phenolic compounds and phenolic acids were found to be together and acid hydrolysis of plant tissues produces ether soluble phenolic acids. The term phenolic compounds can be defined as the plant substances carrying one or more hydroxyl groups in an aromatic ring (Muhammed et al. 2016) (Table 3.1). Most of the phenol compounds are water and ether soluble as they combined with glycosides moiety. In the classic methods for identifying phenolic compounds, 1% of aqueous or alcohol ferric chloride was added to the phenolic compounds and visually can identified be means of intense green, blue, purple, and black colors (Mojzer et al. 2016; Wissam et al. 2012; Renata et al. 2015; Soma and Genitha 2014; Deng et al. 2016). In the typical paper chromatogram, 1% ferric chloride solution and potassium ferricyanide used to detect the phenolic compounds. However, the UV light fluorescence also helps to identify the phenolic compounds by changing the color after fuming with ammonia.

The isolation of phenolic compounds can also be done by acid hydrolysis method. Generally, 2 M of hydrochloric acid was used for acid hydrolysis for 30 min, the solution further extracted with ether solvents. The alkaline hydrolysis further can be done with 2 M of sodium hydroxide solution to isolate the neutral compounds. The residue of phenolic compounds then chromatographed on silica gel in acetic acid-chloroform or ethyl acetate- benzene solvents.

Mostly fruits have considered as a rich source of phenolic compounds in foods over past 20 years. The phenolic compound content may vary depends on the degree of ripeness, climate change, soil composition, storage and location (Fig. 3.3).

Table 3.1 Phenolic compounds from food sources

Phenolic compound	Chemicalstructure	Aerial part	Reference
p-Coumaric acid		 Orange	Gavrilova et al. (2011)
Caffeic acid		 Papaya, Avocado	Golukcu and Ozdemir (2010)
Chlorogenic acid		 Kiwi, Blue Berry	Fu et al. (2011)

Ferulic acid		 Mango, Pineapple	Poovarodom et al. (2010)
Gallic acid		 Pitaya, Banana	Fu et al. (2011)
Vanillic acid		 Strawberry	Poovarodom et al. (2010)
Syringic acid		 Black grape	Russell et al. (2009)

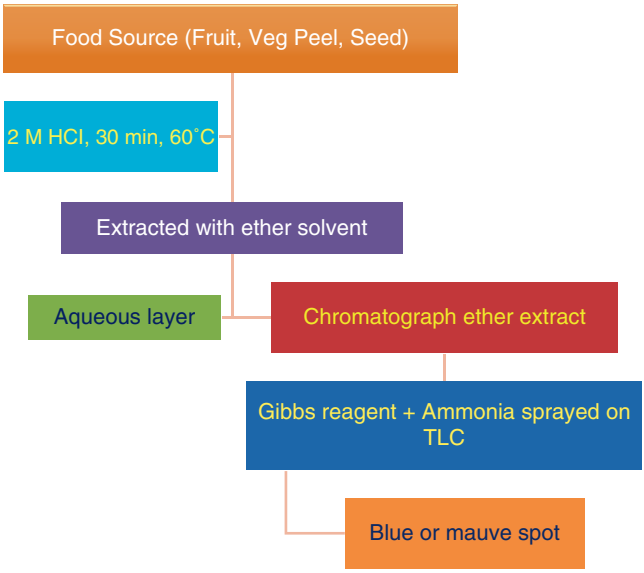


Fig 3.3 Extraction process of phenolic compounds

3.1.2 Extraction of Flavonoids from Vegetable, Fruits and Nuts

The Flavonoids are one of the secondary metabolites of plants and fungus. Chemically, flavonoids contain 15 carbon skeletons with two phenyl groups which attached with oxygen-containing the heterocyclic ring. Flavonoids also called as plant pigment for flowers petals and involve in the process of UV filtration, nitrogen fixation and pigmentation (Sathyadevi and Subramanian 2015; Tajnuba et al. 2016; Muhammed et al. 2015; Bilbao et al. 2007).

Most of the flavonoids are water soluble and they can be extracted with ethanol followed by a partition with petroleum ether. The color of flavonoids can change with a base; thus they can be detected easily. The food sources are rich in flavonoids and flavonoids glycosides; some of the food sources contain single flavonoids with different glycosides moiety. The preliminary identification of flavonoids as a single compound is very rare and often can identify its different class of flavonoids. Mostly the colored flavonoids can be identified preliminary based on their characteristics shown in Table 3.2.

In the typical extraction process, the plant material immersed with 2 M HCl and kept for 30 min at 100 °C. The cooled extracted further extracted with ethyl acetate and the aqueous layer heated to remove ethyl acetate and again extracted with amyl alcohol. The ethyl acetate extract can be chromatographed with a different solvent

Table 3.2 Preliminary identification of different class of flavonoids

Flavonoids	Distribution	Preliminary identification
Anthocyanin	Blue, red flower pigment and found in some leaf and other tissues	Soluble in water, absorption at 515–545 nm
Flavonols	Colorless pigment, found in leaves	After acid hydrolysis shows intense yellow color spot under UV light and maximum absorption 350–386 nm
Chalcones and aurones	Yellow color pigment	Red color precipitate with ammonia
Flavanones	Colorless and found in leaf and fruits	Red color with magnesium/HCl
Isoflavones	Colorless and common in Leguminosae	No specific color test
Flavones	Colorless	Brown color spot after acid hydrolysis

ratio as follows: Forestal (acetic acid: HCl: Water, 30:3:10), 50% aqueous acetic acid, BAW (n-Butanol: acetic acid: water, 4:1:5), Phenol in water and water. The colored amyl alcohol chromatograph with Forestal and in formic acid (Formic acid: HCl: water, 5:2:3) (Mabry et al. 1970) (Figs. 3.4 and 3.5).

In general, most of the fruits contain flavanones one of the sub-class of flavonoids family. They are colorless chemicals and some of the flavonones were yellow or blue color under UV light condition after treated with ammonia vapor. The preliminary detection of flavonones gives intense red color precipitate or solution with magnesium/HCl and also gives positive result by spraying first with alcoholic sodium borohydride and then alcoholic aluminum chloride (Skorek et al. 2016) (Table 3.3).

3.1.3 Extraction of Alkaloids from Food Sources

The alkaloids are naturally occurring nitrogen-containing compounds and found in a variety of food sources including cocoa, pepper, tea, honey and fruits etc., The extraction process of alkaloids entirely different than phenolic compounds and flavonoids. The extraction of alkaloids generally based on two steps in a sequential manner namely, separation of alkaloids crude from non-alkaloidal extract and isolation of each alkaloid from food source using latest separation techniques such as High-performance liquid chromatography, high-performance thin layer chromatography etc., The extraction process mainly depends on alkaline nature of alkaloids, efficiency to form alkaloidal salts with acids and solubility of their salts in high polar solvents (Williams 2012).

The separation of alkaloids from non-alkaloidal fraction must be done using acetic acid. In the typical process, plant material immersed in 5% of acetic acid and boiled at 70 °C for 4 h. The solution filtered and cooled, then ammonium hydroxide

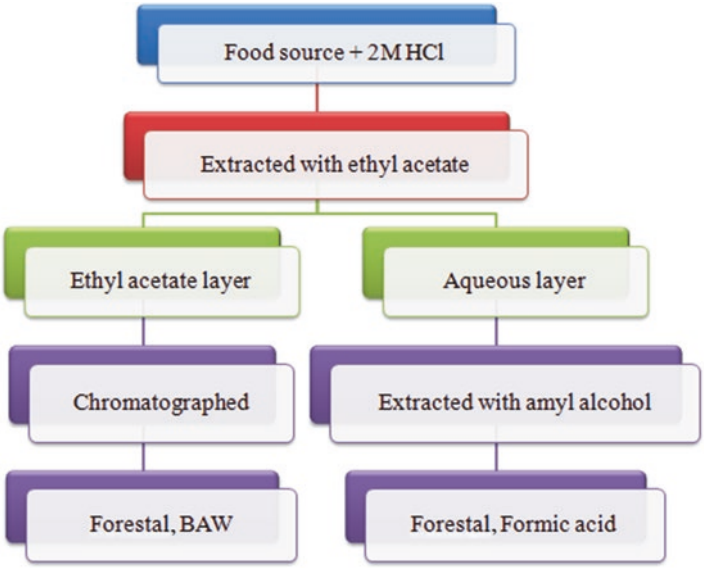


Fig 3.4 Extraction method for flavonoids

solution was added dropwise to change pH into 9–10. The precipitate further centrifuged and washed with ammonium hydroxide. The crude alkaloid extract can be chromatographed to isolate the individual alkaloids.

Instead of the general extraction process, there is some other process which is utilized to extract the alkaloids namely, Stas's otto process, Kippenberger's and Manske's process. The stas' otto states that the previously acidified with tartaric acid food source dissolved with ethanol. The solution de-fatted with petroleum ether, it must be recovered with acids (Fig. 3.5).

In Kippenberger's process, powdered sample digested with tannin in glycerol at 40 °C for 48 h. The residue again heated, cooled and filtered. To the filtrate petroleum ether added to remove all fatty components. Petroleum ether is removed either on electric water bath or exposure to IR lamp. The fat-free part is acidified and shaken with chloroform to remove narcotine, codeine alkaloids. And CO_2 passed to remove morphine, narceine. Alkali hydroxide converts into carbonate and finally subjected to alcohol and chloroform (Fig. 3.6).

In the Manke's process, the sample is defatted with petroleum ether and alcohol added to the residue. Alcoholic extract dissolved in water, pH adjusts to 2 and filtered. To the filtrate ether and chloroform added, non-alkaloidal impurities removed (Fig. 3.7). The organic layer is evaporated and crude alkaloids are collected.

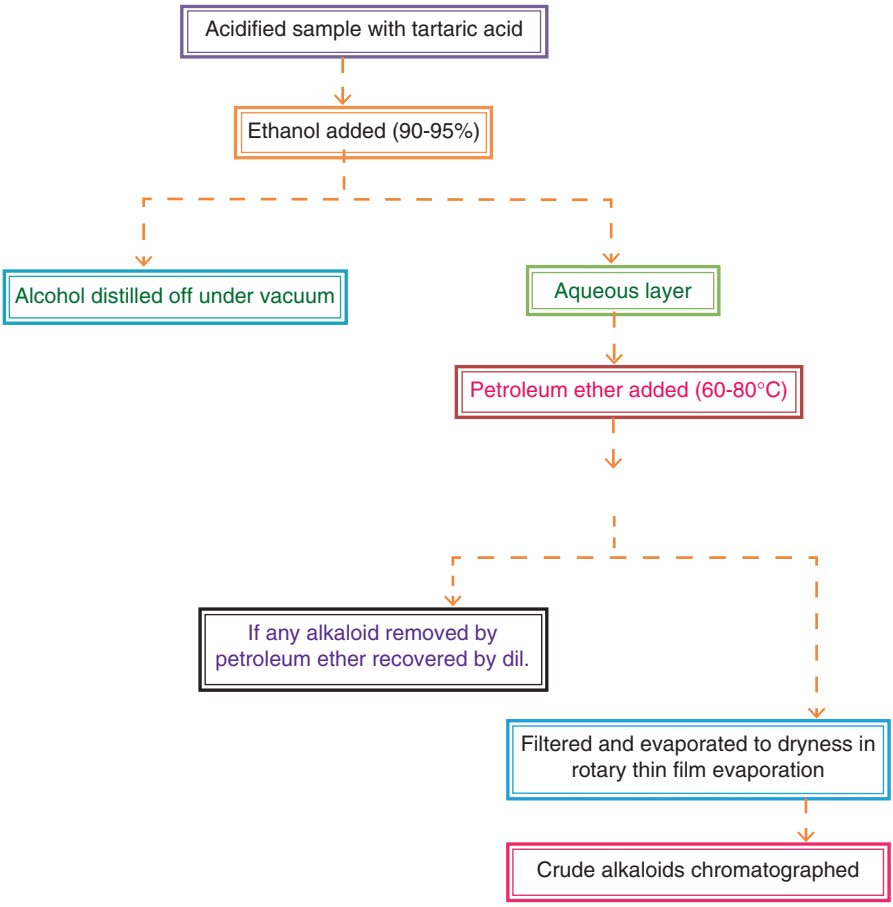
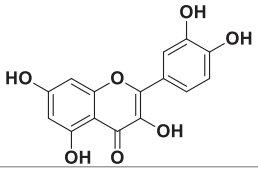
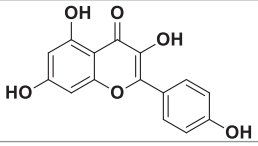
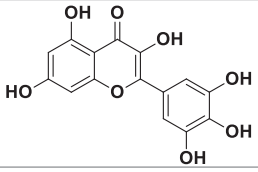
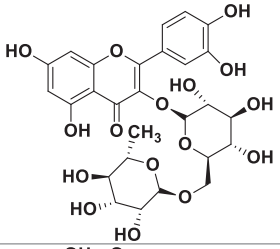
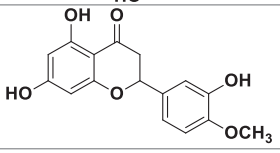
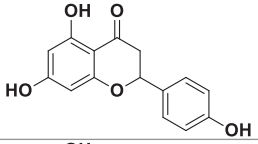
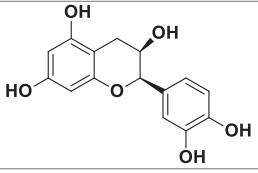


Fig 3.5 Stass otto process for alkaloids extraction

3.1.4 Purification of Alkaloids by Precipitation Method

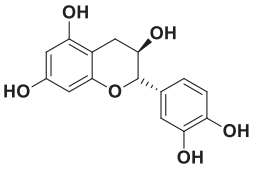
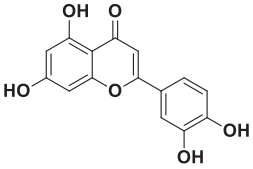
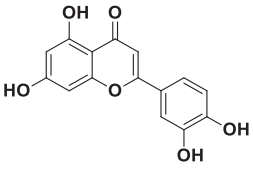
The crude alkaloid fraction further subjected to purification by means of any one or combination of following methods namely, extraction with acid and precipitation with reagents. In the acid extraction method, crude alkaloid mixed with the alcoholic acid solution and extracted with organic solvent. Generally, HCl is not recommended to use for alkaloids extraction due to alkaloidal hydrochlorides are distinctly soluble in the latter. Further, the acid solution mixed with ammonium hydroxide which is then extracted with organic solvent. The slow crystallization can proceed for the formation of alkaloids crystal or the trace amount of organic solvent is removed and chromatographed with a suitable solvent. In case of inference of fatty acids, waxes, oils, pigments or resins, the lead acetate solution is used to

Table 3.3 Different class of flavonoids from food source

Flavonoid class	Compound name	Chemical Structure	Aerial Part	Reference
Flavonols	Quercetin		Pomegranat, passion fruit, jack fruit	Akter et al. (2011)
	Kaempferol		Fig, Cambuci	Vallejo et al. (2012)
	Myricetin		Apple	Rinaldo et al. (2010)
	Rutin		Red grape, Prune, Blue berry	Fu et al. (2011)
Flavanones	Hesperetin		Orange, Grapes	Zhang (2007)
	Naringenin		Grapes, Orange	Zhang (2007)
Flavan-3-ol	Epicatechin		Avocado	Golukcu and Ozdemir (2010)

(continued)

Table 3.3 (continued)

Flavonoid class	Compound name	Chemical Structure	Aerial Part	Reference
	Catechin		Red grapes, Cherry	Kelebek and Selli (2011)
Flavones	Apigenin		Mango, Durian	Poovarodom et al. (2010)
	Luteolin		Lemon, Plum, Watermelon	Fu et al. (2011)

remove them efficiently. The lead acetate present in the solution is removed by passing hydrogen sulfide (Maldoni 1991).

The use of precipitating reagent is other one technique involved in the extraction and isolation process of alkaloids. The dragendorff's, Mayer's and Hager's reagent are commonly used reagent for precipitation of alkaloids. The Reinecke salt is one the complex which easily forms a complex with alkaloids and the solution can decompose with water and acetone (1:1) in presence of silver sulfate. The final alkaloid solution can be further purified with crystallization process (Maldoni 1991).

3.1.5 Aqueous Two-Phase System (ATPS)

ATPS is one the traditional organic-water solvent extraction process which consists of two polymers, one polymer and one kosmotropic salt, or two salts are mixed at a particular temperature. The two phases are made up of water and non-volatile components, thus eliminating volatile organic compounds. In the recent years, it has been used widely in biotechnology, natural products and organic chemistry as non-denaturing and benign separation media. It is a common observation that when oil and water are poured into the same container, they separate into two phases or layers because they are immiscible. In general, aqueous (or water-based) solutions, being polar, are immiscible with non-polar organic solvents (Chloroform, toluene, hexane etc.,) and form a two-phase system. However, in an ABS, both immiscible components are water-based (Fig. 3.8).

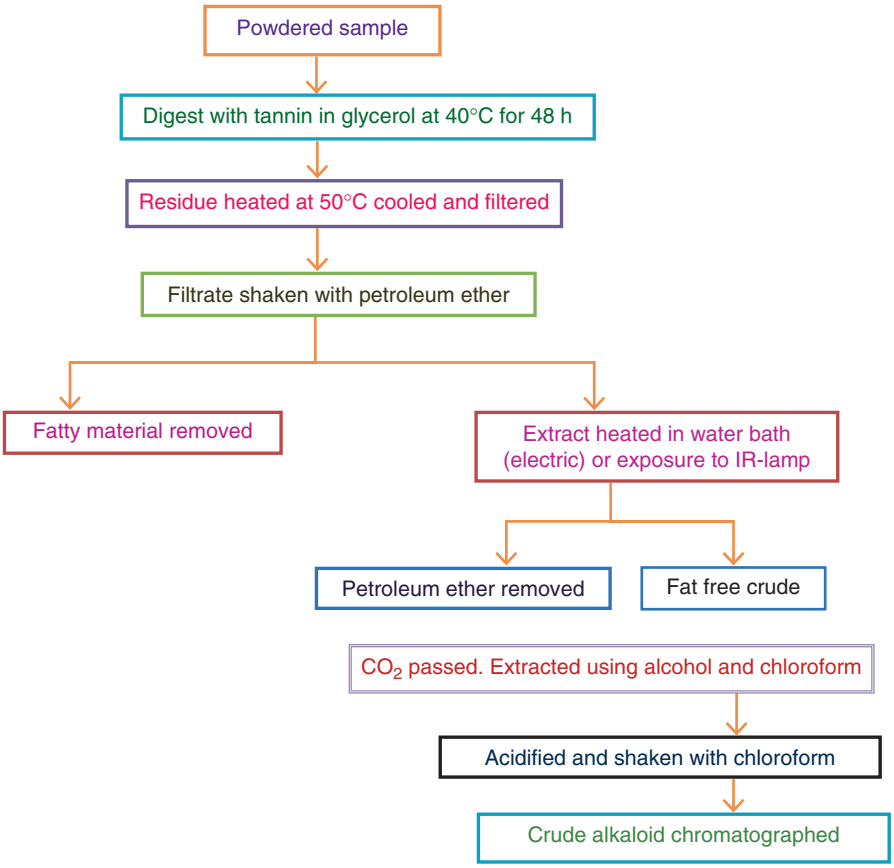


Fig 3.6 Kippenberger's process for alkaloid extraction from food sources

Advantages: They provide mild condition, no harm

- No damage to molecule to be extracted
- The polymer will stabilize the biomolecules, increase the concentration of desired biomolecules and results in the efficient extraction process
- Separation and partition of bioactive compounds occurs rapidly
- Simultaneously used with ion-exchange resin for highly efficient extraction process

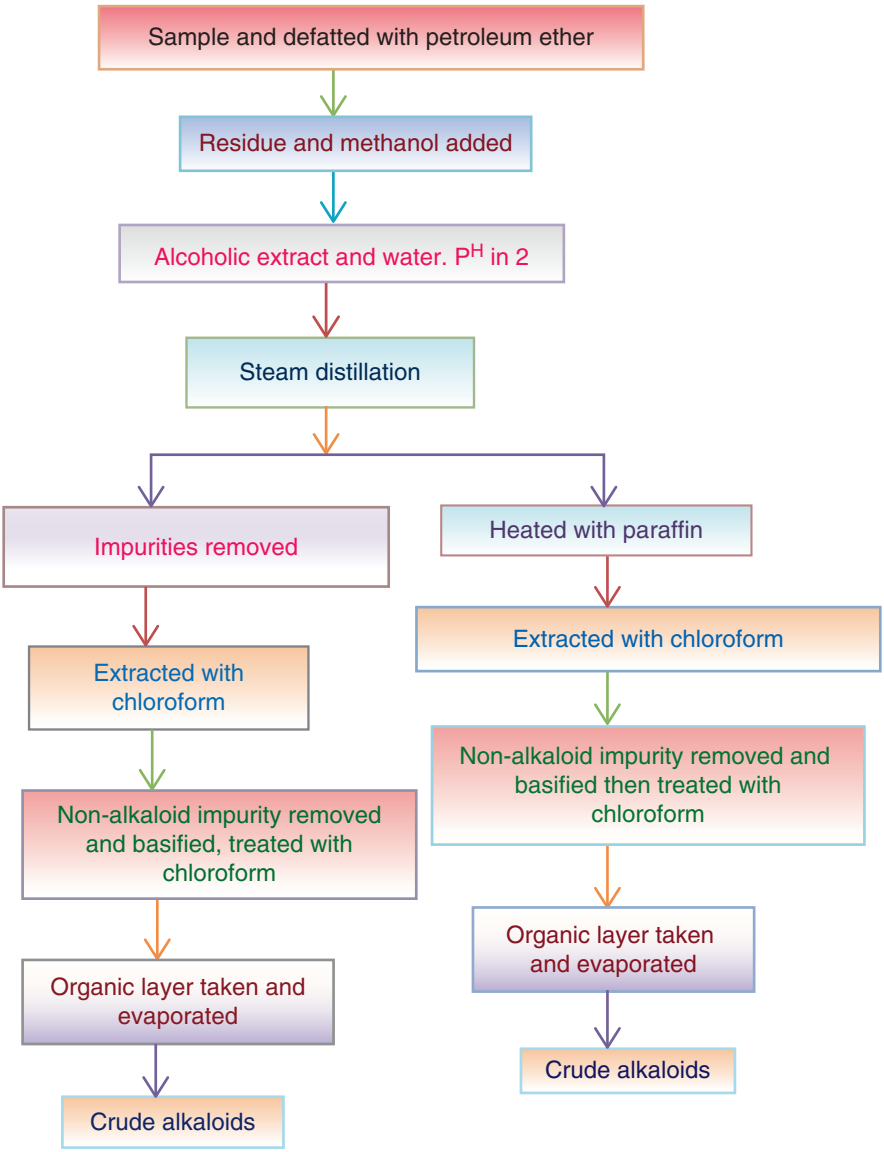


Fig 3.7 Manske's extraction method for alkaloids

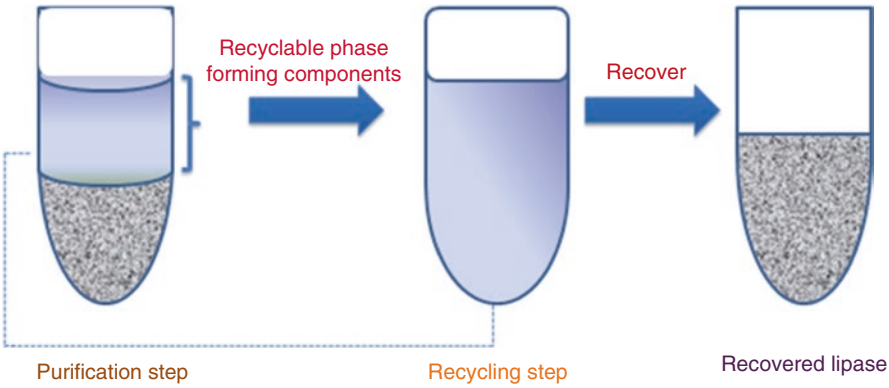


Fig. 3.8 Aqueous two-phase system of extraction

3.2 Conclusion

The different extraction process for bioorganic phase from food source deals with the reagent used in the extraction process, solvent, temperature and pressure. The specific extraction process for particular phytochemicals can be used in the food industry. Phenolic compounds are rich in fruits and this book chapter can help in the extraction process with different methods.

Acknowledgement The authors thank Vellore Institute of Technology, Vellore and DST-FTYS (SB/FT/CS-113/2013) for providing fund and support towards research.

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Chapter 4
Conventional and Non-conventional Approach towards the Extraction of Bioorganic Phase

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Abstract Natural products such as natural food are the richest bio-resource of bioorganic compounds for modern medicines, nutraceuticals, food supplements and pharmaceutical applications. The research and application on natural food started with the extraction techniques that play an important role to the extraction quantity (Yield), quality (extracted phytochemicals) and also to the subsequent analyses accomplished to evaluate the biological and chemicals activities. Various types of technologies with different principles of extraction of bioorganic compounds are available today. Based on the literature the conventional extraction methods show better recoveries of bioorganic substances of natural food. Also, conventional extraction methods facilitate the extraction of high concentration of bioorganic substances with the safe solvents system such as pure ethanol. Moreover, conventional extraction methods is still widely used due to its simplicity. However, the conventional extraction methods is not always suitable for industrial uses due to long extraction time and large consumption of harmful solvents systems such as methanol. Therefore, modern non-conventional extraction methods could be an alternative

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_4

extraction method. Hence, in spite of good results achieved with the conventional extraction methods, modern non-conventional extraction methods was established to search for a faster and better extraction method consuming less solvent, especially those that are unattractive in food industry. This chapter is intended to provide insights on conventional and non-conventional extraction methods with their advantages and disadvantage or limitation.

Keywords Extraction · Natural products · Solvent · Quantity

4.1 Introduction

Natural products such as medicinal plants and natural food are invaluable gift from Mother Nature to human being as natural resources for new drug leads. Natural products from plants, either as crude extract, standardized extracts, active fraction or pure compounds, offer infinite opportunities for new therapeutics phytochemicals. These phytochemicals are of great importance to consumers considering the biological health benefits they bring and their role in curing diseases. In recent years, natural products from medicinal plants has attracted growing attention of world scientist as a source for alternative therapeutics agent for new drug leads (Sasidharan et al. 2011). The usage of natural food in Asia represents a long history of human interactions with the environment. Medicinal plants used for folk medicine comprise a wide range of materials that can be used to treat chronic as well as infectious diseases (Duraipandiyan et al. 2006). According to the World Health Organization (WHO), nearly 20,000 medicinal plants exist in 91 countries including 12 mega biodiversity countries (Sasidharan et al. 2011; Madhumitha et al. 2012). The first steps to consume the biologically active compound or phytochemicals from plant resources are extraction.

The research and application on natural products started with the extraction techniques that play an important role to the extraction quantity (Yield), quality (extracted phytochemicals) and also to the subsequent analyses accomplished to evaluate the biological and chemicals activities. Extraction is the separation of bioorganic substances of natural food from its inert components by using various solvents in standard extraction procedures. A wide range of techniques with different methods and principles of extraction is available nowadays (Azwanida 2015a, 2015b, 2015c). These include various techniques of extraction namely immersion technique, soxhelt method, maceration method, steam distillation method, microwave method and ultrasound method. With such diversity of methods present with different principles of extraction, selection of proper and best extraction techniques needs meticulous evaluation to achieved high extraction quantity (yield) and quality (extracted phytochemicals) of extract. Hence, this chapter describes the principle, advantage and disadvantage of the conventional and non-conventional extraction methods with examples to help in the selection of proper methods. The selection of proper extraction methods are crucial because it is necessary to extract the desired

chemical components from the plant materials for further characterization and biological activity evaluation. Proper extraction methods must be selected to assure that potential active constituents are not lost, distorted or destroyed during the extraction of the plant samples (Nwankwo et al. 2013). Moreover, it is very important to consider the polarity (non-polar to polar and thermally labile) of the compounds as to know the methods of extraction to be considered (Nwankwo et al. 2013). Dry conditions of plant materials also are very important to prevent microbial fermentation and subsequent degradation of metabolites (Seidel 2012) which might affects the extraction quality. Besides that, the grinding of plant material into smaller particles also important to improve the subsequent extraction by rendering the sample more homogenous, increasing the surface area, and facilitating the penetration of solvent into the cells (Seidel 2012). Subsequently, a proper extraction methods will be selected to assure that potential active constituents are extracted. Therefore, specifically, this chapter is intended to provide insights on conventional extraction methods such as immersion, maceration, steam distillation method and soxhlet extraction and the non-conventional extraction methods such as microwave and ultrasound extraction.

4.2 Immersion Technique

Immersion technique is acceptable for both initial and large-scale extraction purposes. In immersion technique, the powdered plant material is dips completely in a solvent in a cylindrical or conical container. After the immersion of the plant material additional filtration of the extract is required to separate the plant material and extract before the evaporation step. Subsequently, the filtrate is concentrated under the vacuum using a rotary evaporator at 60 °C to remove the solvent used for the extraction.

4.3 Soxhelt Method

The extraction of bioactive component from herbal material can be defined as solvent extraction of solid sample, which is commonly known as solid-liquid extraction although the exact term is suggested to be leaching or lixiviation according to physicochemical terminology (Luque de Castro and Priego-Capote 2010; Luque de Castro and García-Ayuso 1998). This process is often carried out using Soxhlet apparatus which was initially used for determination of fat in milk (Soxhlet 1879). This apparatus was invented by the German agricultural scientist, Franz von Soxhlet in 1871 (Fig. 4.1). Although, various modifications have been carried out on it to increase its efficiency, its basic design remains the same (Jennings et al. 1981). The Soxhlet apparatus consists of a vertical glass tube that functions to hold the herbal sample that is to be extracted and this unit has both a siphon and vapor tube built

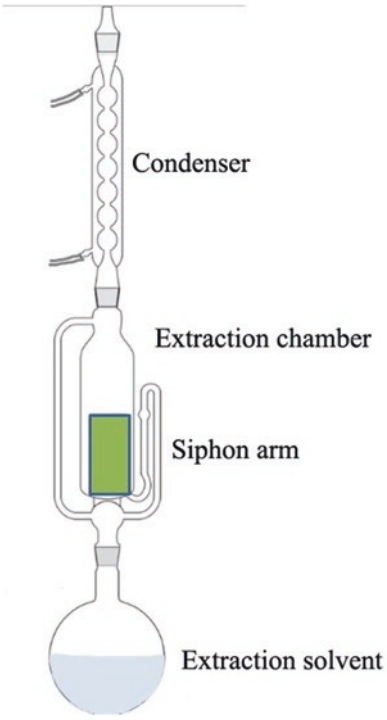

Fig. 4.1 Soxhlet apparatus

into it. The herbal sample is often ground into a fine form to facilitate better transfer of the active component into the solvent and the herbal sample is filled into a porous timble and the timble is often covered for example with cotton. The sample containing timble is placed into the vertical glass tube of the Soxhlet and a reflux condenser is attached to the top of Soxhlet whereas its lower end is fixed to a flask containing the organic or in some cases aqueous solvent. Often the herbal sample is soaked or wetted with the solvent initially. The solvent in the flask is heated by a heating mantle and its vaporises through the vapour tube and the condenser causes the distilled solvent to fall into the extraction chamber. When the level of solvent in the glass tube or extraction chamber reaches the overflow level, it flows back through the siphon tube into the distillation flask carrying with it the extracted constituent of the herb. This overall process is repeated until complete extraction is achieved and this is noticeable when the solvent in the extraction chamber is clear.

The most outstanding feature of this technique is that in comparison with the other common and inexpensive method of maceration is that the sample is brought into contact with fresh solvent repeatedly. This and the increased temperature of the fresh solvent due to the fact that the heat applied to the distillation flask reaches the extraction chamber to some extent, causes increased extraction efficiency. In principle, no filtration is required but often it is carried out as small portion of sample could have 'leaked out' and been siphoned into the distillation flask. However, the

filtration here is not as tedious as that involving the maceration process. The Soxtec apparatus or as mentioned at times as the automated Soxhlet is a closely related technique that makes filtration of the final extract almost unnecessary.

This Soxtec technique is basically based on the Randall modification of the Soxhlet method and an example of commercially available device is the Foss-Tecator Soxtec Avanti apparatus. The extraction technique in the Soxtec apparatus can be divided into three stages which are boil, rinse and evaporation. As with traditional Soxhlet, the sample is placed in a timble and in the boiling stage, the timble is lowered into the boiling solvent whereas immediately after boiling, in the rinse stage the timble is raised above the level of boiling solvent. In the rinse stage, the refluxed solvent percolates or rinses the intended solute out of the herbal sample. During evaporation, solvent flow is blocked from returning to the extraction cup and therefore, it flows out through a tube into a collection tank. The commercially available systems enable exchange from one to other step by switching a lever (Luque de Castro and Priego-Capote 2010; Evans 2009). The Soxtec methods require only 20–25% of the time required for traditional Soxhlet extraction (Anderson 2004). The use of Soxtec apparatus with herbal samples seem to be more in line with the original designs use to separate milk from fat as the technique was used to either isolate fat or obtain oil from herbs or plant samples (Tariq et al. 2016; Bergonio and Perez 2016; Chaisawadi et al. 2005).

4.4 Maceration Method

The word maceration is derived from the Latin *macerare,* describing to soak (Ansel et al. 1995). The maceration technique evolved from the wine making industry which was then employed extensively in the field of medicinal plant research. During this process, the plant materials are immersed in a menstruum as whole, coarsely or powdery form in a tightly closed wide-mouthed vessel with frequent agitation or stirring (Handa et al. 2008). Maceration is simply performed at a temperature between 15 °C and 20 °C for a period of 2 to 14 days or until the soluble matter is dissolved (Ansel et al. 1995). The agitation favours the repeated flow of solvent contacting the surface area of samples. This step also plays a crucial role in reducing the strength of plant cell wall to allow the solvent to penetrate and discharge the soluble phytochemicals. The mixture is then strained using a clean cloth by filtration leaving the marc behind (Fig. 4.2).

There has also been an alternative step to repeated shaking or agitation in maceration. Here, the plant materials are placed into a porous cloth resembling to a tea bag. By suspending the sample bag in the menstruum, a collective portion of dissolved constituents will be seen settling at the bottom of the vessel due to specific gravity. Dipping the bag from time to time will speed up the extraction process (Ansel et al. 1995).

Utilising this conventional method, the choice of solvent will determine the type of bioactive components. The frequently used solvents are water and alcohol, or the

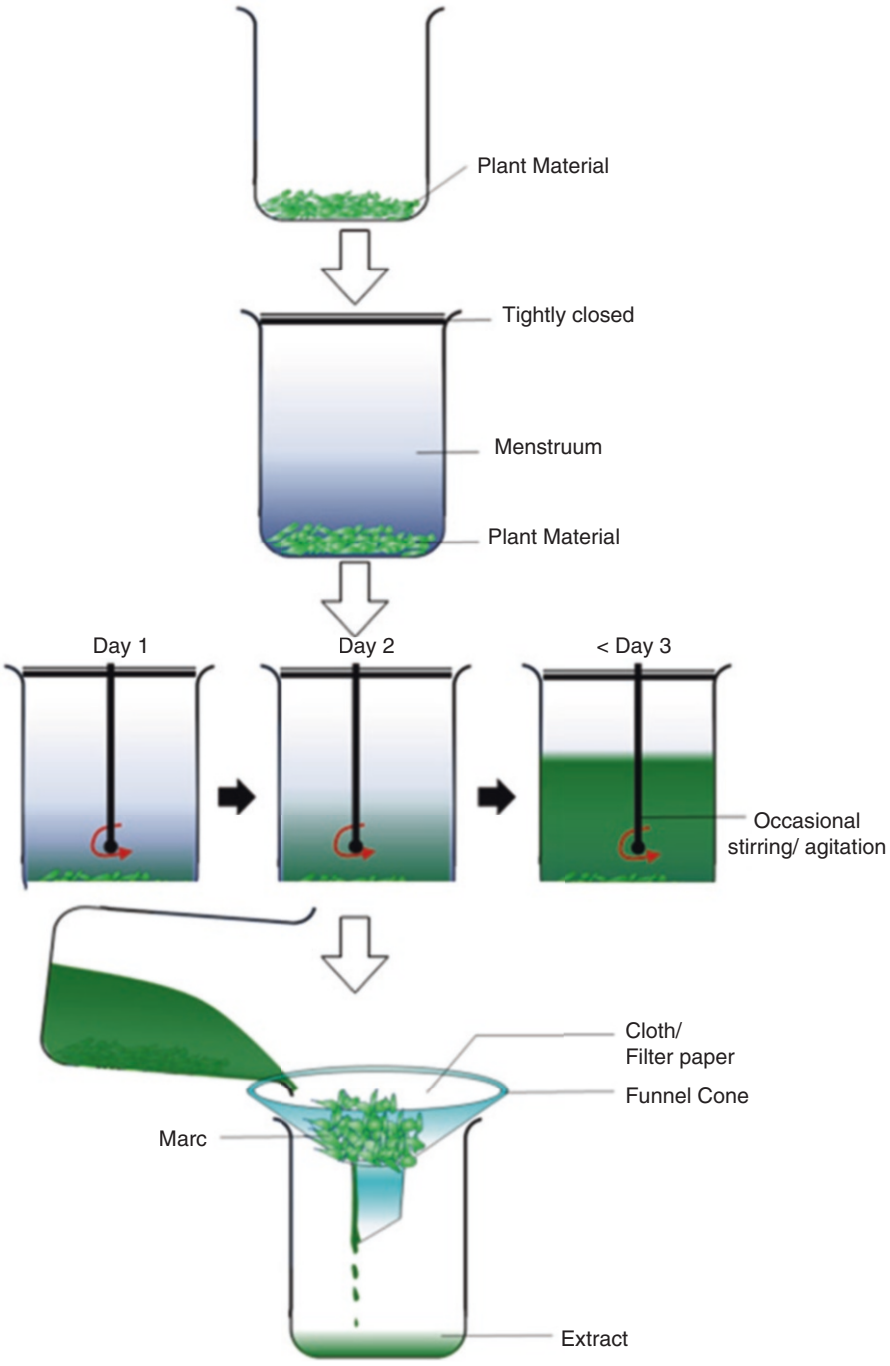

Fig. 4.2 Maceration method work flow

combination of both. Red or white wines are also used occasionally. Precaution should be taken when employing water as prolonged maceration will invite fungal, mold and yeast contamination which is otherwise impossible to occur in alcohol or hydroalcoholic solutions (Handa et al. 2008; Azwanida 2015a, 2015b, 2015c).

The manner by which maceration procedures are further conducted can be listed into following processes; Maceration for organized drugs, maceration for unorganized drugs and multiple maceration. The maceration for drugs are categorised as organized and unorganized as the process differs slightly. Organized drugs possess origins of samples with defined cellular structure such as leaves, roots and barks whereas unorganised drugs are non- cellular (e.g. gum, resin) (Singh 2008).

The maceration for organised drugs requires the marc to be pressed as a considerable amount of liquid is still adhering to it. As for the unorganised drugs, the marc does not required to be express as the necessary constituents are in soluble state where the marc is usually slimy or gummy.

Repeated maceration is a modification to the general process of maceration which is considered more competent than the initial description of maceration process. In the course of pressing the marc, a substantial amount of active components will still remain unexpressed within the marc; hence a double or triple maceration seemed indispensable. The repeated maceration is preferred when the active principles are considered precious (Singh 2008).

4.5 Steam Distillation

Steam distillation is a well-known extraction method, applied especially for the thermal sensitive plant materials. Considering these compounds tend to degrade at higher temperatures, steam distillation ensures that the plant material is not subjected to temperature higher than 100 °C as the hot steam is generated outside the still in a satellite steam generator known as the boiler and the amount of steam can also be promptly controlled.

Briefly, steam distillation process also requires the conventional solvent extraction technique whereby the plant material in the solvent is connected to the condenser (Fig. 4.3). The flask containing plant material is placed in a heating mantle. When the boiling point of the solvent is reached, vapour generated is subsequently condensed through a condenser. The distillate which is the extract can be collected while the solvent can also be separated and reused again (Nahar and Sarker 2012).

4.6 Microwave Method

Microwave could be defined as non-ionising, electromagnetic radiation. In contrast to radio waves, microwaves can be characterized by relatively small wavelength, ranging from 1 mm to 1 m and high frequencies ranging from 300 GigaHertz (GHz) to

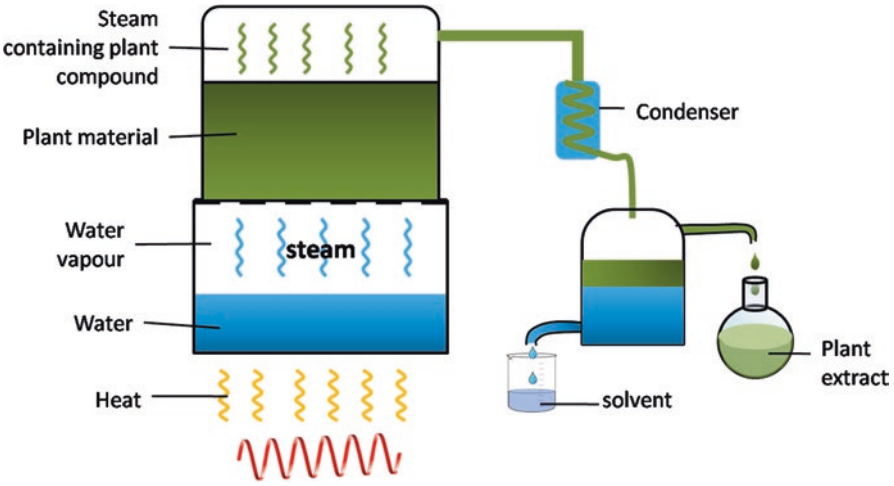

Fig. 4.3 Steam distillation set up

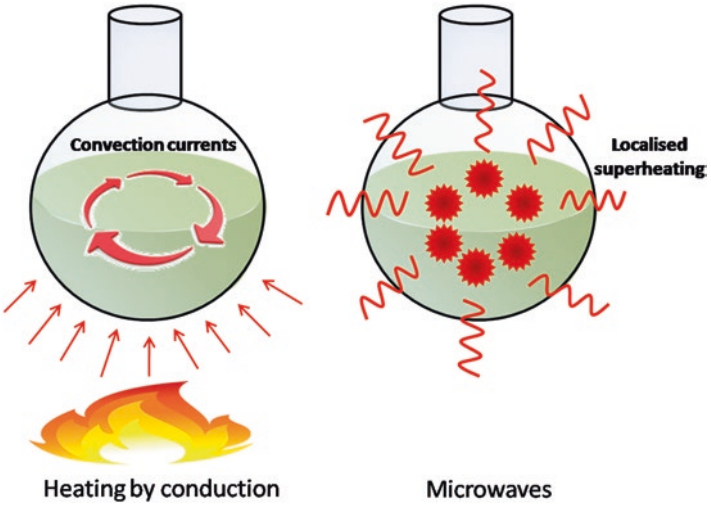

Fig. 4.4 Heat up process by conduction and microwaves

300 MegaHertz (MHz), with the photon energy ranging from 1.24 millielectron Volt (meV) to 1.24 microelectron Volt (μeV) (Hitchcock 2004). Microwaves carry electric and magnetic fields which are perpendicular to each other due to their electromagnetic nature (Kaufmann and Christen 2002). This electric field presents heat through two concurrent mechanisms namely, dipolar rotation caused by the arrangement of molecules carrying dipole moment on the electric field; and ionic conduction (Thue'ry, 1992). Heat energy is basically produced when the vibrating molecules

collide with each other. Thus, it can be deduced that microwaves heats the whole sample synchronously, in contrast to the conventional conductive heating method (Fig. 4.4).

Microwave extraction which was first exploited by Ganzler and his colleague is actually a combination of microwave and conventional solvent extraction (Ganzler and Salgo 1986; Ganzler and Salgo 1987; Ganzler et al. 1990). Microwave heating disrupt the hydrogen bonds contributed by the dipole rotation of the molecules and consequently enhance the diffusion of dissolved ions (Kaufmann and Christen 2002). Solvent nature, solvent volume, extraction time, microwave power, matrix characteristics, and temperature may affect the microwave extraction mechanism (Delazar et al. 2012; Fowsiya et al. 2016).

4.7 Ultrasound-Assisted Extraction (UAE)

An optimal extraction process aims to maximize the yield whilst minimizing the extraction of undesirable by-products, without changing the properties of the target compound. One of the modern extraction non-conventional methods that have made significant progress in the processing of medicinal plant is ultrasound-assisted extraction (UAE). Using this low cost technology, several classes of plant constituents such as oil, bioactives, antioxidants, pigments and other organic compounds have been successfully extricated (He et al. 2016). The important concept behind this technique lies in the frequency of the applied ultrasound ranging from 20 kHz to 2000 kHz that causes cell destruction. Details on the mechanism of UAE as well as the advantages and limitations of this technique will be discussed in this section.

4.7.1 Mechanism of Ultrasound-Assisted Extraction

Plant cells consist of organelles and cytoplasm which are enclosed by walls. UAE utilises ultrasound pressure waves to accelerate the process of extraction through the induction of cavitational damage in the cells using probe system. This effect is achieved through augmentation of cell wall permeability to break down the size of the cell (Sun et al. 2011). The high shear forces thus increase the number of cells directly exposed to the solvent to enhance mass transfer of the soluble constituents into the cells (Toma et al. 2001). The process of extraction can be improved by breaking down the material prior to ultrasound such as through milling or sonication. However, when dried plant materials are used, they have to be subjected to immersion in solvent for hydration purposes to enable bulk transport of the solvents by diffusion and osmosis processes, and rinsing the plant constituents out (Fig. 4.5). Ultrasound may be able to facilitate this process through enlarging the pores of the cell wall and increasing the swelling index during sonication (Toma et al. 2001;

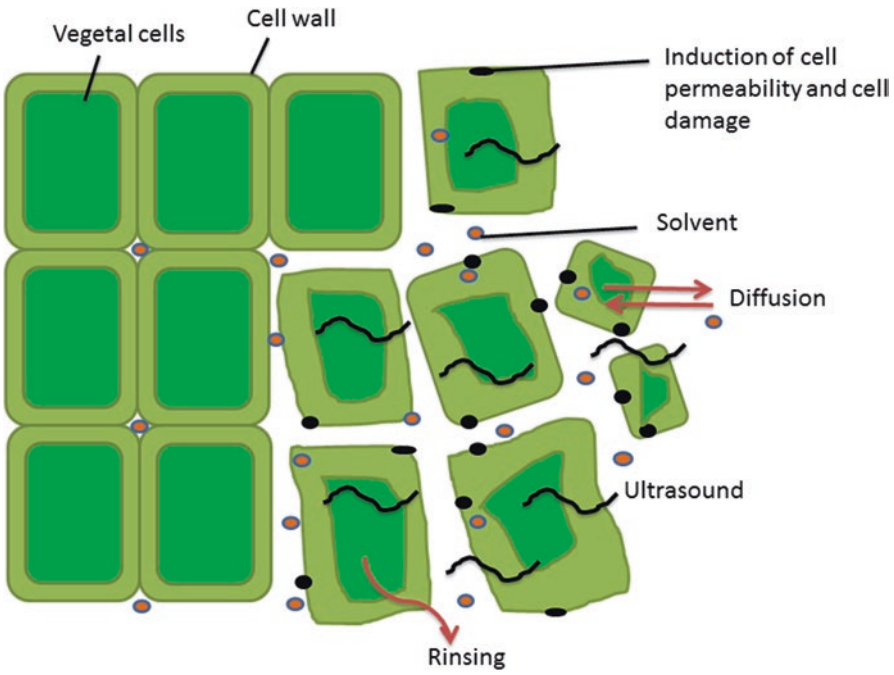

Fig. 4.5 Schematic diagram depicting plant cell structure. Ultrasound frequency enlarges pores on the cell wall to increase cell permeability to allow diffusion of solvent and rinsing out of plant constituents from the cell during ultrasound-assisted extraction

Saleh et al. 2016). The length of time of ultrasound exposure also affects the degree of cell wall disruption. Exposure of plant materials to ultrasound for 30 min and 60 min each results in a steady degradation of cell wall and broken cells structures with undefined shapes respectively (Chemat et al. 2016). In addition, the use of lower ultrasound frequency has been found to be more effective in disrupting cells for optimal yield compared to that at higher frequency in which the material remains unaffected (Toma et al. 2001).

4.8 Advantages and Disadvantages of Various Extractions Methods

Different extractions methods including conventional and non-conventional approach were discussed in this chapter for phytochemical extraction has its own special advantages and disadvantage.

4.8.1 Advantages and Disadvantages of Immersion Technique

The advantages of immersion technique are large amount of plant material can be extracted in apparatus of compact size, cheap and easy to performed. There are several factor to consider when carrying out immersion technique for plant material extraction. The extent to which the material is ground can influence extracts' yields. Hence, powdered plant material should be used for this technique. Moreover, if the plant material is not distributed homogenously in the cylindrical or conical container, the solvent may not reach all areas and the extraction will be incomplete. The other disadvantages of immersion technique are that large volumes of solvents are required and the process can be time-consuming.

4.8.2 Advantages and Disadvantages of Soxhelt Method

The advantages of Soxhlet extraction is that it is a very simple method that requires little training and has been mentioned by Luque de Castro and Priego-Capote (2010) as able to extract more sample mass than most of the latest alternatives such as microwave assisted extraction and supercritical fluid extraction. The above authors also discussed the disadvantages of the technique and mentioned that the main problem of Soxhlet extraction is that long period of time is required. Secondly, the use of heat makes it not that attractive for thermolabile compounds. Samples are usually extracted at the solvent boiling point over long periods, which can result in thermal decomposition of thermolabile target species. The formation of artifacts due to long exposure to organic chemicals has also been mentioned as a problem with the Soxhlet technique (Jones and Kinghorn 2005). The two authors also suggested retaining a sample of the original plant material for analysis in case one of the isolates should later be suspected of being an artifact of extraction methods. In that case they suggested the reference material can be extracted using nonreactive solvents and mild conditions, and the resulting extract analyzed using LC-MS/MS to determine if the compound is present in the original plant material. Some examples of artifacts in herbal plants are the presence of diterpene methyl esters artifacts in extract of *Andrographis paniculata* (Xu et al. 2010). The extraction in that work was by maceration which implies that Soxhlet extraction with usage of heat would pose a bigger risk for artifact formation. Another example of artifact is ginsenoside Rg3 which is present in heat processed ginseng (Christensen 2008) and it has to be mentioned that there are many other examples in scientific literature.

The choice of solvent for Soxhlet extraction is also important and those with low boiling points are generally easier to use from the standpoint that they are more easily concentrated and also because a lower temperature in the extraction chamber is maintained. Acetone, chloroform, dichloromethane, ethyl acetate, and n-hexane or petroleum ether evaporate relatively quickly, are often used (Jones and Kinghorn 2005) whereas water is rarely used.

There have been various modifications to the Soxhlet to increase its efficiency and one of it is to assist extraction with auxiliary energy as in the case with microwave assisted extraction and a commercially available system is Soxwave-100 (Luque de Castro and Priego-Capote 2010; Mandal et al. 2015). Two examples of studies using the apparatus are optimization study on microwave assisted extraction with ginseng samples (Kwon et al. 2003) as well as study comparing this technique with original Soxhlet extraction on antibacterial and antioxidant activity of volatile oils isolated from dried *Schisandra chinensis* Baill. seeds (Teng and Lee 2014). Another example of additional energy supply to increase efficiency of extraction is with the use of ultrasound but as with microwave assisted extraction, it too has not found widespread usage and the original design remains most popular.

4.8.3 Advantages and Disadvantages of Maceration Methods

The maceration process is the most easiest and simple method which do not require laborious or time consuming preparation. To maximize the extraction technique, alteration in temperature as well in menstruum choice can be easily made to suit one's preference; Cold maceration is opted when concerns the extraction of thermolabile therapeutics while different menstruum influence the extraction of different compound polarities. However, the large flow of organic waste compels for a better waste management (Azwanida 2015a, 2015b, 2015c). Apart from this, the traditional maceration method also necessitates longer timeframes with less product yield as compared to other methods such as ultrasound extraction and microwave assisted extraction (Trusheva et al. 2007a, 2007b).

4.8.4 Advantages and Disadvantages of Steam Distillation Methods

The prominent benefit of steam distillation method for plant extraction is the efficiency of the process to extract the heat sensitive bioactive compounds. However, there are few drawbacks of steam distillation method of plant extraction which is important to be taken into consideration. Despite of the longer extraction process, it is believed to induce chemical alterations of the bioactive compounds and loss of most of the volatile molecules while removing the solvent (Rohloff 1999; Khajeh et al. 2004). Furthermore, toxic residues from the solvent can also be a part of the extract and thus it can be considered to possess a very low selectivity of compounds (Al-Marzouqi et al. 2007). Extract recovered through steam distillation method tend to contain high levels of monoterpenes sesquiterpenes and oxygenated sesquiterpenes (Sadjia et al. 2012). Moreover, alterations in the chemical characterization of the compounds have been reported (Fleisher 1991; Fleisher 1990). Advance steam

distillation technology using supercritical fluid extraction whereby carbon dioxide is applied as the solvent have shown to overcome these drawbacks (Hamburger et al. 2004). Nevertheless, optimization of the extraction conditions such as the extraction pressure and the extraction period is proved to produce high yield with best quality (Naji et al. 2008).

4.8.5 Advantages and Disadvantages of Microwave Methods

One of the dominant advantages of microwave extraction is that this method can be considered as an environmental friendly extraction because of its solvent-free operation. Besides being a green technology, microwave extraction is also a cost-effective, time-saving extraction method with a higher extraction rate and reduced solvent usage, in contrast to several conventional extraction methods such as maceration and soxhlet extraction (Delazar et al. 2012). However, microwave extraction condition is highly taken into consideration since some bioactive compounds might end up in thermal degradation, especially Tannins and anthocyanins (Trusheva et al. 2007a, 2007b; Azwanida 2015a, 2015b, 2015c). Meanwhile, small thermal stable phenolic compounds such as gallic acid, ellagic acid, quacertin, isoflavin and trans-reservetrol are troublesome to be extracted through this method (Azwanida 2015a, 2015b, 2015c). Though microwave extraction is a rapid and efficient extraction, the selectivity of bioactive compounds is low and was also reported to extract undesirable wax from propolis (Trusheva et al. 2007a, 2007b).

4.8.6 Advantages and disadvantages of Ultrasound-Assisted Extraction Methods

Ultrasound-assisted extraction is considered as a green and environmental friendly option compared to conventional methods for extraction of natural products (Li et al. 2012) (Fig. 4.6). Under optimized conditions, UAE has been shown to increase the yield of target compounds compared to those using Conventional Solvent Extraction (CSE) method, as shown in studies on total anthocyanins and phenolics extraction from Blueberry Wine Pomace (He et al. 2016). In addition, UAE can offer high reproducibility using minimal solvents and energy consumption and reduced CO_2 emissions (Chemat et al. 2016; Pradal et al. 2016). For example, under optimized parameters, UAE is able to provide superior extraction for boldo leaves compared to a conventional maceration within shorter processing time that resulted in higher yield without compromising the product quality (Petigny et al. 2013). However, despite the many advantages of using UAE, this method is not without any setback. Although UAE method is brilliant for small scale applications, its large

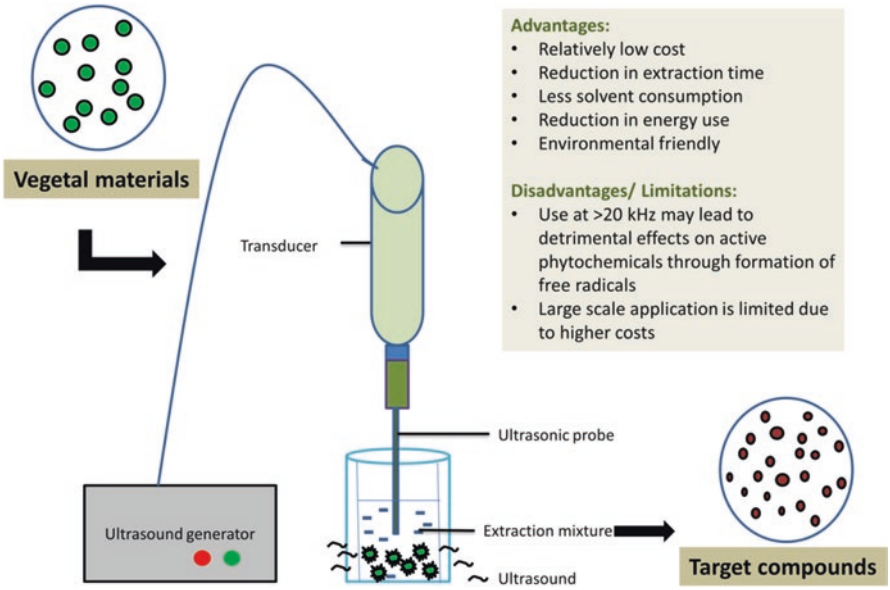

Fig. 4.6 Advantages and limitations of ultrasound-assisted extraction technology in the process of extrication of plant compounds from vegetal materials

scale application is somewhat limited due to higher costs. In addition, ultrasound frequency exceeding 20 kHz may cause adverse effects on the plant constituents through formation of free radicals (Zhang et al. 2015), suggesting caution when using UAE at sub optimal conditions.

4.9 Conclusion

The initial step of extraction process is often a major step in the extraction of bioorganic phase of medicinal plants. The choice of extraction methods such as conventional and non-conventional approach influenced the efficacy and constituents of the final plants extract and play an important role in the biological properties of the extract. In conclusion, there is no common extraction methods is the perfect method and each extraction procedures is special to the plants with its own advantages and disadvantage or limitation as discussed in this chapter.

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Chapter 5
Isolation and Characterization of Bioorganic Phase from Food Source

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Abstract Present and future health care systems are more demanding on the discovery and usage of novel drugs, which should have a potent target system with the pharmacokinetic and pharmacodynamic properties. Available drugs used currently are chemically synthesized and some of them are yet to be studied for their toxicity assessment. Bioorganic phase can be an indispensable field on isolating and identifying the metabolites from the food sources has become trend in recent days. Indian food systems are embedded with the Indian system of medicine. Indian food plants and Indian spices are highly enriched with the medicinal properties. Their applications are vital in industrial and pharmaceuticals. Hence, isolation of the novel compounds is one of the goal in bioorganic phase by various methods, it may be either traditional (decoction, maceration and solvent extraction) or by recent (ultrasonication, microwave assisted and enzymatic extraction) methods. Identification and characterization of compounds can be done through chromatographic techniques and spectroscopic methods. This chapter deliberates with phyto-constituents from the common food plant products such as vegetables, spices and condiments. Their important phyto-compounds having pharmacological actions and how they were isolated, identified and characterized using different methods were discussed. This could help in gaining knowledge on the important compounds and their properties present in food products.

Keywords *Abelmoschus esculentus* · *Cucurbita pepo* · Microwave assisted chromatography · *Piper nigrum* · Super critical CO_2 extraction · Nuclear magnetic resonance

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_5

5.1 Introduction

The major sources of novel chemical diversity are due to natural products like plants, animals and microorganisms than synthesized compounds. They are also the choice of today's world and it is been considered as primarily required component and catalyst for human welfare and in their health care system. Among them, plant products appears more reliable and rewarding source because of its renewability from the perspective of economy and safety. Therefore, there is a huge interest growing in plants research as therapeutics.These factors force the scientists to develop bioprocesses for producing and isolating the compounds from naturally occurring renewable sources for prospective usage in food, cosmetics and pharmaceuticals industries (Oreopoulou and Tzia 2007). Thus, uses of bioactive compounds having multidimensional benefits are gaining importance in current research. In developed countries, a huge demand for safer foods and cleaner production are growing in recent times. Some parts like latex, hull, bark, stalks, pods, seeds, roots and flowers are found useless in some plants,but in point of fact they encloses the important phytochemicals with several bioactive properties (Kaneria et al. 2009; Madhumitha and Saral 2009; Fowsiya and Madhumitha 2017; Anupama et al. 2004).

5.1.1 Indian Spices

Indian spices and condiments are playing the major role in the food industry and it increases deliciousness to the food products by its flavour, aroma and colour. Spices are commonly known as different parts of plants such as leaves, seed, bark, latex, flower, rhizome, stem and fruits. Every spices own its specific characteristics either solitary or combinations for additional quality of the products. Indian resources are enriched with spices and are highly exported to the market, which are indispensable in the food industry. A historical event point out an importance of spices that at the arrival of Portuguese, the Malabar pepper (black pepper) was traded by Vasco da Gama. This discovery made them to maintain their supremacy by accommodating and developing trade market at the South Indian kingdom of Calicut (Prange 2017).

Indian food resources, especially the South Indian traditions in food system are blended with nutrition and medicinal property. Some spices commonly used are ginger (*Zingiber officinale*), omam plant (*Trachyspermum ammi*), cumin (*Cuminum cyminum*), bay leaf (*Cinnamomum tamala*), cinnamon bark (*Cinnamomum zeylanicum*), black pepper (*Piper nigrum*),clove (*Syzygium aromaticum*), mustard (*Brassica juncea*), saffron (*Crocus sativus*), cardamom (*Elettaria cardamomum*), large cardamom (*Amomum subulatum*)and garlic (*Allium sativum*)are essential ingredients to furnish the cookery. Indian system of medicine [ISM] such as Siddha, Ayurveda and Unani are highly employed with these plant sources to cure many diseases (Mishra 2003). Since the modern system of medicine arises, the exploration of compounds

responsible for the particular mechanism was identified in larger extent. There are innumerable medicines were found and still being explored to find out their pharmacological function.

5.1.2 Bioorganic Importance of Indian Spices

"Bioorganic"- term itself explains the origin comes from the combination of biochemistry with organic chemistry. It is an interdisciplinary path, which helps in unravelling scientific mysteries behind the health issues by sharing both the concepts from their respective way. Those obscurities have been solved through bioorganic principles.

Most of the organic compounds from various food and medicinal plants identified are found to be primary or secondary metabolites (Manivel et al. 2008). Since the traditional Indian system used these herbs in their day to day life, the compounds from these sources were identified, isolated, characterized and purified. It is a quite interesting point to note, where the isolation becomes very easy and fewer becomes difficult to purify the products from the interfering substances. Chlorophyll is one of the problems, when isolation is focused on other metabolites from leaf, in case the compound predominantly present in that part. Plant secondary metabolites are commonly classified as alkaloids, flavonoids, terpenoids, steroids, cardiac glycosides and essential oils. Not only in the higher plants, even algae and prokaryotes are capable of producing the organic compounds, which are playing a tremendous role in the field of medicine. For example, penicillin is mainly isolated from the organism called "Penicillium *sps*", and high protein rich cell mass named Single cell protein (SCP) was produced from the algae "Spirulina" (Glazer and Nikaido 2007). So, this chapter is mainly deals with the Indian spices their phytoconstituents and how they were identified. The common extraction and identification of these bioorganic compounds through various techniques were mentioned below in a schematic representation (Fig. 5.1).

5.1.3 Phenolics in Vegetables an Essential Secondary Metabolite

Plant metabolites are an important basis of organic acids, minerals, sugars, dietary fibre and phytochemicals having physical, chemical and biological activities,which are activated towardspathogen attack or tissue damage.They all belong to a number of families and known to evolve from different pathways with specific structural characteristics as follows; Alkaloids are synthesized by shikimic acid pathway and TCA *i.e.* tricarboxylic acid cycle (aliphatic amino acids). Terpenes are synthesised using mevalonic acid and MEP (Non-mevalonate) pathway. They

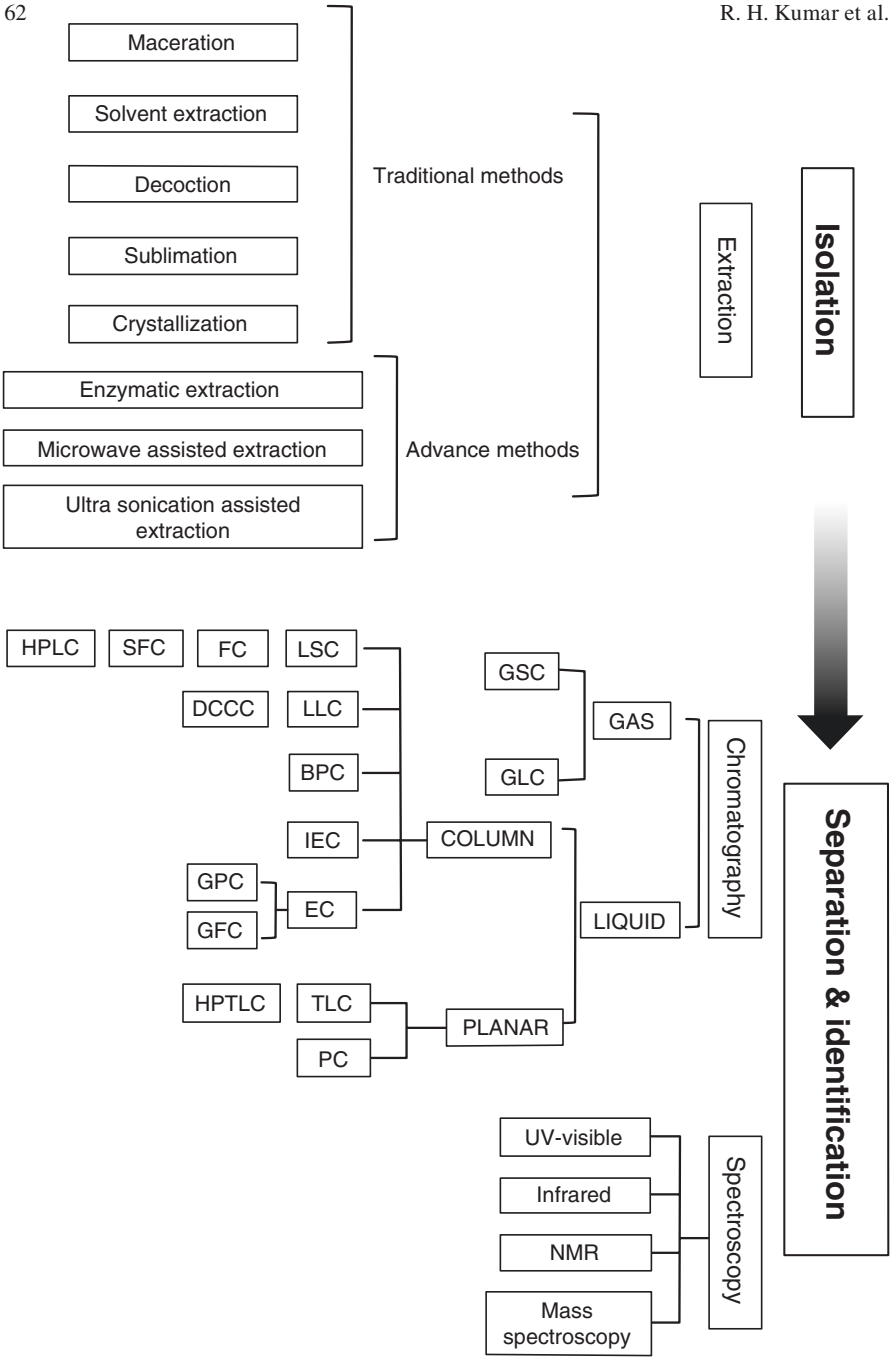


Fig. 5.1 Isolation, separation and identification bioorganic compounds through various process. Gas chromatography (GC); Gas -liquid chromatography (GLC); Gas -solid chromatography (GSC); thin layer chromatography (TLC);High performance thin layer chromatography (HPTLC); Paper chromatography (PC); Liquid-solid chromatography (LSC); Flash chromatography (FC);

are further sub classified to phenols, phenolic acids, flavonoids, quinones, isoflavonoids, flavones, tannins, flavonols, coumarins, tepernoids (condensation of acetate units) and phenyl-propanoids (alteration of aromatic amino acids). By condensation of phenylpropanoid, the flavonoids are evolved with malonyl coenzyme A (three molecules).

Phenolics are mainly synthesized through malonic and shikimic acid pathway but with the involvement of pyruvate, acetate, acetylCoA, amino acids and malonyl-CoA; it also undergoes the metabolic pathways such as pentose phosphate where the shikimate and phenyl-propanoid having phenyl ring with C6 and C3 side chain acts as a precursor. Then, phenylalanine and tyrosine are the two amino acids which specifically involves in producing plants phenolic compounds. Hydroxy-benzoic and hydroxyl-cinnamic acids are the two classes of phenolic acids commonly originate in plant materials (Chandrasekara and Josheph Kumar 2016).

Phenolics are highly soluble in polar solvents and precipitates with proteins. It involves in stimulating phagocytic cells, host-mediated tumor activity and many other physiological activities. It is traditionally used for protecting inflamed mouth surfaces, treatingwounds, diarrhea, hemorrhoids and acts as anti infective by stimulating macrophages (Spatafora and Tringali 2012). In several previous reports, phenols are also established for its antimicrobial properties which are non-toxic than synthetic compounds and nanoparticles (Kumar et al. 2014). Their toxicity level against microbes is depends on the number and position of hydroxyl groups present. Phenols inhibits microbial growth by deprivating their substrate, disrupting membrane or cell homeostasis, inhibiting or inactivating enzyme, by forming complexes with its cell walls and the metal existing which leads to cell death (Nohynek et al. 2013). So in this chapter,we also focus our discussion on rarely explored vegetables having hidden medicinal values.

5.1.4 Bioorganic Compounds from Indian Spices

In olden days, the traditional practitioners believed that every plant has a power of solving health issues. As a modern civilization turned on, educational systems are more implemented and science of findings grown uncontrollably. Pure compounds were extracted, identified and characterized, their mode of action was understood, and they are being isolated or chemically synthesized in large scale. In this chapter, we discuss some of the major Indian food spices and their identified compounds and the method of extraction were discussed below.

Fig. 5.1 (continued) supercritical fluid chromatography (SFC); Liquid-liquid chromatography (LLC); Droplet counter current chromatography (DCCC); Bonded phase chromatography (BPC); High pressure liquid chromatography (HPLC); ion exchange chromatography (IEC); exclusion chromatography (EC); gel permeation chromatography (GPC); Gel filtration chromatography (GFC); Infrared(IR); ultraviolet (UV); Nuclear magnetic resonance (NMR); mass spectroscopy (MS) (Ikan 2008)

5.1.5 Piper nigrum *Linn. (Black Pepper)*

Piper nigram belongs to the family piperaceae. It is native to Indo-Malaysia and grown in large areas of Western Ghats including Maharashtra, Karnataka and Kerala. In Ayurveda, it is known as maricha, vellaja, suvvrita, uushna and krishnaa. In Siddha/Tamil, milagu. It is used mainly in pungent taste foods. For example, soups (veg/non-veg), rasam (an important watery mixer with other condiment including cumin, tamarind and coriander leaf). Pharmacological action such as, carminative, stimulant, bechic, diuretic,anticholerin and antiasthmatic. Bioactive compounds are piperdine, piperine, piperatine, piperyline, piperolein A and B and N-isobutyl-cicosa-trans2-trans4-dienamide (Khare 2008). There are some research out comes which reported on mosquitocidal activity from it amides namely isobutylamides were extracted and studied (Park et al. 2002). Amides are isolated from the acetone extract of pepper.There are three compounds isolated and identified using carbon tetrachloride-ethyl acetate (10:1) as an eluent in column. TLC bands obtained from the mobile phase cyclohexane-ethyl acetate (3:2) were subjected to HPLC by dissolving with mobile phase methanol-water (9:1) and collected fractions (I, II and III) were recrystallized. These samples were examined with NMR spectroscopy.Compound I was obtained (75%) as a waxy solid with a melting point of 86–87 °C. UV absorption showed maximum at 259 nm. IR spectrum showed functional peaks at 3305 and 3290 (NH), 2920 (CH_2),1660and 1610(C=C),1615 (amide C=O), 1540 (unsaturated amide), and 998(trans-CH=CH). ^{1}H–NMR spectrum resulted, δ ($CDCl_3$) 0.89 (s, 3), 0.99 (s,6), 1.20 (b, 6), 2.08 (b, 3), 3.20 (bd, 2, $J = 6$ Hz), 3.75 (b, 1), 5.63–6.16 (m, 3), and 7.26 (s, 1). Compound II was recovered to the tune of 80% from HPLC which arecolourless needles with melting point around 114–116 °C. The UV absorption showed maximum at 260 nm. IR spectral data 3310 and 3290 (NH), 2920 (CH_2), 1655 and 1620 (C=C) and 1630 (amide). Compound III recovered was around 80% from HPLC appeared as a colorless plates with melting point of 120–122 °C. UV absorption showed a maximum at 260 nm. Further analysis like IR spectrum and NMR spectrum were reported. All parametersindicated that the compounds I, II and III as the amides of (E,E)-N-(2-methylpropyl)-2,4-deca-dienamide,(E,E,E)-13-(1,3-benzodioxol-5-yl)-N-(2-methyl propyl)-2,4,12-tri-deca-trienamide and (E,E,E)-11-(1,3-benzodioxol-5-yl)-N-(2-methylpropyl)-2,4,10-undecatrienamide respectively (Su and Horvat 1981). Black pepper is also used in the food preparation for its aroma and taste. In 1999, Jagella and Grosch observed that background reason behind the aroma is due to its monoterpene derivatives such as linalool, α-phellandrene, limonene, myrcene, α-pinene, 3-methylbutanal and methylpropanal. Other odorants also identified which are responsible for its musty off-flavour and mouldy smell are due to 2-isopropyl-3-methoxypyrazine and 2,3-diethyl-5-methylpyrazine. For isolating these volatile compounds, distillation is opted and prior to that, the sample was homogenized with water: dichloromethane (DCM): methanol (4:5:10) mixture three times and excess DCM was used to obtain the extract. The filtered homogenate was dried and run through distillation. The sample was processed as follows (Fig. 5.2) and finally isolated compound were analyzed using HRGC-MS.

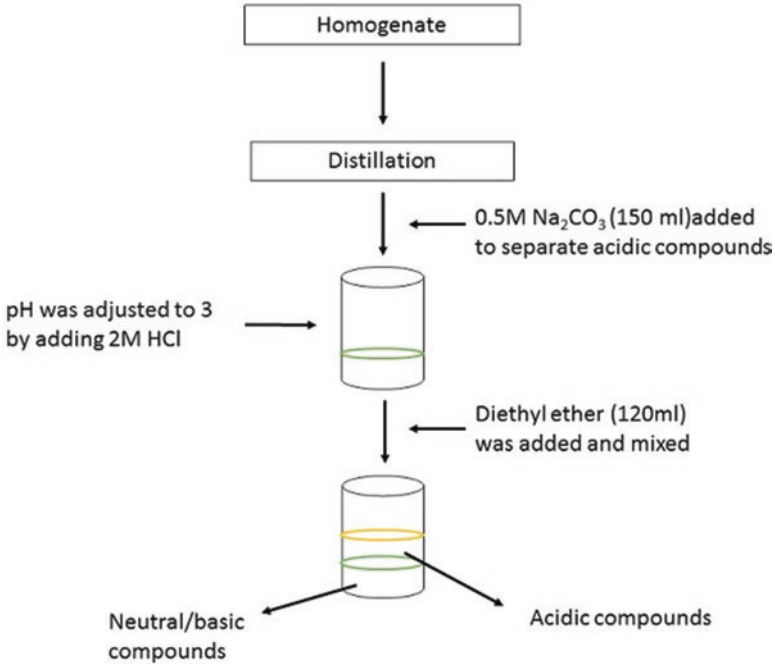


Fig. 5.2 Separation of acidic and basic volatile compounds (Jagella and Grosch 1999)

5.1.6 Curcuma longa *Linn. (Turmeric)*

It is belongs to the family zingiberaceae. It is cultivated throughout India, particularly Western parts of Bengal, Tamilnadu and Maharashtra. In Ayurveda it is called as Haridraa, Priyaka, Kshanda, Haridruma or Gauri. In Siddha/Tamil it is called as Manjal. Pharmacological actions such as anti-inflammatory, hepato-protective, blood-purifier, antioxidant, anti-hyper-cholesterolemic, hypotensive and anti-tumor were reported (Khare 2008). The rhizomes of *C.longa* are rich in curcuminoids a mixture of curcumins, mono-des-methoxy-curcumin, de-methoxy-curcumin, bis-demethoxy-curcumin and other volatile constituents. There are different extraction techniques used to isolate the pure compound curcumin *viz.,* Soxhlet extraction, ultrasonication and microwave-assisted method with various polar and non-polar solvents (Priyadarsini 2014).Curcuminis a yellow color pigment, mainly a hepato-protective prevent from hepatitis and regenerates hepatocytes (Fig. 5.3). For extracting curcumin through various techniques employed (Wakte et al. 2011) is discussed below (Table 5.1).

A shade dried rhizome was powdered and extract was obtained by hydro-distillation. The extract is rich in essential oils and it was analyzed through GC-MS, which provided the hit components such as α-Phellandrene (6.50%), β-Caryophyllene (1.32%), Trans-β-Farnesene (0.54%), Curcumin (10.49), β- Bisabolene (5.71), β-Sesquiphellandrene (9.62), Cis-α-Bisabolene (1.11), Ar-Turmerone (62.88) and γ-Curcumin (1.83) (Mottahedin et al. 2017).

Fig. 5.3 Curcumin

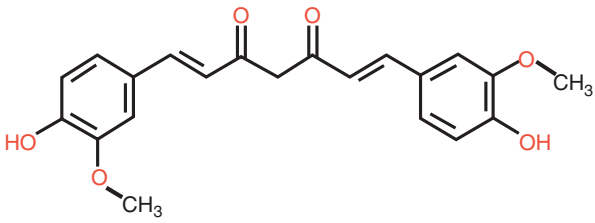


Table 5.1 Curcumin extraction by various methods and its yield (Wakte et al. 2011)

Methods	Soxhlet method	Ultra-sonication		Microwave assisted		Super critical CO_2 extraction
		a	b	a	b	
Sample weight (in grams)	20	20	20	20	20	10
Solvent (in ml)	Acetone	Ethanol/ acetone	Water/ ethanol	Ethanol/ acetone (Presoaking)	Water/ethanol (Presoaking)	CO_2 + ethanol
Extraction condition	8 h	Sample (*C. longa* powder) irradiated (1, 3, 5 or 7 min) prior extraction. Then powder was soaked in solvents and sonicated for 5 min.	Presoaked sample with water/ ethanol at 24 h was extracted by sonication as first method.	Pre-irradiated at 1, 3, 5 and 7mins with 140 W. After pre-irradiation. Sample soaked with solvent was again irradiated at 90 and 60 W under 400 rpm for 5 min	A 24 hours presoaked sample was irradiated at 270 and 50 W respectively for 5 min.	CO_2 with pressure 30Mpa, temperature at 50 °C and flow rate 5 ml/min. Extraction time from 60 to 300 min frequently.
Yield of recovered curcumin (%)	2.1 ± 0.1	Ethanol: 6.57–32.85 at 1–5 min exposure. Acetone: 8–40 at 1-5 min exposure.	Ethanol: 19.70 to 66.66 at 1–5 min. Acetone: 22.15 to 71.42 in 1-5 min.	Ethanol showed 9.71, 29.14 and 48.57 whereas acetone showed 13.71, 41.14 and 68.57 respectively	Ethanol resulted 15.54 to 57.14 at 1–5 min exposure. Water showed maximum 67.01 at 5 min.	69.36 remains constant even after maximum time 300 min (exposure time from 60 to 300 min)

5.1.7 Cuminum cyminum *Linn. (Cumin)*

It belongs to Apiaceae family. It is cultivated in many states of India like Punjab and Uttar Pradesh. In Ayurveda it is called as Shveta-jiraka, Ajaaji, Shukla-ajaaji. In Unani, Safed jeeraa and Kamun. In Siddha/Tamil is Cheerakam, which means maintains internal system of the body. Indian foods, especially in southern part of India used to prepare "rasam" from this seed.Pharmacologicals actions like

carminative, antispasmodic, diuretic, stimulant, antibacterial, anti-diarrhoeal were reported. Seeds of this plant has 14.5% lipids and 14 flavanoid glycosides, 7- apigenin, 5 -luteolinand 2 –chrysoeriol group (Khare 2008).

A study was conducted to measure the essential oil and fatty acid content from the seed of cumin plant, which stated that petroselinicacidis a major component of about 41.42% from total fatty acid, 1.21% of essential oil and traces of chemotypescuminaldehyde/γ-terpinene (Bettaieb et al. 2011).One more study indicated that the total yield of its essential oil content was 3.8% from dried seeds of cumin extracted by conventional hydro-distillation method. GC-MS analysis reported the presence of 37 compounds from 97.97% of oil. Majorly, 36.31% of cuminal, 16.92% of cuminic alcohol, 11.14% of γ-terpinene, 10.87% of safranal, 9.85% of *p*-cymene and 7.75% of β-pinene (Li and Jiang 2004). A synergistic approach with novel flavonoid glycosides 3′,5–dihydroxyflavone7-O-β-D-galacturonide-4′-O-β-D-glucopyranoside showed a bioavailability of antibiotic rifampicin. Enhanced peak concentration (C_{max}) of 35% and 53% of area under the curve (*AUC*) which helps in the permeation of drug (Sachin et al. 2007). Isolation and identification will be discussed below (Fig. 5.4).

The obtained yellow powder has a melting point about 270 °C and soluble in water. The NMR spectrum (DMSO-d6) showed the δ 3.08–3.75 (m, 17H, sugar protons), 4.5(d, 1H, J = 7.21 Hz,H-1′″), 5.21 (d, 1H, J = 6.82 Hz, H-1″), 6.42 (bs, 1H, H-6), 6.65 (bs, 1H, H-8), 6.81 (d, 1H, J = 8.42, H-5′), 7.09(s, 1H, H-3), 7.35 (q, 1H, J = 8.42 and 1.8 Hz, H-6′),7.80 (bs, 1H, H-2′). ^{13}CNMR (H_2O-CD_3OD). δ 165.36(C-2), 104.01 (C-3), 183.19 (C-4), 160.87 (C-5), 99.41(C-6), 163.09 (C-7), 96.31 (C-8), 157.65 (C-9), 106.50(C-10), 122.36 (C-1′), 114.10 (C-2′), 145.37 (C-3′), 148.74(C-4′), 116.81 (C-5′), 120.75 (C-6′), 101.21 (C-1″), 73.25(C-2″), 77.23 (C-3″), 70.72 (C-4″), 76.89 (C-5″), 62.02(C-6″), 103.39 (C-1′″), 75.02 (C-2′″ and C-4′″), 77.71 (C-3′″) 82.07 (C-5′″), 176.44 (C-6′″).

The LC-MS spectrum of compound showed [M+H] + ion at m/z 625.1, [M+H-galacturonic acid] + at m/z 449.1 and [M+H-galacturonic acid-glucose] +at m/z 287 and the presence of galacturonic acid and glucose constituents. Molecular formula $C_{27}H_{28}O_{17}$ (MW: 624) and was identified as3′,5–dihydroxyflavone 7-O-β-D-galacturonide-4′-O-β-D-glucopyranoside (Sachin et al. 2007).

5.1.8 Cinnamomum zeylanicum *(Cinnamon)*

It belongs to the family Lauraceae. It is also known as *C. verum* Presl. It is cultivated through Kerala and less in Western ghats. In Ayurveda, it is known as Utkata, Daaruchini, Tvak, Chochaa, varaanga or daarushitaa. In Siddha/Tamil, it is known as Elavangapattai. It is used in flavored spicy and savory foods. For example, Biriyani and other veg/non-veg gravies. Pharmacological actions reported in Bark-carminative, antispasmodic, astringent, haemostatic and antiseptic. Leaves have antidiabetic actions. All over the world, it is used as the food odorant and to increase the flavor. Cinnamaldehyde is the major cyclic aldehyde (74%) found in its essential

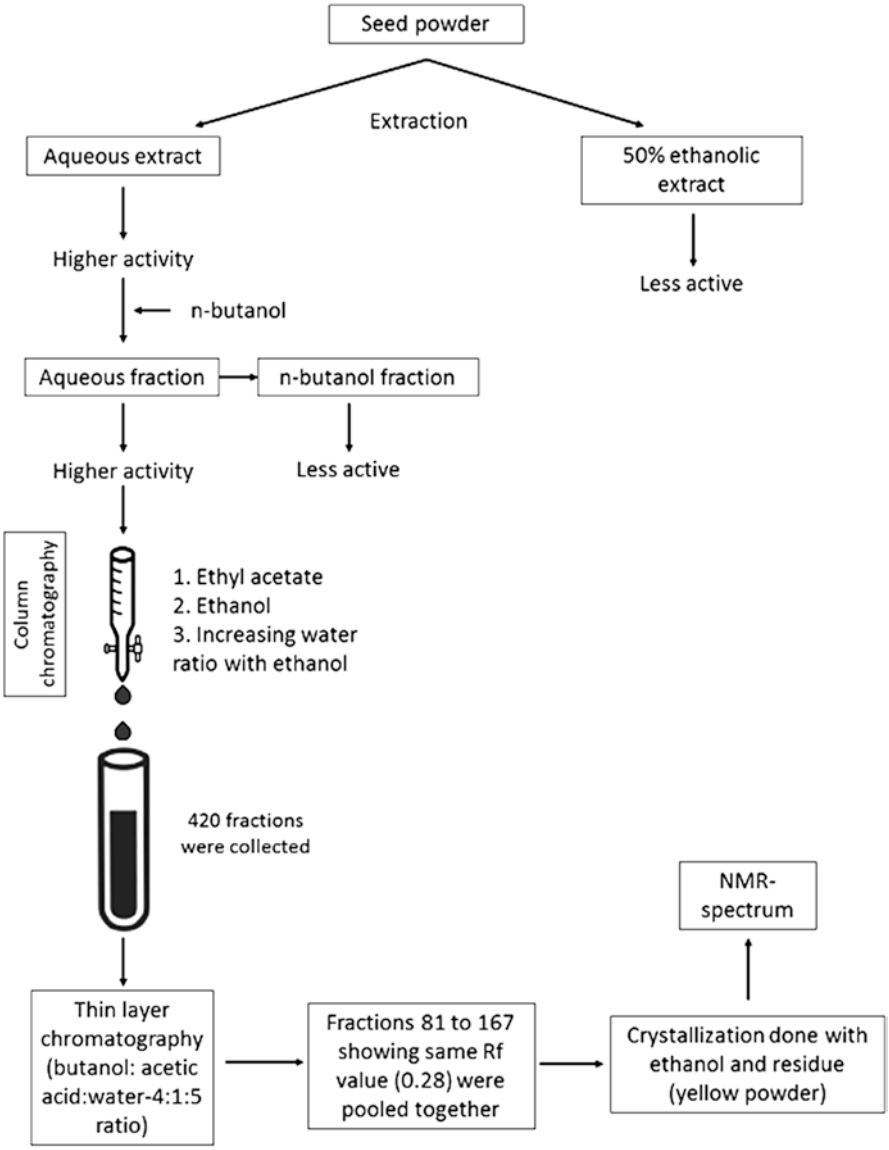
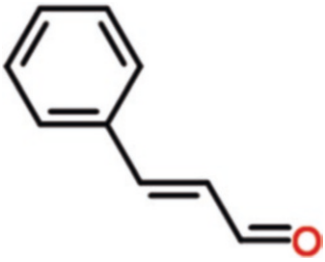


Fig. 5.4 Isolation and identification of novel flavonoid glycosides 3′,5–dihydroxyflavone 7-O-β-D-galacturonide-4′-O-β-D-glucopyranoside from seeds of cumin

oil from bark (Fig. 5.5). Leaf oil consist of eugenol (28–98%) and root bark oil has camphor (60%) as major constituents (Tirtha 2007 and Khare 2008).

Other constituents like ortho-methoxycinnamaldehyde and eugenylacetatewere also reported in the fresh cinnamon bark (Handa et al. 2008).Volatile oil was obtained from the powdered cinnamon fruit stalks (50 g), mixed with ice-cold water

Fig. 5.5 Cinnamaldehyde



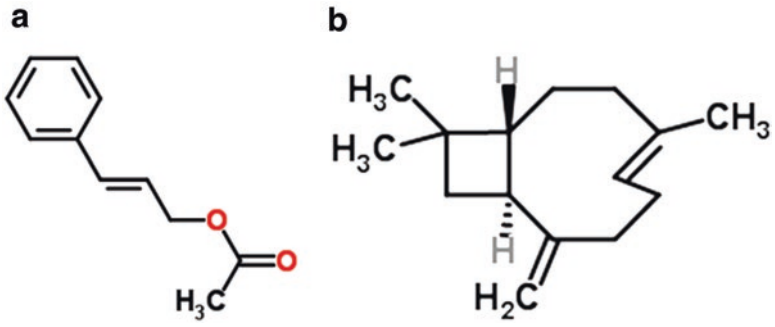


Fig 5.6 **(a)**(E)-Cinnamyl acetate. **(b)** (E)-caryophyllene

(150 ml) and run through hydro-distillation using clevenger with condense apparatus. This yielded up to 0.40 ml of light yellow volatile oil having sweet floral odor. A GC-MS analysis was reported to have twenty-seven compounds, in that (E)-Cinnamyl acetate (36.59%) and (E)-caryophyllene (22.36%) (Fig. 5.6) were found to be predominant compounds (Jayaprakasha et al. 2003).

Biological activity of cinnamon bark and leaf reveals that bark extract found have higher activity for amylase inhibition (IC50: 214 ± 2 to 215 ±10 g/mL), butyrylcholinesterase inhibition ((IC50: 26.62 ± 1.66 to 36.09 ± 0.83 g/mL) (Arachchige et al. 2017).

5.1.9 Allium sativum *Linn. (Garlic)*

It belongs to Liliaceae or Alliaceae family. It is cultivated throughout the central Asia (India). In Ayurveda, it is named as Lashuna, Arishta, Ugragandha, Yavaneshta, Mahaushadh or Rasona. In Siddha/Tamil, Ullippoondu, Vellaippoondu. Pharmacological actions present in garlic are antibiotic, fungicide, anti-thrombotic, anthelmintic, hypotensive, hypoglycaemic and hypocholesterolaemic (Khare 2008). They are rich in sulfur bound compounds, derived from the sulfur-containing amino

acid cysteine such as diallyl disulfide, allicin isoxidized product of diallyl disulfide and ajoene is the decomposed product of allicin (Pengelly 2004). Here below the compound allicin isolation will be discussed in brief.

To four kilogram of garlic cloves (ground) mixed with five liters of 95% ethanol and agitated for thirty minutes. Then the mixture was filtered, it yields about 5.2 Liters (have 2.5 to 4 mg of allicin per ml). The concentrated extract by the removal of ethanol was obtained and distillated. Aqueous distillate was collected and for maintaining the flask volume of 500 ml, water was added drop wise. After complete distillation, 9 liters of aqueous distillate was collected. Three liters of this aqueous distillate was collected and 500 ml of ethyl ether was added and recovered. Followed by 300 ml of ether mixed for four time and recovered. Then all recovered ethyl extracts were combined evaporated under reduced pressure. The yielded waxy residue was mixed with 250 ml and 10 ml of n-hexane was added to separate the oily substance from the aqueous portion. Then the aqueous extract stored in frozen temperature. Further, the pure product was obtained by mixing the aqueous extract with one-fifth volume of ether for four times and combined. The ether was removed under reduced pressure. At final, 4 g of oil was recovered from 4 kg of garlic cloves (Cavallito and Bailey 1944).

5.1.10 Elettaria cardamomum *Maton.(Cardamom)*

It belongs to the family zingiberaceae. Its habitat is throughout India, Sri Lanka and Burma. In India, mostly hill stations are cultivated with cardamom plants mainly Western Ghats. Area includes Karnataka, Kerala. In Tamil Nadu, Nilgiris, parts of Madurai and Tirunelveli. In Ayurveda, it is called as Elaa, Bhrngaparnikaa, Tutthaa, Prithvikaa, Dravidi, Truti. In Siddha/Tamil, it is known as Yelakkaai or Elam It has a pungent and sweet-hot-pungent taste, also with unique aroma. It is used in the preparation of sweets and savory food dishes. The pharmacological actions such as carminative, digestive stimulant, anti-grip, stomachic, anti-emitic, anti-asthmatic and antispasmodic and antiseptic activity were reported. Cardamom well known for its flavor and aroma it is due to its essential oil. Major constituents includes are 1,8-cineole, α-terpinyl acetate, limonene, linalool, α-terpineol and sabinene (Khare 2008 and Tirtha 2007).

The comparative study on extracting volatile oil from three different types of extraction (Hydro distillation, solvent extraction and supercritical CO_2 extraction) shows that all the volatile compounds from the oil were observed to be different concentration (%) from each type of extractions. Some compounds identified only in specific type of extraction and not in other types, which was represented in a Table. 5.2 below with total 45 compounds and their presence (%). For supercritical CO_2 extraction, two set ups were opted and it was given (Table 5.2).

Table 5.2 Total hit compounds from different types of extraction procedures and their concentrations (%). Set 1 indicates the charge with particles sizes (250−425 μm); set 2 indicates particles sizes (>850 μm)

S. No	Compounds	Super-critical CO_2 extraction		Hydro-distillation	Solvent extraction
		Set 1	Set 2		
1.	Sabinene	3.2	3.1	3.0	0.5
2.	Myrcene	2.4	2.2	2.1	6.6
3.	Limonene	5.6	3.7	3.5	36.4
4.	1,8-cineole	21.4	21.0	27.4	23.5
5.	Terpinolene	1.0	0.8	0.7	8.6
6.	n-nonane	–	–	–	0.5
7.	Tricyclene	0.5	0.4	0.2	0.5
8.	α-pinene	0.9	1.1	1.3	0.6
9.	β-pinene	0.3	0.3	0.3	0.2
10.	n-octanal	–	–	0.2	–
11.	α-phellandrene	–	–	–	1.5
12.	α-terpinene	–	–	0.3	2.7
13.	*p*-cymene	–	–	–	0.4
14.	(*E*)-β-ocimene	0.3	–	0.2	3.2
15.	γ-terpinene	0.4	0.4	0.6	3.3
16.	*cis*-sabinene hydrate	0.9	0.9	0.4	-
17.	p-cymenene	–	–	–	0.3
18.	Linalool	5.4	5.4	6.6	2.1
19.	*cis-p*-menth-2-en-1-ol	–	–	0.1	0.5
20.	*p*-mentha-1,5-dien-8-ol	–	–	0.1	–
21.	terpin-4-ol	0.7	0.7	2.1	0.8
22.	*m*-α-terpineol				1.8

(continued)

Table 5.2 (continued)

S. No	Compounds	Super-critical CO_2 extraction		Hydro-distillation	Solvent extraction
		Set 1	Set 2		
23.	α-terpineol	2.8	3.2	5.0	0.4
24.	*cis*-sabinene hydrate acetate	0.7	1.0	0.2	0.3
25.	hexyl 2-methyl butyrate	–	–	0.1	–
26.	Neral	–	–	0.3	–
27.	linalyl acetate	8.2	8.6	3.3	–
28.	Geranial	0.6	0.6	0.5	0.5
29.	Neo-dihydrocarveol acetate	–	–	0.1	–
30.	Methyl geranate	–	–	–	0.2
31.	α-terpinyl acetate	42.3	44.2	37.7	0.3
32.	Neryl acetate	–	–	0.3	–
33.	Geranyl acetate	1.6	1.4	1.7	–
34.	(*E*)-α-ionone	–	–	0.1	–
35.	(*E*)-β-farnesene	–	–	–	0.8
36.	γ-gurjunene	–	–	0.1	–
37.	γ-himachalene	–	–	–	0.5
38.	(*Z*)-α-bisabolene	–	–	–	0.5
39.	(*Z*)-γ-bisabolene	–	–	–	0.5
40.	(*E*)-nerolidol	0.8	1.1	0.8	–
41.	NI[a]	–	–	0.2	0.2
42.	NI	–	–	0.3	0.2
43.	Triacontane	–	–	–	0.5
44.	Diitriacontane	–	–	–	0.7
45.	Tetratriacontane	–	–	–	0.3

[a]Denoted as unidentified compound

5.1.11 Beneficial Common Vegetables as a South Indian Food

5.1.11.1 *Amaranthus tricolor*, A Leafy Vegetable

Amaranthus species belongs to *Amaranthaceae* are being cultivated as vegetables for human consumption. They are found in countries of Southeast Asia. Although their leaves are enriched with carotenoids, calcium, dietary fibre, vitamin C, protein and iron; its bio-availability is destroyed or reduced due to theirhigher content of oxalic acid. Amaranthus are dicotyledonous (C4) herbaceous plants. Approximately, it includes 70 species in that 17 species produces edible leaves and three produces food grains (Khanam and Oba 2013). They are also been applied for external inflammations, as a diuretic, and against bladder pain. Betacyanins are present in amaranthus, used as common food colorant, have quite more previous reports compared to nonbetacyanin constituents. Some of the nonbetacyanin constituents are listed (Fig. 5.7). Betalains are the derivatives of dihydroxy-phenylalanine by under taking a ring opening mechanism of oxidative 4 and 5-extradiol, they are also described as conjugates of chromophore betalamic acid. Those pigmentedcomposition are known to actively participate in antioxidant activities, radical scavenging, against oxidative stress disorders, antiviral, anticancer, antiparasitosis and α-amylase inhibitory activites (Wu et al. 2006).Amaranthus species also contains amarantin, isoamarantin, betaine, amino acids and sterols.

5.1.11.2 Extraction and Isolation of Compounds from *Amaranthus tricolor*

Leaves were soaked in ethyl acetate (1 L) for 6 h and the soaked leaves were subjected for hot water extraction to yield the residue. It was fractionated further by Medium-Pressure Liquid Chromatography (MPLC) constructed of LBP-V pump which operates at10-15 psi in a silica gel chromatography with thecolumn size 40 cm × 30 mm i.d. Totally, seventy fractions were eluted. From that, 1 to 20 fractions collected with hexane, were indicated same by thin-layer chromatography (TLC) and thus it was pooled and gave the yield of 100 mg.Fractions from 21 to 35 eluted with hexane: chloroform (1:1) yielded 150 mg of residue. Fractions 36–55 eluted with chloroform were condensed to yield 40 mg of residue. Finally, fractions 56–70 eluted with $CHCl_3$ (chloroform): MeOH (methanol) (9:1) yielded 300 mg of residue. Then the final fraction, which showed active inhibitory activities for cyclooxygenase enzymes (COX) were chosen for isolation using $CHCl_3$, $CHCl_3$/MeOH (9:1) and $CHCl_3$/MeOH (8.5:1.5) as mobile phases. Since the fraction B (100 mg) and C (50 mg) was only found potential, again they were purified by Preparative Thin Layer Chromatography (PTLC). The processed compounds 1 (70 mg), 2(8 mg), 3(9 mg) were afforded with the solvents ($CHCl_3$/MeOH) in the ratio of 9:1 and 93:7.Apart from their anti-inflammatory activity, these compounds are also have antitumor property against human cancer cell lines such as SF-268 (Central

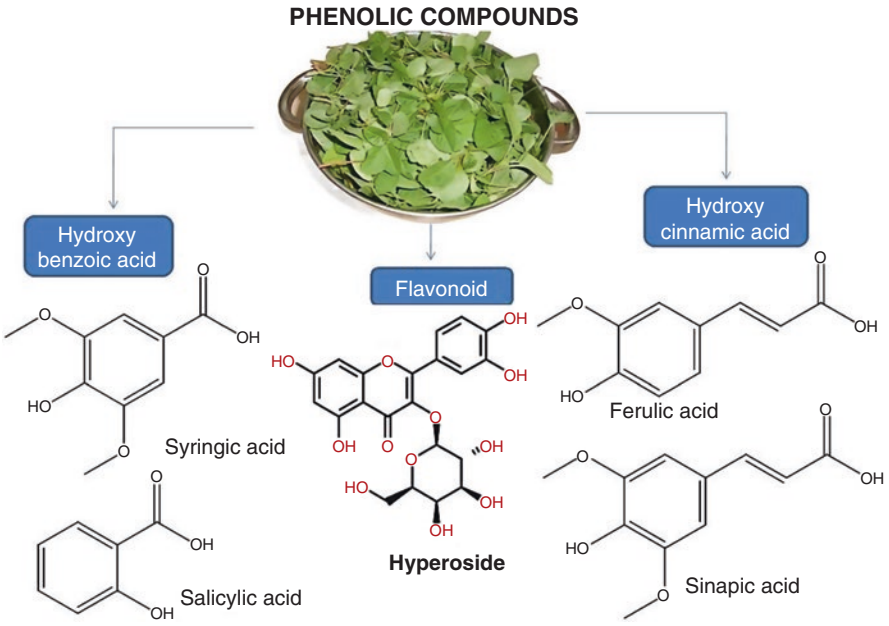


Fig. 5.7 Phenolic compounds from *Amaranthus tricolor* leaves

Nervous System cancer), MCF-7 (breast adenocarcinoma), AGS (gastric cancer), HCT-116 (colon cancer) and NCIH460 (lung cancer)

5.1.11.3 1, 2-Dilinolenoyl-3-Galactosylglycerol

The compound 1 was dissolved in the solvent combination of $CDCl_3$ and CD_3OD for ^{1}H NMR and ^{13}CNMR analysis. The ^{1}H NMR spectrum exhibited the peak at δ_H5.29 (12H,m, H-9′-16′′), a multiplet proton at δ5.20 (1H, m, H-2) it may be an unsaturated fatty acid, δ4.29 (1H, dd, J = 3.5, 12 Hz, H-1a), δ4.14 (1H, dd, J = 7, 11.0 Hz, H-1b), an anomericsignal at δ4.13(1H, d, J=7.0, H-1′′′) which may be a glycoside, δ3.87 (1H,dd, J = 4,9.5 Hz, H-3a), δ3.82 (1H,dd, J = 2.5,1.0 Hz, H-4′′′) was assigned as glycerol backbone, δ3.78 (1H, dd, J = 6.5,12.Hz, H-6a′′), δ3.70 (1H, d, J = 5, 11.5 Hz, H-6b′′′), δ 3.64 (1H, dd, J = 6, 11 Hz, H-3b), δ 3.50 (1H, d, J =7, 9.5 Hz,H-3′′′), 3.44(2H, J=7.0,dd, 9.5 Hz, H-5′′′, 2′′′), 2.73(8H, t, J=5, 5 Hz, 11′,11′′,14′,14′′), δ2.24 (4H, t, J = 7,5 Hz, H-2′′′,2′′′), δ1.99 (8H, m, C-8′,8′′,17′,17′′), δ 1.24 (CH_2s), δ0.9 (6H, t, J = 8 Hz, CH_3s, 18′,18′′); The ^{13}CNMR analysis and the following peaks were demonstrated as δ 173.8(C-1′), δ173.5(C-1′′) ppm, they were assigned as carbonyl and fatty acid signals. The olefinic carbon peak were observed at δ131.8 to 127 (C9′,10′,12′,13′,15′,16′,9′′,10′′,12′′,13′′,15′′,16′′). The anomeric carbon peak was raised at 103.8 (C-′′′).Presence of oxygenated

carbons (eight) was formed between δ74.7(C-5′′′) and δ61.5(C-6′′′). δ73.2(C-2′′′), δ71.1(C-2′′′), δ70.2(C-2), δ68.7(C-4′′′), δ67.8(C-3), 62.6(C-1),δ34.1 (C-2′), δ33.9 (C-2′′), δ29.5–28.9 (CH_2s), δ27.0 (C-8′, 8′′), δ25.4(11′,11′′), δ25.3(14′,14′′), δ24.6(3′,3′′), δ20.3(17′,17′′), δ14.0(C-18′,18′′). Occurrence of Galactosyl group was confirmed by coupling constant (C-3 and C-4) in sugar moiety. Hence, the structure was predicted as galactosyl diacylglycerol. But the fatty acid resultant after the process of saponification with methanolic potassium hydroxide was further methylated with diazomethane. At the end, the fatty acid methyl esters were appeared as 1,2-dilinolenoyl-3-galactosylglycerol.

5.1.11.4 1-Linolenoyl-2-Palmitoyl-3-Galactosylglycerol

The spectrum was elevated at the following peaks; δ_H5.24(6H, m, H-9′ to16′ except at 11 and 14), 5.15(1H, m, H-2), 4.24(1H, dd, *J*=2.5,12 Hz, H-1a), 4.11 (1H, dd, *J* =7, 11 Hz, H-1b), 4.10(1H,d,*J*, 7 Hz,H-1′′′), 3.82 (1H, dd, *J* = 5.5, 11 Hz, H-3a), 3.78(1H, d, *J* = 2, 5 Hz, H-4′′′), 3.74(1H,dd,*J*=6.5,12 Hz, H-6a′′′), 3.65(1H, d, *J* = 5, 11.5 Hz, H-6b′′′), 3.6 (1H, dd, *J* = 6, 11 Hz, H-3b), 3.42(1H, dd, *J*=7, 9.5 Hz, H-3′′′), 3.38 (2H, d, *J*=7, 9.5 Hz, H-5′′′, 2′′′), 2.69 (4H, t, *J* = 5.5 Hz,11′,14′), 2.22 (4H, t, *J*=7,5 Hz, H-2′, 2′′), 1.95(4H, m, C-8′, 17′), 1.19(CH_2s), 1.14(CH_2s), 0.86 (6H,t, *J*, 8 Hz, CH_3s, 16′′,18′). The spectrum of ^{13}CNMR was shown peaks at certain area; δc173.8(C-1′),173.2(C-1′′), 131.3–126.5(C-9′,10′,12′,13′,15′,16′), 103.5(C-1′′′), 74.6 (C-5′′′), 73 (C-2′′′), 70.7(C-3′′′), 69.9(C-2), 68.3(C-4′′′), 67.2(C-3), 62.3(C-1), 60.8(C-6′′′), 33.6(C-2′), 33.5(C-2′′), 29.0–28.5(CH_2s), 26.6(C-8′), 25(11′), 24.9(14′), 24.3(3′), 20(17′),13.4(C-18′,16′′). Palmitic and linolenic acids were also occurred respectively. And esterification of glycerol back bone was taken place at 1-and 2- position. Thus, they displayed their isolated compound as 1-linolenoyl-2-palmitoyl-3-galactosylglycerol.

5.1.11.5 Compound 3 as 1-Linolenoyl-2-Steroyl-3-Galactosylglycerol

The ^{1}HNMR spectral data was expressed their peaks at; δ_H5.24 (6H, m, H-9′,10′,12′,13′,15′,16′), 5.15(1H, m, H-2), 4.3(1H, dd, *J* = 2.5,12 Hz, H-1a), 4.11(1H, dd, *J* = 7.5, 11 Hz, H-1b), 4.1(1H, d, *J* = 7 Hz, H-1′′′), 3.88 (1H, dd, *J* = 5.5, 11 Hz, H-3a), 3.77 (1H, d, *J* = 2.5 Hz, H-4′′′), 3.71(1H, dd, *J* = 6.5, 12 Hz, H-6a′′′), 3.66(1H, d, *J* = 5.5, 13 Hz, H-6b′′′), 3.64 (1H, dd, *J* = 6,11 Hz, H-3b), 3.45 (1H, dd, *J* = 7.5, 9.5 Hz, H-3′′′), 3.39 (2H, d, *J* = 7, 10 Hz, H-5′′′,2′′′), 2.7(4H, t,*J*,6 Hz,11′,14′), 2.23(4H, t, *J*, 7.5 Hz,H-2′,2′′), 1.97 (4H, m, C-8′,17′), 1.22 (CH_2s), 1.17(CH_2s),0.88(6H, t,*J*, 8 Hz,CH_3s,18′′,18′). Instead of palmitic acid as of in compound2, a stearic group was present. It was next subjected to GC-MS analysis for identification of fatty acids by comparing their retention time with molecular ions and the commercial standard compounds (Jayaprakasam et al. 2004).

5.1.11.6 Crude Sample Preparation for Isolation of Betacyanins (Red Violet), Betaxanthins (Yellow) and Betalamic Acid Compounds

The fresh leaves of *A. tricolor* (200 g) with 90 days growth was selected, frozen, and then homogenized using liquid nitrogen. These compounds were extracted using 80% methanol and it was placed at 25 °C for 40 min along with continuouslystirring. The filtrates were then centrifuged for half an hour at 10,000 rpm.These pigmented fractions which were isolated exists only in the plants belongs to the Caryophyllales order (Cai et al. 2005).

5.1.11.7 Purification of Compounds by Gel Filtration Chromatography

Sephadex was packed in a LH-20 column having 20×1.0 cm size in which milli-Q (autoclaved) water was used to elute the samples. Three pigmented bands of betalin were separated, collected and freeze-dried for safety storage. In HPLC analysis, SB-C18 column equipped with 5 μm, 250 ×4.6 mm size was involved, for that solvent A 0.005 mol/L KH_2PO_4 (potassium phosphate) and solvent B 5% CH_3CN(acetonitrile) was used as a mobile phase. For first 0–5 min, 100% of solution A; while after 5–10 min, 50% solution B; then10–20 min later, 100% solution B; again at 20–30 min,100% solution A was injected in the flowrate 1 mL/min. These three pigmented compounds peaks were visible at different wavelength range like 536, 475 and 430 nm.

In FTIR spectrum, the representative functional group of betacyanins was detected at the vibration from 1653 to 918 cm^{-1}. The wave number in the range from 3400 - 3100 $cm^{-1}$and from 600 - 474 cm^{-1} might be appeared due to the presence of $-NH_2$, −OH, and C−S group from its component such as protein/amino acid and also because of the trace amount of water present in the pigment. For LC-MS analysis, the instrument was usually embedded with C18 column in 100 × 2.1 mm wide, 5 μm particle size, 25 °C temperature and 1490 bar column back pressure. A volume of 10 μL of formic acid (0.1%) and CH_3CN was used as an elutent in the 0.25 mL/min flow rate (Biswas et al. 2013).

5.1.12 Cucurbita pepo *L.* *–Pumpkin Fruit*

Cucurbita pepo belongs to the cucurbitaceae family, it exhibits hypoglycemic, antihypertensive, immunomodulatory, anti-mutagenic, anti-hypercholesterolemic, intestinal antiparasitic, anti-inflammatory, antalgic and inhibitory to hepatitis C virus. It is enriched with polysaccharides, aminoacids, fattyacids, carotenoids, minerals and vitamin E.

5.1.12.1 Extraction, Isolation and Characterization of Fruit Flesh Compounds

The sliced fruit flesh was dried indirectly by using solar energy as a drying system. Here, the exhaustive extraction method was used along with soaking for extracting the crude compounds from 250 g of grinded flesh powder by using methanol as solvent. The remaining water residue was again extracted with chloroform to yield 7.3 g of oily orange crude extract. An aqueous crude extracts (orange) of rind and flesh were dissolved in water followed by chloroform extraction. In TLC evaluation, under UV detection these extracts displayed the non polar orange bands which are characteristic features of carotenes. The bands turned into blue colour on treating with concentrated H_2SO_4. Along with that, the UV non absorbing less/middle polar components emitting pink to violet bands represented steroidal, terpenoidal and fatty acids compounds.

Sephadex LH-20 was used as stationary phase or adsorbent, in which dichloromethane (DCM) or 40% methanol distinguishes four fractions; fraction I was isolated with 3.55 g yield, fraction II with 2.2 g, fraction III with 3.82 g and fraction IV with 1.78 g. As fraction II was separated as a mixture, it undergoes silica gel column chromatography ($100 \times 2cm^2$) to deliver compound 2(309 mg) and 3(220 mg) using cyclohexane–DCM as elution. From fraction III, Compound 4(220 mg) and 5(120 mg) was isolated and compound 6(322 mg) from fraction IV. These fractions were analyzed for *in vitro* cytotoxicity against HEPG2 (liver carcinoma), MCF7 and it was also reported to have moderate antibacterial activity against gram positive *Bacillus subtilis* and *B.cereus.*

By GC-MS analysis, the first oily fraction was assigned as dodecane, tetrahydrothiophene and tetradecane. Fraction II consisted of two compounds (1 &3) as follows; the ^{1}H NMR spectrum of compound1 displays multiplet signals (three) at 5.43 to 25 and 4.37 to 4, due to the appearance of olefinic methines and sp^3oxymethines or methylenes. Another multiplet signals formed between 2.8 and 0.97 are because of other methylene chains end up with terminal triplet methyl group. Difference in the chemical shift of methylene protons represents its neighbouring to sp^2 /sp^3 carbon systems. In ^{13}C NMR spectra, ester carbonyls were positioned between 173 and 172, multiple sp^2 carbons of olefinic was found between 132 and 127 ppm and sp^3 (two) oxy signals of methines and methylenes. At last, numerous sp^3 signals for methylene and methyl carbons were placed between 34 and 14 ppm. Thus, the predicted structure was triglyceride fatty acids mixture. Compound 3 as (9Z, 12Z)-9,12-octadecanoic acid; linoleic acid. From fraction III, compound 4 was identified as calotropoleanyl ester. The compound 6 obtained from fraction IV was considered as a novel to this fruit but it has earlier report from the leaves of *Cissus quadrangularis* (Badr et al. 2011)

5.1.13 Abelmoschus esculentus- *Lady's Finger*

It is an annual herbage plant comes from malvaceae family. And widely planted for its tender fruit; in places from Africa - Asia, South European - America and it is known to be cultivated easily. Along with its nutrition discovery, it is considered as the first choice in healthy vegetables and provided to the Olympic athletes (Kolawole and Bukola 2010). It has previous reports on consisting phenols, flavonoids and aminoacids like coumarin, scopoletin, hyperoside, uridine and phenylalanine (Lu et al. 2011).

5.1.13.1 Crude Extraction

Using 70%methanol, the fruits of *A. esculentus* were extracted. This methanolic extract was re-extracted with petroleum ether and ethyl acetate. Then, only the water soluble fraction was subjected to column chromatography by Diaion HP20. The fraction eluted with methanol:water (2:8) was found as a mixture of compound. The concentrated fraction was again dissolved with sterile distilled water to carry out column chromatography with Sephadex LH-20 as a stationary phase. From that, one hundred milligramsof compound 1 and two gramsof compound 2 was obtained using MeOH:H_2O (2:8) and (1:1) solvent ratio as elutants respectively.

5.1.13.2 Elucidation of Structures

For ^{1}H NMR (400 MHz) data, the compound 1 was dissolved in CD_3OD. It showed a signals for 1,3,4-trisubstituted phenyl moiety at δ7.57(dd, 1H, J = 8.4, 1.2 Hz), δ7.69 (d, 1H, J=1, 2 Hz),and δ6.85 (d, 1H, J=8, 4 Hz); two protons at δ6.189(s,1H) and δ6.381 (s, 1H); anomeric (1) protons of glucopyranoside at δ5.25 (d,1H, J=7,6 Hz); isolated protons(3) at δ3.68 (s,3H); peak for 4′′methyl and simultaneously for 6 glycosyl protons were found between δ 3.199–3.719. The ^{13}CNMR (100 MHz) and DEPT spectra of compound1 displays twenty two carbon signals in which fifteen flavonol aglycone, one methoxyl and six of one glycosyl moieties. It was interpreted as flavone glycoside with β-sugar units. The ^{1}H and ^{13}CNMR spectrum were definitely assigned with the interference of HMBC and HSQC analysis. Its molecular formula was determined as $C_{22}H_{22}O_{12}$ by HRESIMS analysis with m/z 479.118[M + H]$^+$. The signals assumed as sugar units revealed the appearance of 3-substituted β-Dglucopyranosyl units. In HMBC, the correlations of ^{13}C and ^{1}H gave similarity from H-1″ δ5.250 to C-3 δ 135.625 and thus they established compound1 as β-Dglucopyranosyl moiety which was located at C-3 aglycone; the attachment of methyl H δ3.684 (s, 3H) to Glu-C4 of β-Dglucopyranosyl and δ3.456 (Glu-H2) was associated with δ104.306 (Glu-C1). Thus, elucidated the structure as **5,7,3′,4′-tetrahydroxy-4′′-O-methylflavonol-3-O-β-D- glucopyranoside**.

Compound 2 having molecular formula as $C_{27}H_{30}O_{17}$ was elevated the peaks in ^{1}HNMR as follows, δ7.690(d,1H, *J*=2),7.65(dd,1H, *J*=8.4, 2.4 Hz),6.85(d,1H, *J* = 8.4 Hz), 6.39(s, 1H), 6.18(s, 1H), 5.23(d,1H, *J*= 7.6), 4.14(d, 1H, *J* = 7.6) while in ^{13}CNMR δ179.53(C-4), 165.98(C-7),163.006(C-5),158.87(C-2),158.47(C-9),149.84(C-3′),145.91(C-4′),135.59(C-3),123.53(C-6′), 123.09(C-1′),117.52(C-2′),116.07(C-5′),105.75(C-10),104.58(C-1′′),103.98(C-1′′′),99.88(C-6), 94.82(C-8),77.99(C-5′′),77.87(C-5′′′),77.77(C-3′′),77.60(C-3′′′),75.74(C-2′′),75.08(C-2′′′),71.31 (C-4′′),71.284(C-4′′′),69.569(C-6′′),62.507(C-6′′′) and predicted the compound as **5,7,3′,4′-tetrahydroxy-3-O-[*β*-D-glucopyranosyl-(1→6)]-*β*-Dglucopyranosideflavonol** (Liao et al. 2012).

Momordica charantia – Bitter gourd.

In many Asian and African countries, this is the plant which has been reported for its anti-diabetic properties. A few cucurbitane triterpene, that are of both aglycones and glycosides were isolated with their bitterness/ non bitterness (Murakami et al. 2001). The compounds such as Momordicosides K and L; Momordicines I are considered as the principles for their bitterness. Even these compounds are also having similarities like 7-OH/*O*-b-D-glucopyranosyl groups, C-9 formyl and unsaturation at C-5 and C-6 position. These are the criteria expected for its bitterness and in spite of that the higher content of saponins is also having some roles in providing such taste.

Dried and powdered gourds (20 kg) were extracted with methanol at room temperature. Methanol extract (415.8 g) suspended in water was re-extracted with ether, ethyl acetate and *n*-butanol and afforded 61 g, 42 g, and 298 g of crude extracts. The ether extract (27 g) was subjected to silica gel column chromatography using hexane–EtOAc solvents to obtain 24 fractions. From that, 5th fraction was subjected to a Sephadex (LH-20) column to afford 3 sub-fractions. Using HPLC on ODS RP-18, the mixed compounds of 10and 11was yielded to 53 mg from 5–3 fraction. Through Sephadex purification, the fraction 9 was given a compound 9 with the yield of 3.4 mg. Then, the thirteenth fraction was precipitated in EtOAc to provide 178 mg of compound4. By size exclusion chromatography, fraction 17 was sub-fractionated to three fractions. The fraction 17–2 was applied to silica gel column chromatography using the solvent ratio Hexane: EtOAc: Et_2O (4: 3: 1) to offer a compound 5 (175 mg). Finally, the 20th fraction was divided to 3 sub fractions by Sephadex chromatography. The fractions from 20–2 were purified on silica gel chromatography with Hexane: EtOAc (6: 4–100%) solvent gradient and gave compound 6 with 25.2 mg yield, compound1 with 3.2 mg, compound 5 with 76 mg and compound 7 with 21.3 mg.

The EtOAc fraction (3 g) undergoes silica gel column chromatography using CH_2Cl_2: MeOH: H_2O (15: 3: 1- lower phase) and EtOAc solvent gradient to afford eight fractions. Compound 2 (9.3 mg) was isolated from fraction 1 by both the silica gel column chromatography and HPLC (RP-18 ODS) with *n*-hexane:EtOAc (7: 3–100% EtOAc) and 95% MeOH. The purification of fraction 3 was carried out by Sephadex and ODS RP-18 using CH_3CN: H_2O (13: 7) as solvent, which gave 7.8 mg of compound 3.When the *n*-butanol fraction was subjected to DIAION column, it

was eluted with H_2O: MeOH (H_2O, 50% MeOH, MeOH and acetone. Hence, 8.4 mg of compound 8 was eluted from 16.2 g fraction with the combination of silica gel using CH_2Cl_2: MeOH: H_2O (15: 3: 1-low phase); CH_2Cl_2: MeOH (9:1,4:1);$CHCl_3$: MeOH (17: 3).aselutantand ODS RP-18 using MeOH: H_2O (9:1) as elutant.

Compound1 was isolated and its molecular formula is$C_{31}H_{52}O_3$. In ^{1}H NMR, seven quaternary methyl groups were exhibited at δ_H:0.70, 0.92, 0.98, 1.04, 1.21, 1.31; one secondary methyl signals at δ_H0.88; two oxygen-bearing methines at δ_H 3.43 and δ_H3.51; three olefinic protons at δ_H5.57 and δ_H5.59 and a methoxyl group was found at δ_H 3.34. Compound 3 eluted (Hexane: Ethyl acetate 7: 3–100% ethyl acetate and 95% Methanol. Compound 5 (Hexane: Ethyl acetate: Ethanol; 4: 3: 1) was described by confirming with X-ray analysis as **3*β*, 7*β*, 25-trihydroxycucurbita -5, 23(*E*)-dien, 19-al** having aldehyde group (Harinantenaina et al. 2006). Compound 6–9 were isolated from hexane: ethyl acetate (6: 4–100%) and determined by comparing its physical and spectroscopy data as **5*β*,19-epoxycucurbita-6,23(*E*)-diene-3*β*,19,25-triol;5*β*,19-epoxy-19-methoxycucurbita-6,23(*E*)-diene-3*β*,25-diol** (an amorphous powder); momordicoside L and *para*-methoxybenzoic acid ($CHCl_3$: MeOH 17:3). Compound 10 and 11 was **sitosterol** and **stigmastadienol**, they are aglycones of charantin.

By ^{13}C NMR, a resonance of a methoxyl group carbon along with thirty carbon signals was assigned to trihydroxycucurbita-5, 23-dien with resonance of quarternary methyl group at δ_C 28.7. Presence of methoxyl group at C-7 and two hydroxyl groups at C-3 and C-25 were identified. The examination of COSY correlations from H-6 to H-8 analyzed the position of oxygen bearing methane at C-7. HMBC correlations among H-3 and C-2 to C-5; H-23 and C-24, C-25 validates two oxygen-bearing carbons at C-3 and C-25. Again by HMBC spectrum, the peak between methyl group at δ_H 0.98 and C-8 to C-10 demonstrate the availability of supplementary methyl group at C-19. The methoxyl group might be situated at C-7 and β-oriented, as the methoxyl protons at δ_C3.34 showed longer range of correlation to the oxygen bearing carbon found at δ_C76.7. And the NOESY correlations were found between the H-7 and CH_3–30. The hydroxyl group orientation at C-3 was supported by the coupling pattern H-3(δ_H 3.51, br s) signal. Thus the structure of compound 1 was deduced to be **3b, 25-dihydroxy-7b-methoxycucurbita-5,23 (*E*)-diene.** By following the same procedure, the compound 2 and 3 isolated were interpretated as **3*β*-hydroxy-7,25-dimethoxycucurbita-5,23(*E*)-diene** and **3-*O*-*β*-D-allopyranosyl-7*β*,25dihydroxycucurbita-5,23(*E*)-dien-19-al.**

5.1.14 Oil Seeds

5.1.14.1 *Sesamum indicum* L.

It is an oldest crop which was cultivated from the period of 1500 BC in the countries of Middle East, Asia and Africa.It holdseighth place among the thirteen top oil seed cropsin the World's oil market which covers 90% of world production of edible oil

(Adeola et al. 2010). It belongs to the family pedaliaceae and it can grow in both tropic and temperate zones. As additive, it promotes flavor and texture to eatables (biscuit, bread, and salad dressing). In general, their notable chemical constituents shows its economical importance and quality; which are foundto be 60% of oil content in which30–46% are fatty acid compounds (Alyemeni et al. 2011), 25% protein, 5% ashand 28–45% of carbohydrate(Nohynek et al. 2013). Including vitamin B1, it does also contain micro-minerals (iron, zinc, manganese) and macro-elements (phosphorus, plays in kidney functions, bone and cell growth while magnesium in balancing acid and alkaline of the body).

5.1.14.2 Extraction of Defatted Milled Seeds

Extraction of bioactive compounds from the natural solid material (sesame seed) is a mass transfer process, which inputs transfer of solvent into the inner transport (matrix), dissolution of solutes (solubility) and then release of solutes to the external transport (global solvent phase). Likewise, here a sub critical or super heated water extraction method was initiated. It was carried out using water as solvent keeping it at under high temperatures (more than boiling point) and pressure preferably high for maintaining its liquid form. These conditions favours the below changes, water viscosity and surface tension are reduced thus its diffusivity characteristics are subsequently improved that could reduce the mass transfer limitation and enhance their product yields. Unless the hydrogen bonding ability of usual solvents, the crucial problems were avoided from the conventional method are beneficial; long processing techniques, usage of larger amounts of solvents whose residues are often forbidden to food regulations.Through Gas Chromatography - Mass Spectrum (GC-MS) report, it was identified to compose 47% linoleic acid, 37% oleic acid, 9% palmitic acid, 60% β-sitosterol and 91% ɣ tocopherol.

5.1.14.3 Elucidation of Phenolic Compounds from Sesame Seed Oil by HPLC- DAD Chromatogram

It was performed with HPLC-DAD (Diode Array Detector) Model Agilent 1260 and column size C18 (4.6×100 mm, 3.5 µm) was used. Solvent system used in the ratio methanol:acetic acid:deionized water, 10:2:88 and 90:2:8. Identification of structure as described in Fig. 5.8 and quantification of peak at retention time 1 min, 257 nm absorbance, 8 µg/g concentration (peak area) of hydroxybenzoic acid compound; 2.8 min, 308 nm, 2.5 µg/g of sesamol; 3.3 min, 273 nm, 1.8 µg/g of quinic acid; 3.9 min, 294 nm, 3.6 µg/g of protocatechuic acid; 5.5 min, 278 nm, 1.7 µg/g of catechin; 6.2 min, 274 nm, 4.3 µg/g of syringic acid; 6.6 min, 246, 288 and 328 nm, 12.6 µg/g of rosmarinic acid hexoside; 7.2 min, 230, 314 nm, 11.3 µg/g of 3-O-p-coumaroylquinic acid; 9.1 min, 256 and 360 nm, 4.98 µg/g of ellagic acid pentoside; 9.9 min, 267 and 320 nm, 2.5 µg/g of kaemferol-3-feruloylsophoroside-7-glucoside; 11.7 min, 270 and 320 nm, 3.82 µg/g of

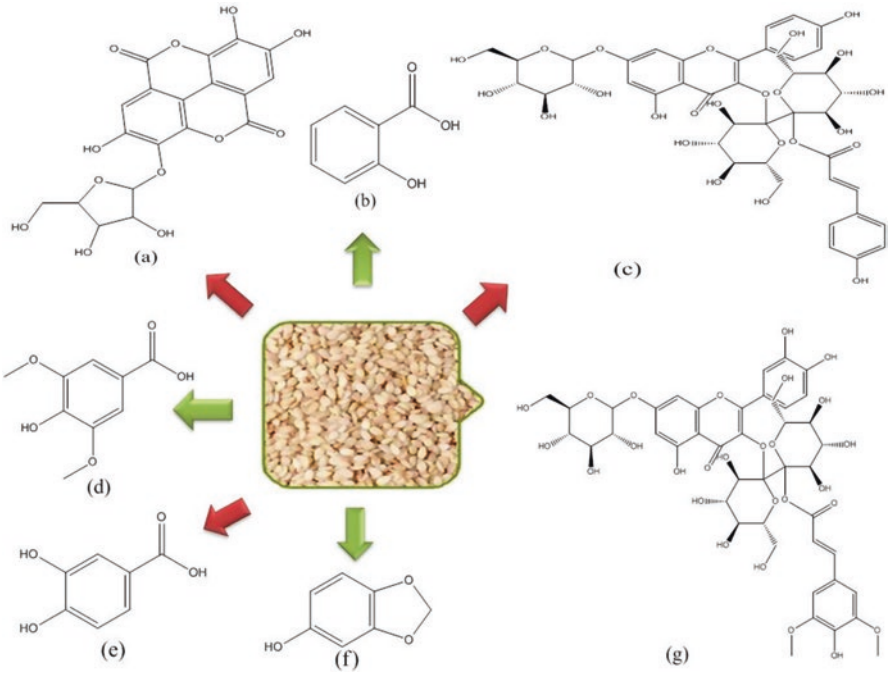


Fig. 5.8 Structures of potential and beneficial compounds derived from sesame seed oil. **(a)** ellagic acid pentoside **(b)** hydroxybenzoic acid **(c)** kaempferol-3-(*p*-coumaroyl bi glucoside)-7-glucoside **(d)** syringicacid **(e)** protocatechuic acid **(f)** sesamol **(g)** quercetin-3-(sinapoylbi glucoside) -7-glucoside

kaempferol-3-(*p*-coumaroyldiglucoside)-7-glucoside; 12.6 min, 248, 270 and 338 nm, 2.93 μg/g of quercetin-3-(sinapoyldiglucoside)-7-glucoside; 14 min, 252, 284 and 354 nm, 1.89 μg/g of quercetin-3-O-D-galactopyranoside; 17.6 min, 265 and 338 nm,3.24 μg/g of quercetin- 3-O-triglucoside; 27.2 min, 258 and 280 nm, 1.4 μg/g of epicatechin; 28.1 min at 294 and 326 nm, 5.3 μg/g of quercetin-3,4-diglucoside-3-(6-feruloy-glucoside) (Zeb et al. 2017) .

In sesame seed, the presence of compounds like lignans sesamin and sesamolin are responsible for maintaining their actual serum lipid levels, antioxidant activities (Kumar and Singh 2014) especially resistance to oxidation and liver function. Sesame lignans can extend the shelf life of natural foods (preventing from browning reactions of fruit pulps) or in processed foods undergone higher temperature treatments (Yeo et al. 2011). They are also been applied for demulcent, laxative and emollient (Anilakumar et al. 2010). These lignans apart from providing stability to the seeds, they also lower cholesterol levels in human body. It acts against human cancer cell lines like (SK-MEL) malignant melanoma, HT-29 (colon cancer) and hepatoprotective towards cypermethrin inducing toxicity by altering tumour necrosis factor-α (Soliman et al. 2015). Remarkably, it could reduce the major risk factor

causing cardiovascular and diseases related to oxidative stress (Gouveia et al. 2016). Interrelations of chemical features with physicochemical functions are falls in the following ways; higher degree of unsaturation is projected by greater iodine value, which demonstrates the number of double bond in oil/fat and oxidative stability. It is also an important fact, as the oxidation of lipids will deteriorate the quality of edible oil in turn it affects their nutraceutical properties. Peroxide value (3.8 meq/kg) is an index of rancid condition of oil forms due to oxidation. Lower rancidity represents higher resistance to peroxidation and also gives a longer storage life to oil. Acid value can indicate free fatty acid content occurs due to enzymatic activity and detects if any spoilage in vegetable oils. High level of free fatty acid might results in unpleasant oil taste. These parameters are very helpful in signifying and differentiating the quality of oil. Thus, they are described as a rich source of nutrients and thereby it reflects their positive effects on human concerns.

Olive Oil Olive oil phenolic compounds have become more popular nowadays due to their health benefits. Other than that, those compounds give sensory and stability to olive oil. In olive oil, phenolic profile was determined by the quantity of phenolic glycosides present in their tissues and based on the activities of its endogenous enzymes reacts on these glycosides as they may disturb those phenolic compounds (Hachicha et al. 2016).

Olive Oil Extraction Olive fruit (1 kg) was crushed using a steel (stainless) hammer mill which holds 5 mm sieve and it can operate at 3000 rpm. The resultant olive paste was malaxed at 22 °C for 30 min. Later it was mixed and kept for centrifugation for 1 min at 3500 rpm. Then, the oil was stored in a dark glass bottle with nitrogen bubbling and maintained at −20 °C until analysis.

Chromatographic Analysis for Identification and Quantification of Phenolic Compounds by HPLC-MSD In brief, 2 g olive oil was dissolved in 0.015 mg mL^{-1}syringic acid which was vigorously stirred for 30 sec and 5 mL of methanol:water (80:20) was added into that. It was then incubated in an ultrasonic bath for 30 min at room temperature. After that, it was centrifuged for 25 min at 5000 rpm, this methanolic extract was further filtered using a PVDF filter (0.45 μm). HPLC (HP 1100 series Agilent Technologies) analyses of phenolic extracts were performed with 2.6 μm, C18 Kinetex column in 100 mm × 3 mm size. Water with 0.5% formic acid was used as a mobile phases (A) and acetonitrile (B) at a flow rate of 0.5 mL min^{-1}. Only sample volume of 5 μL was injected for analysis (Hbaieb et al. 2017).

In olive oil, the determination of phenolic constitute is an essential quality parameter. The phenols in olive oil resist them from oxidation and thereby phenols prevent olives from bitterness. The foremost phenolic compounds identified in olive oil are verbascoside, secoiridoids consisting hydroxytyrosol *i.e*. oleuropein aglycone and decarboxymethyl oleuropein aglycone; tyrosol *i.e.*ligstroside aglycone and decarboxymethylligstroside aglycone. Along to that, an oxidized form of eleno-

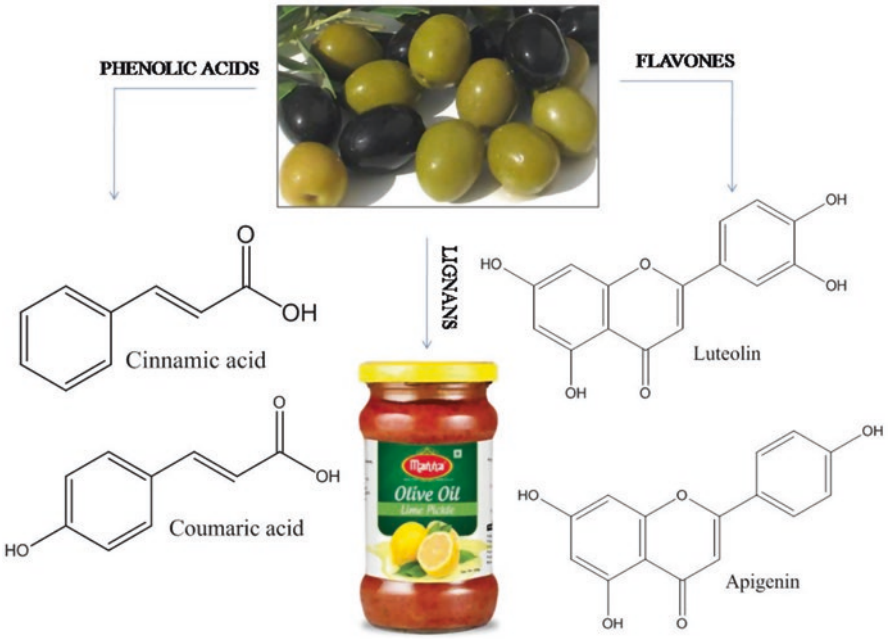


Fig. 5.9 Common phenolic compounds reported in olive oil

lic acid aglycone, hydroxytyrosol and free forms of tyrosol as well noticed. Other known phenolic molecules belongs to different chemical classes were identified as mentioned in Fig. 5.9. It includes phenolic acids like caffeic acid and ferulic acid; lignan like acetoxy-pinoresinol (Servili 2014).

5.2 Conclusion

Bioorganic phase for isolating the numerous compounds were discussed in this chapter in detail. There is no doubt on various food sources having a beneficial role in different fields including textile and pharmaceutics. However, obtaining phytoconstituents will be eco-friendly and non-toxic. Thus, this report explains in details about, how the food sources especially Indian food products having a potential phytoconstituents will help mankind in his day today life. There are some phytocompounds like curcumin from *Curcuma longa* become an important anti-cancer drug and essential oils from vegetable like lemon, cinnamon and orange were obtained and utilized in food and pharma industries for adding flavors in their products. Hence, we conclude that the organic compounds from these food sources will be utilized for isolating such active compounds in future.

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Chapter 6
Cardamom: A Multipurpose Species in Food and Commercial Needs

Aparanjitha Rajpur and K. Samratha

Abstract Cardamom is a seed pod mostly known for its culinary and medicinal properties. It is grown in India, Sri Lanka, Tanzania, and Guatemala. Each green pod on the plant contains about 15 to 20 seeds. Cardamom is available in two different types, black cardamom (elaichi) and green cardamom (Elettaria). Black cardamom pods are larger than green cardamom pods. Their seeds have a unique taste and smell. Cardamom, commonly mentioned as the queen of spices for its taste and aroma, is known to mankind since its beginning. It is noted for its aphrodisiac property, delicious aroma and also used as a common folk remedy for treating stomach aches. The major components present in cardamom oil are a-pinene, b-pinene, sabinene, terpinen-4-oil, a-terpineol acetate, myrcene, a-phellandrene, 1,8-cineole, p-cymene, y-terpinene, terpinolene, linalool, linalyl acetate, a-terpineol, limonene. The dried fruits of large cardamom (Amomumsubulatum Roxb.), a high-value, low-volume spice crop grown only in the three eastern Himalayan countries, are widely used in foods, beverages, perfumes, and medicines. Small green cardamom (Elettariacardamomum) have significant antibacterial activity, supplementation on blood glucose indices, lipids, inflammatory profiles, and liver function. The current review inevitably describes the morphology and explores the phytochemical constituents, commercial utilization of the cardamom and its pharmacological activities.

Keywords Cardamom · *Elettaria cardamomum* · Amomum subulatum

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_6

6.1 Introduction

Cardamoms are the dried fruits of perennial herbs, there are two kinds of cardamoms available, one is true cardamom or small cardamom belongs to the genus Elettaria, Nepal cardamom or black cardamom belongs to the genus Amomum which belongs to the family Zingiberaceae. The genera are native to India (major producer till the late twentiethcentury) Nepal, Bhutan and Indonesia. It is a perennial plant, having tall pseudostem encircling leaf sheaths. Depending on the variety, a fully grown cardamom plant can be about 2–4 m in height. The stem is the rhizome, having subterranean habits, plant is shallow rooted with roots confined to the soil's top layer between 15 to 25 cms and run laterally to about 70 to 75 cm. Leaves are glabrous or pubescent. Leaves are about 30–50 cms in length and 10–15 cms in width. Flowers are borne on panicles and arise from the underground rhizome. The floral stalks are erect in the "Mysore' variety, prostrate in 'Malabar' variety and intermediate in 'Vazhukha'.Panicles appear from January onwards and the flowers emerge in April and continue till August. Fruits mature in about 3 to 4 months' time after flowering and are globose or ovoid or narrowly ellipsoid to elongate in shape, trilocular, containing 15–20 seeds. Capsules vary from pale to dark green in color. On maturation, the seeds turn black to darkish brown in color. Normally, an adult plant would produce about 2000 fruits weighing at harvest around 900 gms which on drying and curing would give about 200 gms.(Giby et al. 2009). Fig. 6.1

Fig. 6.1 Cardamom plant

6.1.1 Harvest and Processing

Cardamom plant starts to bear suckers or seedlings after two or three years of planting. The capsules start coming by 120–135 days after the formation of suckers or seedlings. Harvesting starts from June–July and remains till January–February in Kerala and Tamil Nadu. While in Karnataka, harvesting starts in August and continues till December–January. Harvesting is done for an interval of 15–30 days. Formation of dark green color of rind and black colored seeds is the indication of capsules attaining physiological maturity, after which they are harvested. Capsule harvesting leads to splitting of capsules and green color loss during the curing process. Processing of immature capsules yields uneven sized and shriveled. Freshly harvested capsules are cleaned in water. Extended storage after harvest can have an adverse effect on the products' quality. The procedure, involving indirect heating, which can reduce the moisture level of the fresh capsules from 80 to 10–12% is termed as curling. The maturity of capsules and curing temperature influences the color and quality of processed cardamom. A temperature of 40–45 °C is maintained during curing at all stages of drying which helps in retaining the green color. The last two hours of curing involves a gradual temperature rise from 50–60 °C and this helps in removing the floral remnants during polishing. Increased temperature in drying can also lead to loss of oil from the seeds. The two common methods for drying cardamom are Fig. 6.2:

1. Natural (Sun drying)
2. Flue curing Natural (Sun drying)

Fig. 6.2 Black Cardamom (Amomum subulatum) and Green cardamom (Elettaria cardamomum)

6.1.2 Natural (Sun Drying)

The fresh capsules are dried under the sun after harvesting for five to six days or more. Natural drying does not retain green color and leads to splitting of capsules. Improper drying due to rainy or cloudy weather conditions can result in deterioration of the quality of the capsules. Capsules dried under sun are not favoured for export and it is commonly practiced in some parts of Karnataka.

6.1.3 Flue Curing

This method produces high-quality green cardamom. It has a curing which is firewood based has flue pipes for conveying the hot air, house comprising a furnace for burning the wood and drying racks for stacking the trays. Drying 1 kg of fresh cardamom requires almost 3–4 kg of firewood and the curing room is closed, after staking the trays on the drying chamber racks. Hot air is generated by burning firewood and is circulated through the flue pipes. This process raises the room temperature (40 °C to 50 °C) and the capsules sweat and gives off the moisture at this period. Moisture is removed using exhaust fans. Soon after the removal of water vapor, the temperature in the chamber is maintained at 45–55 °C again for 18–24 h and the ventilators are closed. At the final stage, temperature is increased to 60–65 °C for another 1–2 h. The curing chamber is maintained at 65 °C to avoid capsule splitting and hence prevents losing of volatile constituents. Thus the high quality of cardamom in about 24–30 h is obtained.

6.1.4 Cardamom Products

- Seeds - Cardamom

Cardamom seeds pods are produced by decorticating the capsules and are done with the use of a plate mill or disc mill

- Powder - Cardamom

Cardamom, in powdered form, gives the maximum flavour to the food products and this form fails to give the aroma quality due to rapid loss of volatile constituents.

- Oil- Cardamom

Cardamom oil is produced by steam distillation of powdered seeds and it has vital essential minerals.

- Cardamom capsules

Cardamom capsules with contain phenolic compounds, lipids, volatile oils, and sterols. Cardamom (both green and black) has terpenes in their essential oils., α-terpineol, 1,8-cineole found in black cardamom and1,8-cineole, α-terpinyl acetate, in green cardamom Fig. 6.3.

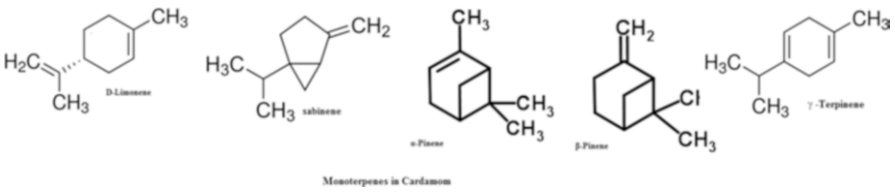

Fig. 6.3 Monoterpenes present in cardamom

6.1.5 Chemical Components

About 29 components were found in the cardamom essential oil. The monoterpene oxygen and carbohydrates derivatives are also present in it. The monoterpene oxygen derivatives were represented by β-linalool (4.829%) α-terpinyl acetate (39.032%), eucalyptol (31.534%) and α-terpineol (4.127%), the monoterpene carbohydrates by sabinene (4.308%). The pharmacological function of the components is not confined to their antimicrobial activity, some have antioxidant (pinene, limonene), analgesic function (citral), antitumor (borneol, linalool), and anti-inflammatory (pinene, sabinene) (Asbahani et al. 2015). The geraniol has antimicrobial, antitumor, insecticidal (Madhumitha et al. 2012) and antioxidant function and the β-caryophyllene has anti-inflammatory, anti-colitis, and antispasmodic activities (Asbahani et al. 2015; Lawrence 2004). Cardamom pods have 2% of fixed oil consisting mostly C16 fatty acids (palmitic acid and oleic). In the ground cardamom, the content of essential oil is lower (2–4%) and the oil contains mainly 1,8 cineole(up to 70%) plus pinene(%16).

6.1.6 Extraction

Extraction of Cardamom seeds is performed by using solvents like methanol (El-Segaey et al. 2007), diethyl ether (Syed Abdul Rahman et al. 2010), water (Suneetha and Krishnakantha 2005), and ethanol (Nanasombat and Lohasupthawee 2005) and are used for extraction Fig. 6.4.

The cardamom pods are extracted with liquefied gases through sub-critical propane and supercritical carbon dioxide extractions (Hamdan et al. 2008). When compared to carbon dioxide, propane was found to be efficient to seed oil recovery at the sub-critical condition with the less ratio of solvent or solid and good quality attributes (Hamdan et al. 2008). The important constituents of the extracts were 1,8-cineole and terpinyl acetate. Depending on the conditions of extraction like solvent, temperature and working pressure, the content of the compound in the final extract varies. $C_2H_2F_4$ (1,1,1,2-tetrafluorethane) is possibly liquefied gas, which is certified for the production of extracts for its use in food and flavor industry Table 6.1.

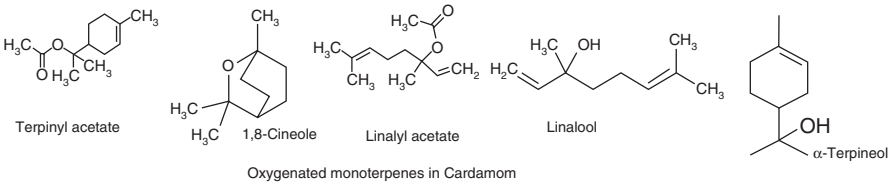

Fig. 6.4 Oxygenated monoterpenes present in cardamom

Table 6.1 Chemical composition of the cardamom extract

Components	%
Monoterpenes	
Sabinene	3.9
d-limonene	2.3
Myrcene	1.9
α-Pinene	1.9
β- Pinene	0.4
γ -Terpinene	0.3
Oxygenated monoterpenes	
Terpinyl acetate	36.8
1,8-cineole	29.2
Linalyl acetate	5.2
Linalool	3.1
α-Terpineol	1.6
Geraniol	0.9
Geranial	0.8
Terpinen-4-ol	0.6
Sabinene hydrate	0.3
Fenchone	0.6
Neral	0.3
Geranyl acetate	0.3
Carvyl acetate	0.2
Terpinyl propionate	0.1
Sesquiterpenes	
β-selinene	0.3
γ-Cadinene	0.2
Germacrene	0.1
Oxygenated sesquiterpenes	
Nerolidole	0.9
Phenyl Propanoids	
Anethole	2.1
p-cymene	0.1
Others	
Decenal	0.1

6.1.7 Obtaining of Extract

The cardamom seeds are pulverized in an attrition mill (0.15–0.25 mm size), the extract obtained is 1 cubic decimeter $C_2H_2F_4$ (1,1,1,2-tetrafluorethane) laboratory-extractor (Nenov 2006) maintained at 0.5 MPa-pressure, 18–20ºC-temperature and extraction time 60 min. The chemical composition is determined by GC analysis using an Agilent 7890A gas chromatograph equipped with FID detector and HPINNOWAX Polyethylene Glycol column (60 mm × 0.25 m) at temperature: 70 °C for 10 min with film thickness 0.25μmm, carrier gas helium, 1 ml/min constant flow with injector split ratio 50:1.

The dried fruits of E. cardamom are crushed and methanol is used to extract in a Soxhlet apparatus above the steam bath for 24 hrs. The solvent is removed under reduced pressure and in terms of starting material the extract yield of 10% (w/w). The total methanolic extract was treated with petroleum ether (60–80 °C) and solvent recovered under reduced pressure gives the petroleum ether soluble fraction. The essential oil from the dried fruits of E.cardamomum was obtained by steam distillation using a Klevengerappa- ratus. The essential oil (EO) yield was 4.8% (v/w) and EO content was determined by water distillation in a laboratory glass apparatus of the British Pharmacopoeia (Balinova and Diakov 1974; Stoyanova 2006).

6.1.8 Uses of Cardamom

Cardamom has a resinous fragrance and unique taste. Black cardamom is smokey, however not bitter, aroma, with coolness like mint. It is an important ingredient in Arabic coffee, they own coffeepots that can keep several cardamom pods in their spouts and use cardamom in combination with other spices in their dishes. It is a well-known spice in Northern and Eastern Africa. Scandinavian countries use cardamom in cookies and sweetbreads. Nordic countries use cardamom for baking and a common ingredient in Indian cooking. Both types are used in Asia for making sweet and savory dishes, mainly in the south. Spiced tea and traditional Indian sweets use green cardamom and included in aromatic bitters and herbal teas (Maharshi et al. 2015).

6.1.9 Pharmacological Uses

Green cardamom has been used by Indian Ayurvedic practitioners and ancient Greek and Roman physicians as a treatment for asthma, bronchitis, constipation, indigestion and helps in stimulating appetite in anorexia, hypertension, diarrhoea, dyspepsia, epilepsy, cardiovascular diseases, ulcers, gastrointestinal disorders and

vomiting. Likewise, black cardamom is used by Ayurvedic and Unani practitioners for ailments like rectal diseases, dysentery, liver congestion, gastrointestinal disorders and genitourinary complaints (Sameer et al. 2015).

6.1.10 Treatment of Asthma

Cardamom (Elettaria cardamomum) has marked use for the treatment of asthma. Cardamom has potential to relax airways. The extract of cardamom is evaluated for carbachol mediated bronchoconstriction in rats under anesthesia. It may dose-dependently (10–100 mg/kg) suppresses the carbachol (1 mu mol/kg) or increase the inspiratory pressure. The study gives an evidence for the use of cardamom in asthma as it has got a bronchodilatory effect through Ca++ antagonist mechanism (Arif Ullah Khan et al., June 2011).

6.1.11 Gastrointestinal Diseases

Large cardamom is used in Unani for gastrointestinal disorders. Different fractions of crude methanolic extract of an essential oil, petroleum ether (60–80 °C), methanolic and ethyl acetate fractions are studied in rats for their capacity to inhibit the gastric lesions caused due to aspirin, ethanol and pylorus ligature. The effects on mucus wall, an output of pepsin and concentration of gastric acid were noted. The crude methanolic extract and fractions of *A. subulatum* essential oil, petroleum ether, and ethyl acetate, inhibited gastric lesions caused by ethanol but not those which were induced by pylorus ligation and aspirin. There is an increase in mucus wall in pylorus-ligated rats due to ethyl acetate fraction. The results propose a direct protective effect on gastric mucosal barrier with ethyl acetate fraction. The decrease in gastric motility through petroleum ether and essential oil fractions suggest the gastroprotective action of the test drug. These investigations validate the use of large cardamom in gastrointestinal disorders by Unani physicians (Jafri et al. 2001; Jamal et al. 2006).

6.1.12 Diet-Induced Metabolic Syndrome – Green and Black Cardamom

The different types of cardamom used for cooking. The rats are treated with corn starch and *trans* fats (H) for 16 weeks. *Trans* fat rats had metabolic syndrome which leads to visceral obesity with glucose intolerance, hypertension, cardiovascular remodelling and non-alcoholic fatty liver disease. Food is supplemented with 3%

dried black or green cardamom for the final eight weeks only. The major volatile components are the closely related terpenes, 1,8-cineole in black cardamom and α-terpinyl acetate in green cardamom. High-carbohydrate, high-fat and black cardamom rats have shown a reversal of plasma triglycerides, total body fat mass, with decreased visceral adiposity, diet-induced changes, systolic blood pressure, structure and function of the heart and liver.

6.1.13 Detoxify

Cardamom is great for liver cleansing and detox. Green cardamom has the ability to remove toxins from the body, thus helps in detoxification. Using cardamom regularly can gradually remove the toxins and enhances blood circulation. It helps in removal of waste through kidneys. Phase I detoxification people will experience intolerance to caffeine while caffeine would not affect people with overactive system. Cardamom spices enhance the phase I enzyme which detoxifies caffeine. Hence addition of cardamom powder to tea or coffee is good especially for a person who is sensitive to caffeine.

Supplementation of cardamom powder enhanced glucose intolerance significantly ($p > 0.05$) and helps in the prevention of abdominal fat deposition in the case of HCHF diet fed rats. They also developed high-fat deposition, dyslipidemia, and liver inflammation compared to control rats. Cardamom powder supplementation helped to prevent the rise of lipid parameters ($p > 0.05$) in HCHF diet fed rats. Also the fat deposition and inflammatory cells infiltration in the liver were normalized with the supplementation (Gopalakrishnan et al. 1990). Moreover, increased lipid peroxidation, decreased antioxidant enzymes activities and increased advanced protein oxidation product level significantly ($p > 0.05$) both in plasma and liver tissue which were seen in HCHF diet were modulated by cardamom powder. HCHF diet also increased the ALT, AST and ALP enzyme activities in plasma which are also normalized by cardamom powder supplementation in HCHF diet fed rats. In addition, cardamom powder supplementation ameliorated the fibrosis in liver of HCHF diet fed rats (Md Mizanur Rahman et al. 2017; Mensor et al. 2001).

6.1.14 Antidepressant

Weakness and mental fatigue can be cured with the refreshing and uplifting effect of cardamom oil. However, there are no *in vivo* studies till today to establish the mood elevating potential of cardamom oil. The study evaluated the antidepressant activity of cardamom oil by using marble burying test in rats. The number of marbles buried with test extract treated rats was found to be 4 ± 0.577 and the number of marbles buried with control-treated rats was found to be 11 ± 2.64 6. Hence numbers of control-treated rats are more than the marbles buried by the test treated

rats. By the decrease in a number of marbles buried with cardamom oil treated rats when subjected to depression clearly indicates the presence of mood-elevating components in cardamom oil.. Hence the active constituents in the cardamom oil may be responsible for antidepressant activity (Kadiri Sunil Kumar et al. 2016).

6.1.15 Oral Health

Oil of cardamom seeds is used in the treatment of a toothache, to treat infections of teeth and gums, Extracts of E.cardamom resulted in antimicrobial activity against S.mutans and C.Albicans, which are the primary pathogens of dental (Swathi et al. 2016). The n-hexane extract of E.cardamom exhibits broad-spectrum antimicrobial activity against Propionibacterium acnes, S.mutans, Trichophytonmentagrophytes, and Pittosporumovale. The in-vitro antimicrobial activity of both black and green cardamom fruit extracts was studied against Candida albicans, Saccharomyces cerevisiae, Lactobacillus acidophilus, Staphylococcus aureus, and Streptococcus mutans. The most susceptible microorganisms were S.aureus was followed by C.albicans, S.cerevisiae, and S.mutans (Srinath and Lakshmi 2014; Pearley et al. 2016).

6.1.16 Control in Cholesterol Levels

The result showed that increase of cholesterol in high carbohydrate, high fiber compared to non-treated rats. Cardamom significantly decreased cholesterol concentration in high carbohydrate, high fiber diet fed rats. Moreover, their is a raise in LDL cholesterol level in high carbohydrate, than to untreated rats.

6.1.17 Cancer Prevention

The bioactive compounds are cancer fighters specially breast cancer, ovarian cancer, and prostate cancer. Cardamom accommodates antioxidants that shield the stress, elderly and contest conjoint illnesses. In vivo studies showed a rise in glutathione, an antioxidant enzyme found naturally in our bodies (Jie Zheng et al. 2013).

6.1.18 Bad Breath

It was believed that, it has efficiency against halitosis. Simply chewing the seeds eliminates bad odors. Because of an effective cure for the most offensive breath cardamom is used in chewing gums.

6.1.19 Anti-Carious

Cardamom is used to treat tooth and gum decay. It relieves hoarseness of voice and smoothens a sore throat. (Shailene Fotedar et al. 2014).

6.1.20 Antiseptic and Antimicrobial

The essential oil present in cardamom has a high degree of antiseptic and antimicrobial properties. Adding few drops of it in water and using as a mouthwash, disinfects the oral cavity of all germs. The cardamom infusion is used to treat a sore throat, pharyngitis relaxes uvula and hoarseness during the infective stage of influenza (Agaoglu et al. 2005; Atanasova et al. 2010; Isao et al. 1991).

6.1.21 Stimulant

Cardamom essential oil revitalizes your entire body. This effect increases the spirits in cases of depression or fatigue. It activates enzyme and hormonal secretion, circulation, gastric juices, peristaltic motion, and excretion, thus maintains proper metabolic activity throughout the body (Rasheeda et al. 2013; Teneva et al. 2016).

6.1.22 Warming

Cardamom oil possesses a warming effect, which heats up the body and promotes sweating. Thus helps to clear congestion and coughs. It relieves symptoms of the common cold, provides relief from headaches that result from illness and can be used to cure diarrhea caused by extreme cold.

6.1.23 Aphrodisiac

The arousing effect in cardamom oil helps in curing sexual weakness, impotence, frigidity, loss of libido and erectile dysfunction. The studies have been carried out in humans to investigate possible pheromones, possible receptors for their action, their properties and mechanism of action. Till today studies prove that production and perception of pheromones by humans is through olfactory communication.

6.1.24 Flavouring

Cardamom is a crucial compound in Kahwa, because of its antibacterial activity, it can be used as food preservative, in sweets. The seeds and fruits of cardamom can add to bring a variety of taste to rice, meat, and flavor to coffee, tea. We can preserve the food items with less amount of cardamom oil, so it never spoils the flavor, quality of food.

6.1.25 Cosmetics and Chewing Gum

Cardamon oil gives a spicy taste, so it can use in chewing gums and in beauty products as cooling agents.

6.1.26 Cardamom Oil as Skin Permeation Enhancer

Monoterpene increases the skin permeation properties, which is extracted from cardamom oil. The transdermal delivery effect of indomethacin in ethanol/water vehicles was studied through in vitro and in vivo studies. The cardamom oil pre-treatment enhances the penetration of indomethacin in both in studies. The indomethacin flux decreased as the length of the pretreatment increased. Cardamom oil has shown equal enhancement on the penetration of indomethacin along with cyclic monoterpene mixture having components of oil, it is the major component which changes the barrier property of stratum corneum. It indicates cardamom oil contains three minor components namely alpha-pine (6.5%), alpha-terpineol (0.4%), beta-pinene (4.8%), it increases the permeation of indomethacin by a synergistic effect with 1,8-cineole (59.3%) and d-limonene (29.0%) (Huang et al. 1999).

6.1.27 Gold Nanoparticles Using Elettaria cardamomum Aqueous Extract

Green synthesis of gold nanoparticles using Elettaria Cardamomum extracts. It is an Eco-friendly method. We can synthesize the gold nanoparticles by reduction of an aqueous solution of $HAuCl_4$ at room temperature. Reduction of Au^{3+} to gold nanoparticles can be observed by changing the color, P^H changes, and UV spectroscopic analysis. Particles sizes can be confirmed by observing XRD analysis, it indicates the greater reduction potential of Elettaria cardamomum extract. These extract can use to the synthesis of other nanoparticles (Pattanayak and Nayak 2013; Fowsiya and Madhumitha et al. 2017).

6.1.28 Other Uses

Cardamom oil can be used to reduce oral problems like a toothache, bad smell, eliminates the dangerous effects of the poison and tobacco.

6.2 Conclusion

Cardamom is the household spice for diverse cuisines in all parts of India. It is an ancient plant species in India, which is having very good medicinal properties. This review gives detailed information on various chemical constituents present in cardamom, its morphology, extraction of the chemical constituents and their pharmacological activity.This infers that compounds isolated from the different plants have therapeutic activity in the management and treatment of diseases with less number of adverse drug reactions. Present research is focused on herbal drug discovery. The drugs derived from natural products have the wide variety of application in the field of medicine.

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Chapter 7
Total Synthesis of Natural Products Existence in Fruits and Vegetables

Nasireddy Seshadri Reddy and S. Mohana Roopan

Abstract This book chapter scrutinizes the total synthesis of natural products extricate from fruits and vegetables and its biological activities allied to certain diseases. Generally, natural products are extricated from plants and their products. Which render nutrition, phytochemicals, vitamins, fibers, and minerals etc.., these are manifest numerous biological activities such as antioxidant, antibacterial, anti-inflammatory, and antifungal activity etc., hostile to chronic diseases like cancer, Alzheimer's, heart disease, arthritis, and asthma etc., at a certain level, and gift with good health. Natural products are present in the free form or associated with glycosides in little quantity, sometimes difficult to isolated in pure form. Therefore, total synthesis plays a major role in the current engrossment, synthesis and its study allied to biological activities.

Keywords Total synthesis · Frutis · Flavonoids · Phenolic compounds · Vitamins

7.1 Introduction

Natural products are boon to our good health. It has a wide range of applications in healthcare products like sunscreen lotion, beauty creams, shampoos, in the pharmaceutical industry as antituberculosis, anticancer, anti-HIV, antiarthritis, antimalaria drugs, in the food industry as an additive, flavoring agents, color to food, nutrient food products and in chromatography as coloring agents to visible, in nanotechnology as green synthesis of nanoparticles like CeO_2 with *Moringa oleifera* peel extract (Surendra and Roopan 2016), capped zinc oxide nanoparticles with *Carissa edulis* fruit extract (Fowsiya et al. 2016), silver nanoparticles with *Carissa carandas* (Anupama and Madhumitha 2017).

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_7

Phytochemicals are non-nutrient, biologically active compounds are available in plants and its products. Phytochemicals are classified into phenolics, alkaloids, nitrogen-containing compounds, organosulfur compounds, phytosterols, carotenoids (Liu 2004).

Phenolics are the secondary metabolites of plants. Phenolics manifest numerous biological activities like antioxidant, antibacterial, antifungal, anti-inflammatory etc., hostile to chronic diseases like anticancer, heart disease, Alzheimer's disease (Willett 2002; Liu 2004). Fruits and vegetables are the major sources of phenolics like pineapple, kiwifruit, beets, potatoes, carrot, blueberry, plum, raspberry, cranberry (Wolfe et al. 2008). Anthocyanins are responsible for the color of some fruits, vegetables, and grains.

Carotenoids are the unsaturated conjugated compound. Carotenoids are responsible for the color of the fruits, leaves, and vegetables. These are present in carrots, papaya, mangoes, potatoes, pumpkin, cassava (Adewusi and Howard 1993), mustard greens, watercress etc. Carotenoids are important photosynthetic pigments, useful for improving vision, and show antioxidant properties, cardiovascular diseases (Fassett and Coombes 2009; Fowsiya and Madhumitha 2017).

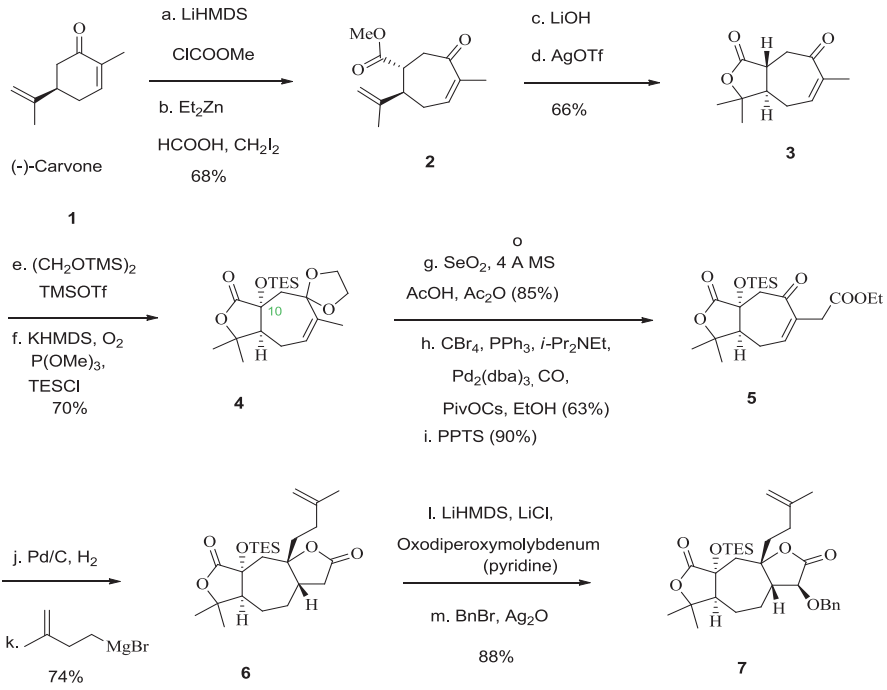
Vitamins are crucial nutrients required to our body. The accessory of vitamins is used to treat certain diseases. Vitamin A incorporates the compounds retinol, retinal. Because of its antioxidant property, it helps to increase the eye vision. B complex vitamins are the large group of vitamins working as coenzymes or as precurse of enzymes. Vitamins C is important in collagen synthesis and also a superb antioxidant to decrease oxidative stress. Glycoalkaloids are plant toxins fabricate for protection hostile to parasites (Irvine 1961), predators, insects, pathogens. Acetogenins are the class of natural products mainly extricated from Annonaceae family (Alali et al. 1999; Zafra-Polo et al. 1998; Zeng et al. 1996; Hemalatha et al. 2013; Hemalatha et al. 2015). Acetogenins acts as pesticides, antiparasitic agents, antitumor, antifeedant.

Natural products are present in a free state or associated with other compounds like glycosides, these are also present in less quantity, sometimes difficult to get in pure form. We need to increase quantities of target products, biologically active compounds in industry levels for current needs. Total synthesis starts with simple, commercially obtainable precursors. Total synthesis is the route of synthesis of medicinally active compounds, natural products in huge quantity regarding industry levels. Because of its importance in various fields like agriculture, pharmaceuticals, food industry, in chromatography techniques and structure miscellany, many researchers have been working on the total synthesis. This book chapter scrutinizes total synthesis of some chief natural products available in fruits and vegetables.

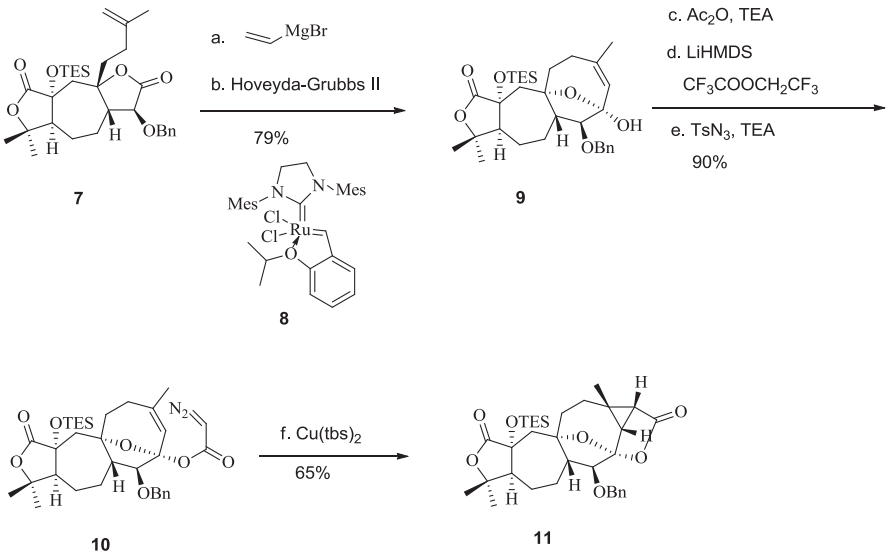
7.2 19-Dehydroxyl Arisandilactone A

Schisandra chinensis is also termed as five –flavor berry or wu wei zi because it bears five basic flavors of bitter, salty, sour, sweet and spicy. Schisandra chinensis is a traditional medicinal plant in China, it has been used as a sedative, tonic agents, also a treatment for rheumatic lumbago and its related diseases. Some of the nortriterpenoid show inhibitory activity against HIV-1, tumors, and hepatitis (Xiao et al. 2008; Shi et al. 2015). Total synthesis of biologically active nortriterpenoid such as schindilactone A (Xiao et al. 2011), Ruflordlactone A (Li et al. 2014; Goh et al. 2015), Schilancitrilactones B and C (Wang et al. 2015), Propindilactone G (You et al. 2015), have been prepared. Biologically active compounds such as (+)-arisandilactone A (Cheng et al. 2010a) and (+)-arisandilactone C (Cheng et al. 2010b) are isolated from the Schisandraceae family.

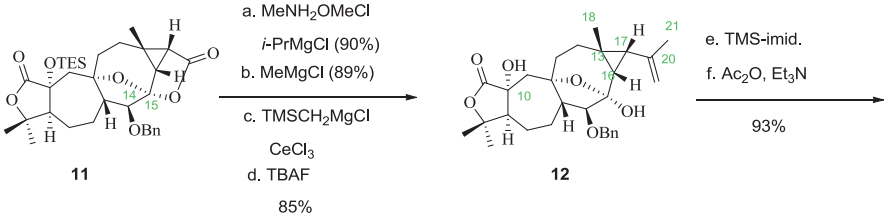
Conversion of (R)-(−)-carvone to cycloheptenone was achieved by using a Mander's methoxycarbonylation, followed by ring expansion reactions to give **2** in 68% yield (Mander and Sethi 1983; Xue et al. 2005). Compound **2** was hydrolyzed by using LiOH and the resultant acid was transformed to lactone (Yang et al. 2005) to give **3** in 66% with AgOTf. Silyloxy group at the C10 position of compound **4** was achieved by reacting the compound **3** with $(CH_2OTMS)_2$/TMSOTf (Hwu and Wetzel 1985). Under an O_2 atmosphere, the resultant ketal ester was treated with KHMDS in the presence of $P(OMe)_3$ followed by TESCl to give **4** in 70% yield as a single diastereomer (Gardner et al. 1968). Compound **4** was treated with SeO_2 in the being of AcOH, Ac_2O (Naf et al. 1991). The resultant allylic alcohol was submitted to bromination (Appel 1975) and palladium catalyzed carbonylation (Milstein 1982) to give an ester in 63% yield, after deprotonation of enone by PPTS to give **5** in 90% yield. Compound **5** was subjected to palladium catalyzed hydrogenation (92%) and Grignard reaction (80%) to give compound **6** in 74% as a single diastereomer. Which hold bislactone rings. Due to the being of the bulky triethylsilyloxy group in compound **6**, both hydrogenation and Grignard reactions to appear at less hindered face. To attain stereoselective alpha-hydroxylation, compound **6** was treated with LiHMDS, LiCl (Adam and Prechtl 1991) at −78 °C. The resultant compound was oxidized with oxodiperoxymolybdenum(pyridine) (Vedejs et al. 1978) to give a secondary alcohol, the resultant compound was reacted with $BnBr/Ag_2O$ (Scholl and Grubbs 1999) to give compound (bislactone) **7** in 88% total yield as a single diastereomer. The high stereo selective alpha-hydroxylation was encouraged by the bulky triethylsilyloxy group.

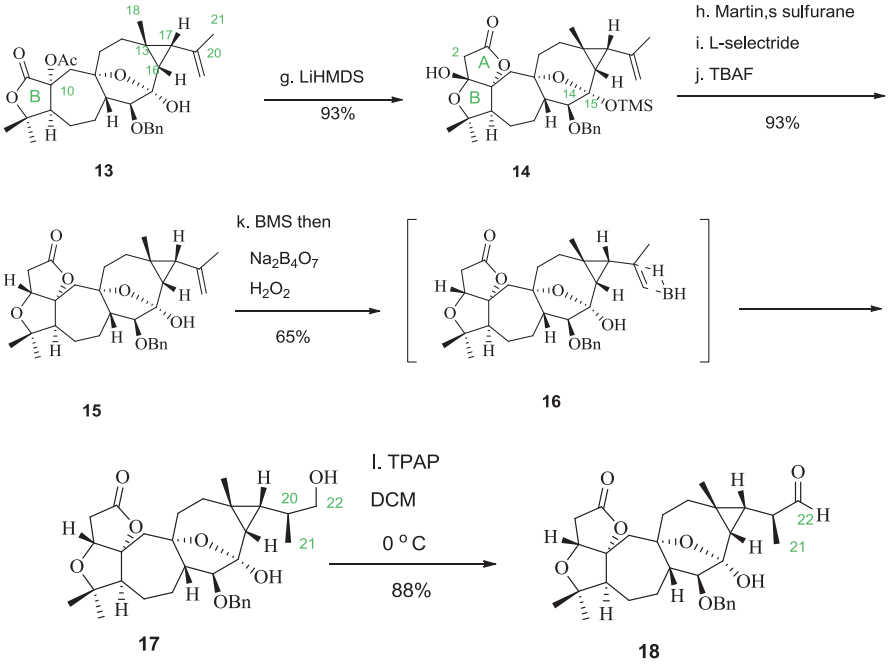


Compound **7** was subjected to the second- generation Hoveyda-Grubbs catalyst in toluene at 80 °C to give the potential for in situ epimerization of hemiketal during the ring closing mechanism reactions. The resultant compound **7** was treated with vinyl magnesium bromide (Figueroa et al. 2007) to give an epimeric mixture of hemiketals, were then subjected to an RCM in the presence of Hoveyda-Grubbs (Garber et al. 2000) catalyst **8** in toluene to give the desired compound as a single diastereomer in 79%. Compound **9** was reacted with acetic anhydride/triethylamine in the being of DMAP. The resultant enolate was subjected to $CF_3CO_2CH_2CF_3$ at −75 °C, reacted with TsN_3 to give the compound **10** in 90%. The synthesis of the unflexible and hugely strained intermediate **11** can be achieved by reacting the compound **10** with a transition metal catalysts such as CuI, $Cu(acac)_2$, CuCl, $Cu(tbs)_2$, $CuSO_4$, $Rh(OAc)_4$ to give **11** in 65% yield.



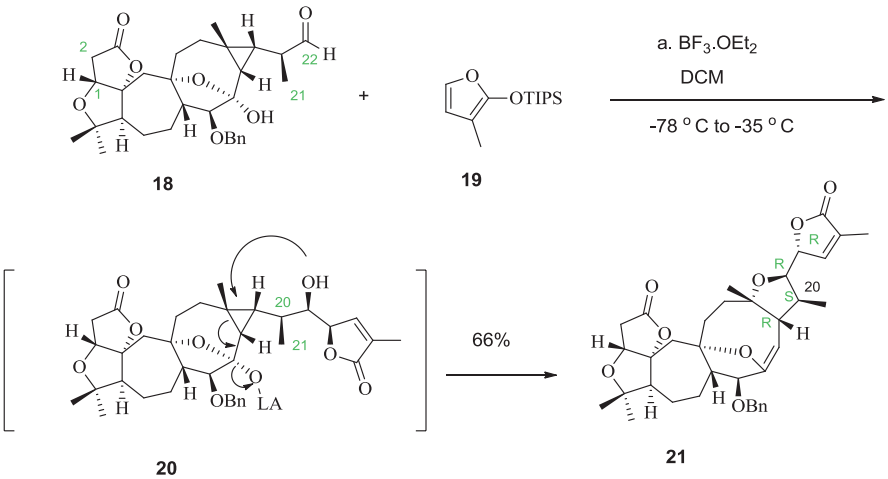
Conversion of lactone ring **11** to the terminal olefin was achieved when it reacted with $MeNH_2OMeCl$, *i*-PrMgCl in THF (Williama et al. 1995) to give the compound in 90%, the resultant compound was then reacted with MeMgCl to give ketone in 89%. Peterson olefination (Peterson 1968) was achieved when the resultant compound was reacted with $TMSCH_2MgCl$, $CeCl_3$ in THF (Li and Yang 2004). The resultant compound was subjected to desilylation with TBAF. We should protect hydroxyl group being in compound **12** with TMS-imidazole, Ac_2O, Et_3N to give the compound **13** in 93%. **13** reacted with LiHMDS to give **14** via Dieckmann type reaction. Dehydration of hydroxyl group at C23 was offered by subjecting the compound **14** with Martin's sulfurane (Martin and Arhart 1971). The resultant unsaturated compound was reduced with L-selectride (Ganem and Fortunato 1975), followed by desilylation with TBAF to give **15** in 93%. Synthesis of alcohol was achieved by subjected the compound **15** to BMS (Cossy et al. 1999) in THF, followed by oxidation with hydrogen peroxide, in the being of borox (Brown and Rangaishenvi 1988) to give **17** in 65%. Oxidation of alcohol achieved by reacted the compound **17** with TPAP in DCM to give **18** in 88%.



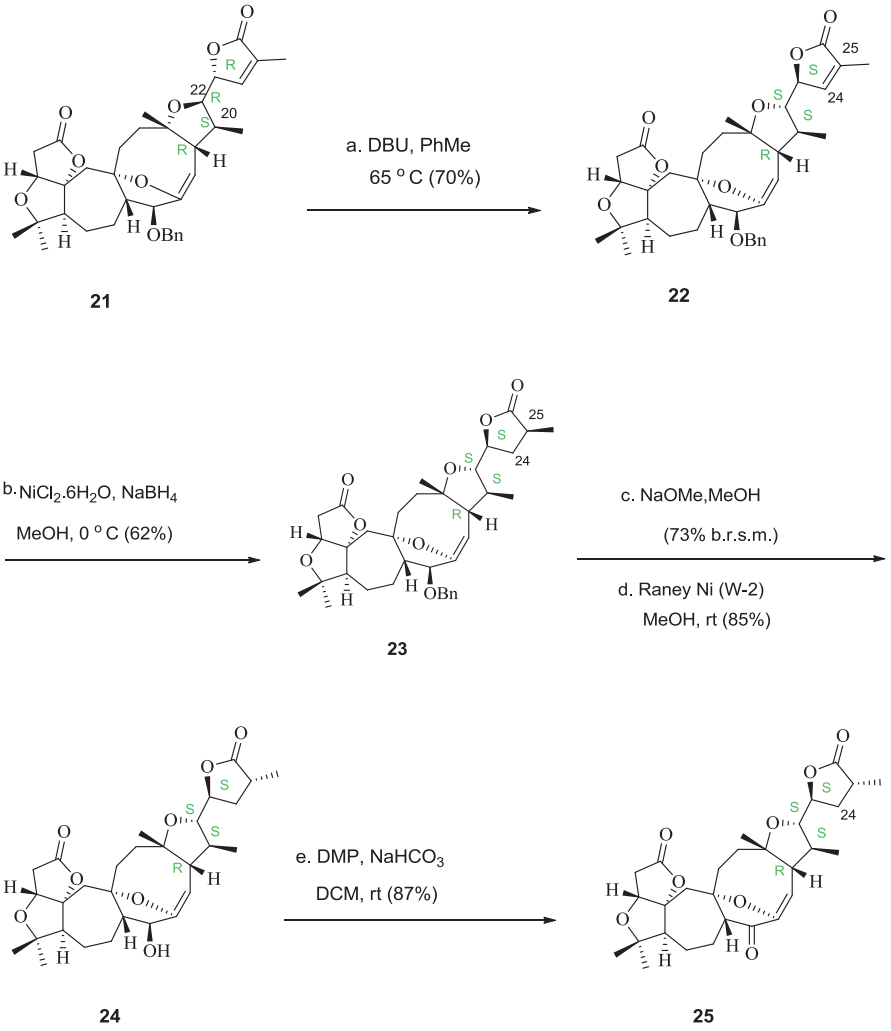


13 14 15 16 17 18

Compound **18** was coupled with **19** in the being of BF_3**.**OEt_2 in DCM at −78 ° C. The reaction moves forward through the vinylogous Mukaiyama Aldol Reaction, homo Michael reaction to give **21** in 66%. Inversion of stereogenic centers at C22, C23 of **21** was attained by reacting the compound **21** with DBU. The double bond at C24, C25 of **22** was chemoselectively reduced with $NiCl_2.6H_2o/NaBH_4$ to give the compound **23** in 62%. Invertion of stereochemistry at C25 was achieved by reacting the compound **23** with NaOMe in methanol, then the resultant compound underwent debenzylation with Raney nickel to give **24** in 85% yield. Oxidation of **24** with DMP to give **25** in 87% yield.



18 19 20 21



21 22 23 24 25

7.3 Annona Acetogenins

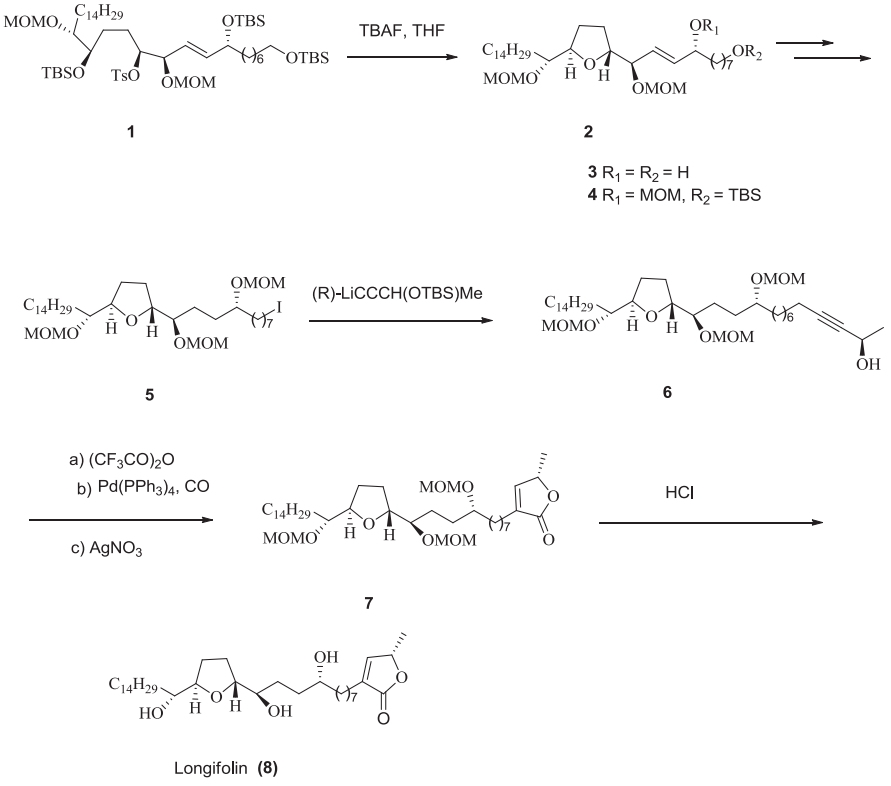
Annonaceous Acetogenins extricated from Annonaceae species (Zafra-Polo et al. 1996; Zafra-Polo et al. 1998; Zeng et al. 1996; Alali et al. 1999).These are planted biochemicals, Acetogenins shows a derange of biological properties such as pesticidal, antiparasitic agent (Irvine 1961), antifeedant, antiprotozoal, antitumor (Zeng et al. 1996), immunosuppressant activity.

Acetogenins shows inhibitory activity on mitochondrial complex-**I** (Gonzalez et al. 1997) (inhibitory activity on the NADH oxidase).It shows more effect opposed

to multidrug-resistant tumors (in nanomolar concentrations). Acetogenins shows the effect on COX-2 (anti-inflammatory effect), angiogenesis and cancer metastasis (Gonzalez et al. 1997).

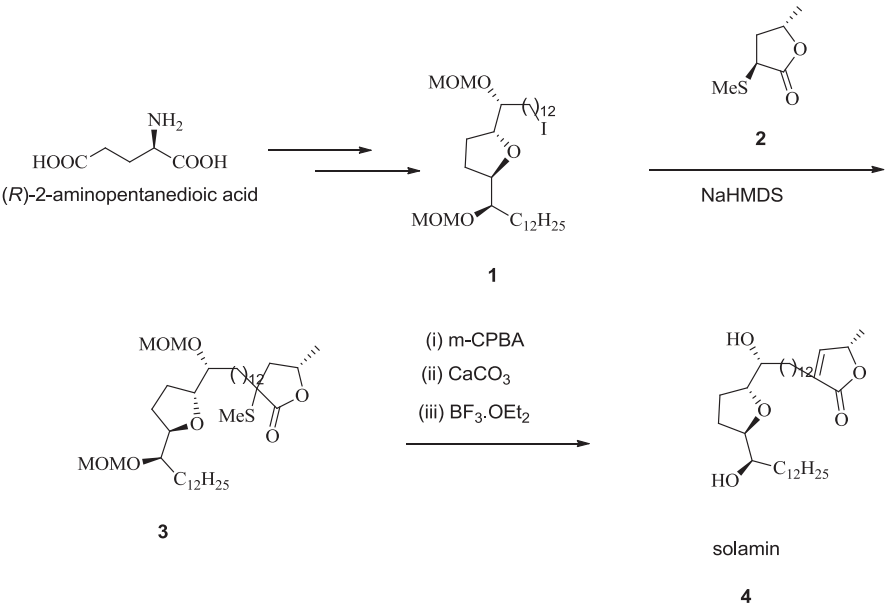
7.3.1 *Longifolicin*

Compound **2** (Marshall and Jiang 1998) was attained by reacting the compound **1** with TBAF in THF to give the cyclic product (THF). Compound **3** was attained by the simultaneous protection of secondary hydroxyl group and halogenation of the primary hydroxyl group. **5** reacted with a chiral propargylic alcohol to give **4**. The resultant compound underwent allenyl palladium hydrocarbonylation with $(CF_3CO)_2O$, Pd catalyst, CO, and $AgNO_3$. The resultant compound underwent acid hydrolysis (cleavage of protected groups) to give longifolene.



7.3.2 Solamin

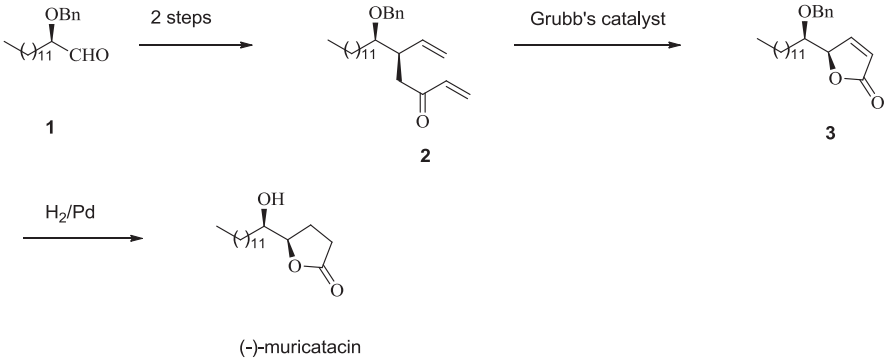
Solamin is a cytotoxin withdrawn from Annona muricata seed (Myint et al. 1991). Compound **1** was synthesized from D-glutamic acid. Lactone **2** reacted with a base (NaHMDS) to give an intermediate enolate. The resultant enolate reacted with **1** to give the main compound **2**. Solamin was attained by oxidation of sulfide (with m-CPBA), followed by thermal elimination (with $CaCO_3$), and deprotonation (with Lewis acid).



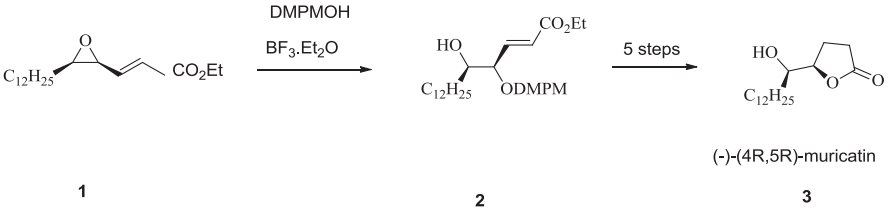
7.3.3 Muricatacin

Muricatacin was extricated from the seeds of Annona muricata (Rieser et al. 1991). It manifests biological activities as cytotoxins opposed to tumors.

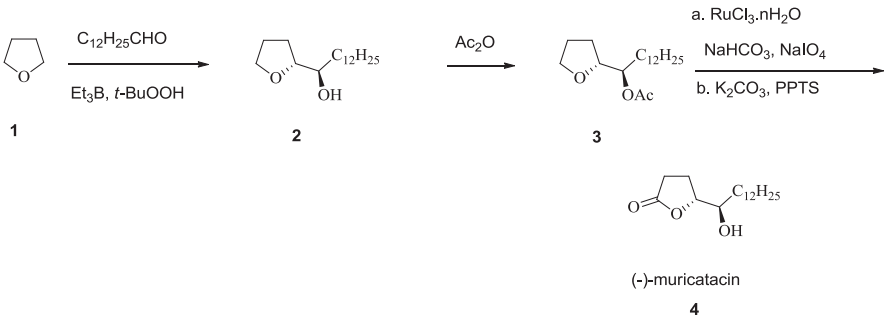
2 reacted with Grubb's catalyst undergone RCM (Carda et al. 2002) to give **3** (with the elimination of ethane), **2** was derived from the compound **1** by two steps. Muricatacin was obtained by selective reduction with H_2/Pd.



(−)-(4R, 5R)-muricatacin obtained by Lewis acid assisted stereo and region selective ring opening of a substituted vinyl epoxide.



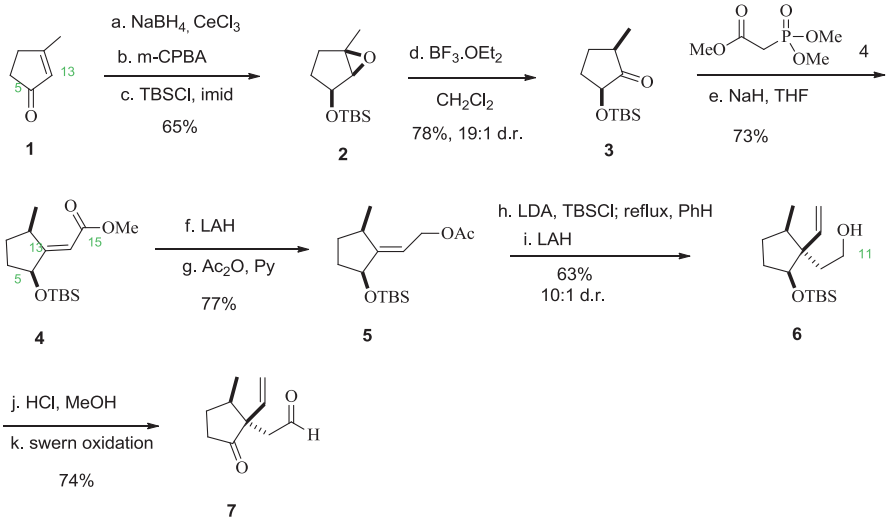
(−)-muricatacin was synthesized by Yoshimitsu in 2003. Alpha C-H hydroxyalkylation **2** was attained by, THF worked with tridecanal using Et_3B and TBHP. Protected hydroxylation **3** was attained with acetic anhydride. **4** obtained by oxidation with ruthenium trioxide under modified Sharpless conditions followed by deprotection.



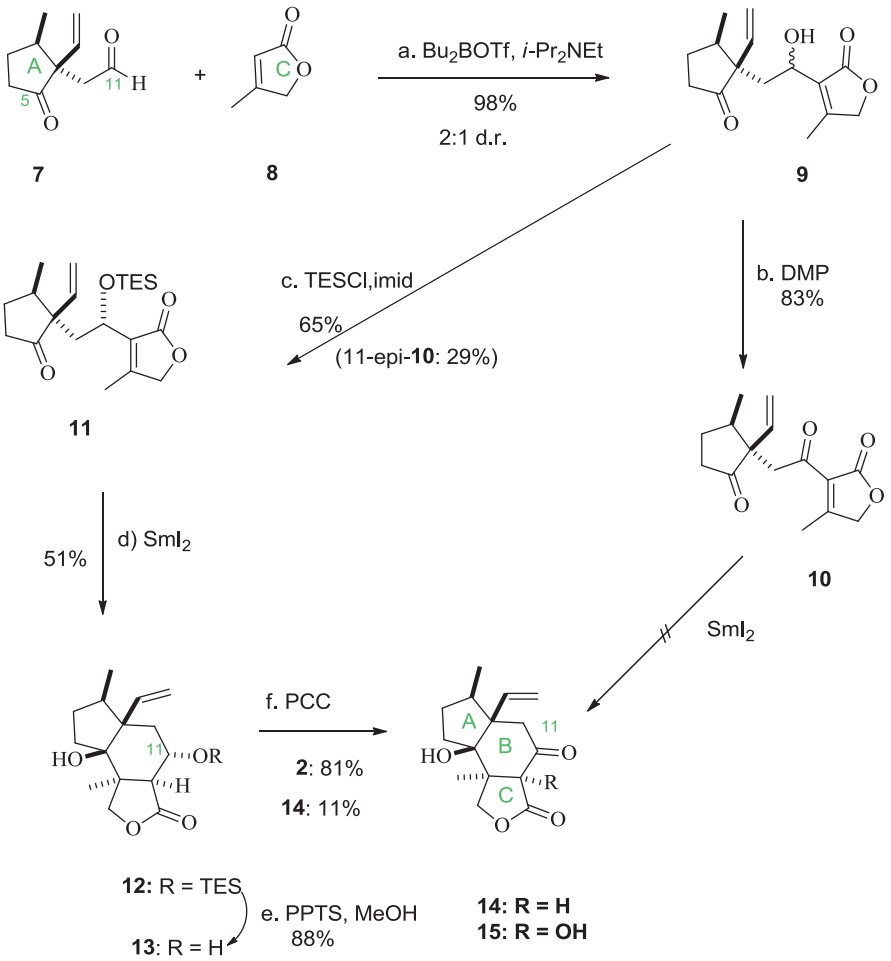
7.4 Jiadifenolide

Jiadifenolide is a sesquiterpenoid, it manifests biological activity (neurotrophic activity) (Kubo et al. 2009). It is extricated from Illicium jiadifengpi (Kubo et al. 2009). It is applied to foods, beverages, biriyani.

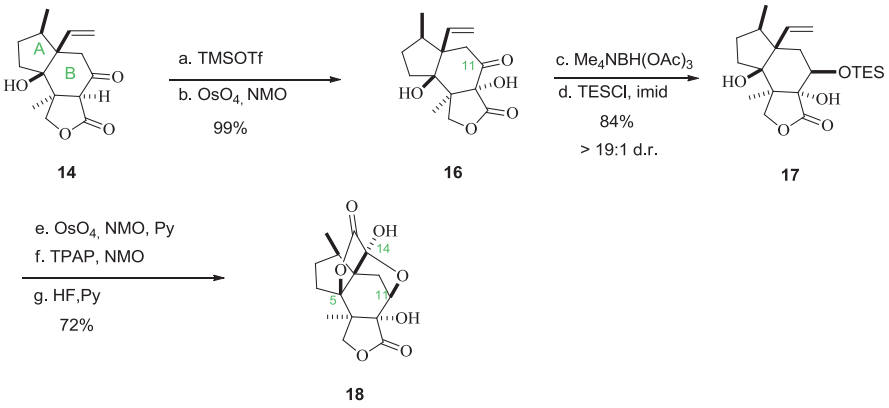
To attain the allylic alcoholic group **1** subjected to reduction with Luche reagent. The resultant compound was undergone hydroxyl-directed epoxidation with m-CPBA, then reacted with TBSCl to give protected hydroxyl compound **2** in 65%. Stereochemistry at C2 of **3** was reached by reacted the compound with Lewis acid (Kita et al. 1997) (epoxide opened from the less crowded side) to give **3** in 78%. **3** reacted with phosphonates through Horner- Wordsworth-Emmons reaction to give alkene **4** in 73%. **5** attained by simultaneous reduction followed by acylation to give allylic acetate in 77%. **5** underwent Ireland thermal rearrangement preferentially at the less hindered alkene pi face (C13) with LDA, TBSCl (TBS ketene acetal) (Ireland et al. 1976) in benzene. The resultant compound underwent reduction with LAH to give alcohol **6** in 63%. Aldehyde compound **7** was attained by simultaneously subjected to acid hydrolysis followed by swern oxidation.



7 and **8** (Gogoi and Argade 2006) reacted with Bu_2BOTf, base to give Aldol coupled product **9**. The resultant Aldol product underwent protection with TESCl, followed by stereoisomerization with a base to give **11** in 65%. Single cycloadduct **12** was attained with freshly prepared SmI_2 through chelated boat type transition structure. **12** underwent acid hydrolysis, followed by simultaneous oxidation to give **14** in 81%. The reaction does not proceed to give **14** via **10.**



TMS-enol ether was attained by reacting the compound **14** with TMSOTf and NEt_3, the outcome compound underwent chemoselective desilylation to give tertiary alcohol at C10 of **16** in 99%. Stereochemistry of C11 was directed by C10 hydroxyl group. **16** underwent reduction with $Me_4NBH(OAc)_3$ (87%), followed by protected (Saksena and Mangiaracina 1983; Evans et al. 1988) with TESCl, imidazole to give **17** in 96%. Pyridine accelerated diol formation of the C13-terminal alkene of **17**, the resultant compound subjected to oxidative lactonization to give E ring in 84%. Desilylation was attained with HF, followed by subsequent hemiacetalization to give **18** in 72%.

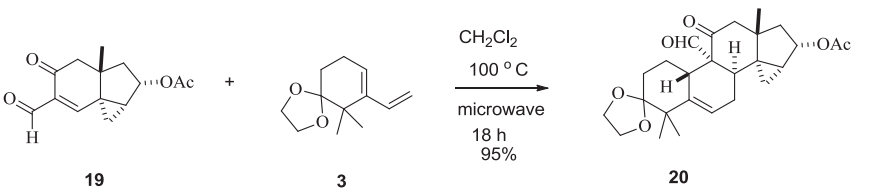


7.5 Cucurbitacins

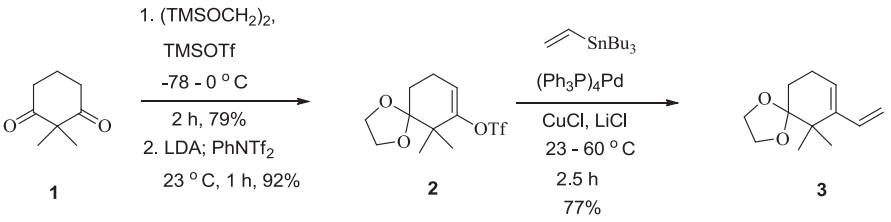
Cucurbitacin is a class of biochemicals (steroids) being in the family of Cucurbitaceae such as pumpkin and gourds. These are being in the form of glycosides. It's derivatives existence in various plant families such as Brassicaceae, Scrophulariaceae, Cucurbitaceae, Elaeocarpaceae, Datisscaceae, Desfonfaniaceae, Polemoniaceae, Primulaceae, Rubiaceae, Rosaceae, Sterculiaceae, Thymalaceae, in some mushrooms (russula) and marine mollusks.

These are cytotoxins and fight against herbivores. Cucurbitacins provide bitter taste in plant foods (Shang et al. 2014). Cucurbitacins shows various biological properties (Lang et al. 2012; Lang et al. 2014) such as anti-inflammatory (Kapoor 2013), antiparasitic (Miro 1995; Chan et al. 2005; Graziose et al. 2013), antiproliferative (Chan et al. 2008), hepatotoxicity (Zhang et al. 2014), laxative, antitumoral (Miro 1995; Valente 2004), antiviral, antibacterial, anticancer properties (Alghasham 2013; Kapoor 2013).

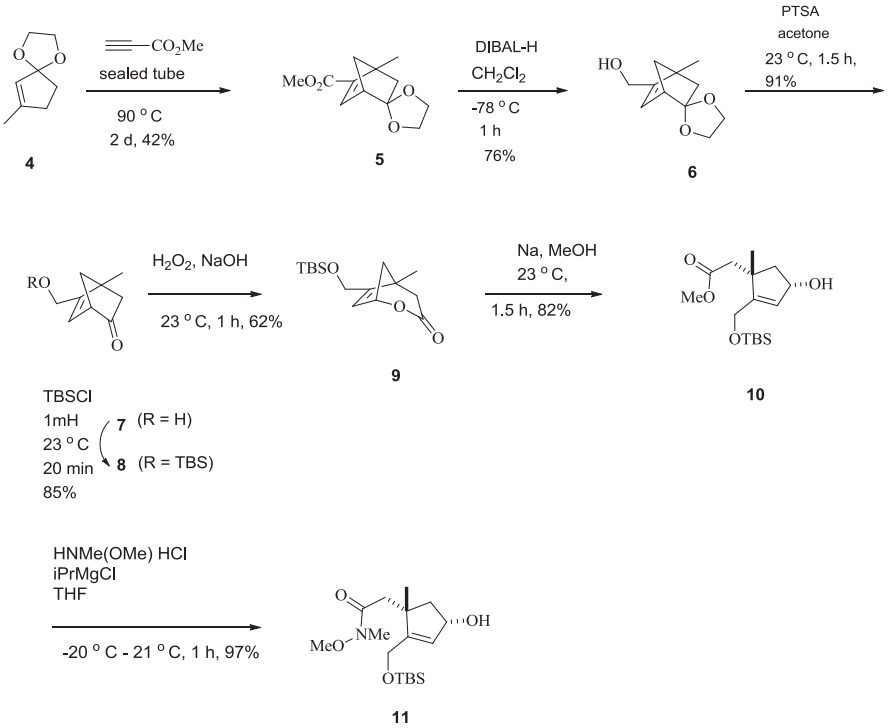
Tetracyclin triterpenoids Cucurbitacin B and D **20** was attained by simple Diels-Alder cycloaddition of diene and dienophile.



One of the ketones being in 2, 2 dimethyl cyclohexene 1, 3-dioneDiene **1** protected under Noyori's conditions followed by reacting with LDA, $PhNTf_2$ to give enol triflate **2** in 92%. **3** formed as a result of stille coupling between triflate and tributylvinyl tin compounds to give an overall yield of 77%.

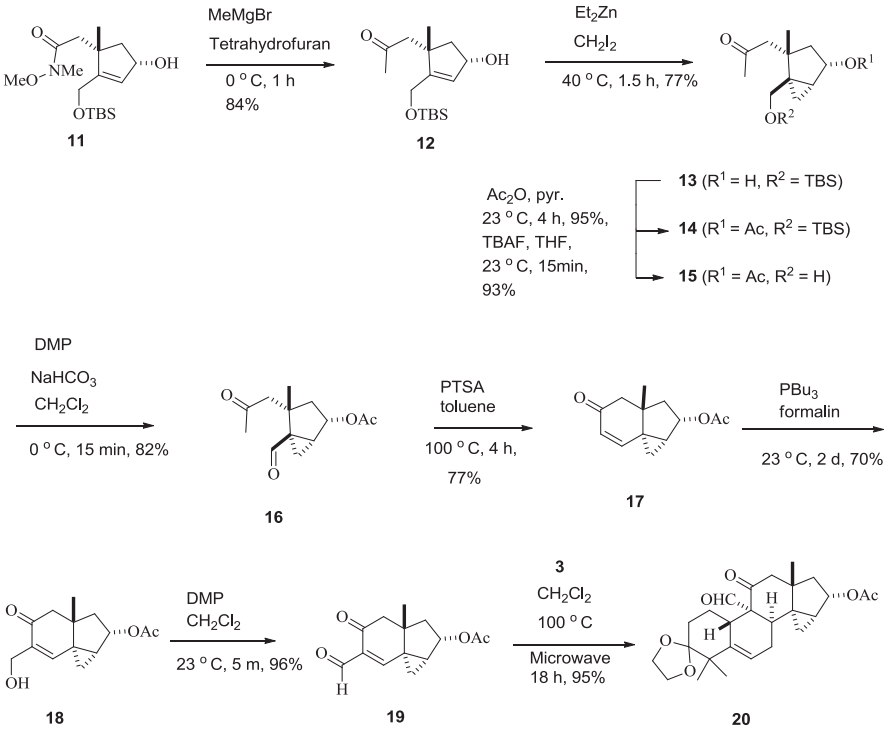


Synthesis of norbornenone ethylene ketal **5** was attained by reaction between methyl propiolate and ethylene ketal of 3-methylcyclopent-2-enone under Diels-Alder conditions. Ester group being in the compound **5** was reduced with DIBAL to generate analogous alcohol **6**. Which was underwent hydrolysis of the ketal group followed by protection of primary alcohol with TBSCl to generate **8. 8** reacted with hydrogen peroxide, sodium hydroxide under Baeyer-Villiger oxidation followed by hydroxyl group protection with TBSCl to generate **9** in 85%. Lactone reacted with sodium metal in methanol to generate analogous ester **10** in 82%. Weinreb amide **11** was attained by reacting with N, O-dimethyl hydroxylamine hydrochloride and isopropyl magnesium chloride in tetrahydrofuran.



Weinreb amide reacted with a Grignard reagent to generate corresponding methyl ketone **12** in 84%. Hydroxy directed cyclopropanation was attained under

Simmon Smidth conditions to generate **12**. The resultant compound underwent secondary hydroxyl protection followed by primary hydroxyl group deprotection with TBAF **15**, which was then subjected to Dess-Mortien oxidation followed by intramolecular Aldol condensation to generate enone **17.** Enone subjected to tributylphosphine and formaldehyde under Baylis –Hillman reaction to generate analogous alcohol **18**, the resultant compound subjected to Dess- Mortine oxidation to generate activated dienophile **19**. Diene reacted with dienophile **3** under Diel-Alder cycloaddition to generate tetracyclic triterpenoids.



Dihydrocucurbitacin B underwent oxidation with PCC and barium carbonate to generate derivatives **2** and **3** (Lang et al. 2012). Oxidation of **1** at C2 is the stable isomer in basic medium (Fig. 7.1).

Cucurbitacin glycosides existence in the form of β-isomers (Chan et al. 2005). 16-oxo-dihydrocucurbitacin- B reacted with trichloroacetimidate in the being of TMSOTf (Schmidth and Toepfer 1991) to generate O-glycosylated derivative (Fig. 7.2).

Azide derivative **7** was attained by simultaneously chain extension with 4-bromobutyryl chloride catalyzed by DMAP and pyridine followed by reacting with sodium azide (Fig. 7.3). Azide derivative of dihydro cucurbitacin underwent cycloaddition with a protected alkyne in the being of copper sulfate as a catalyst to generate triazole derivative **9**. Dihydrocucurbitacin show anti-inflammatory,

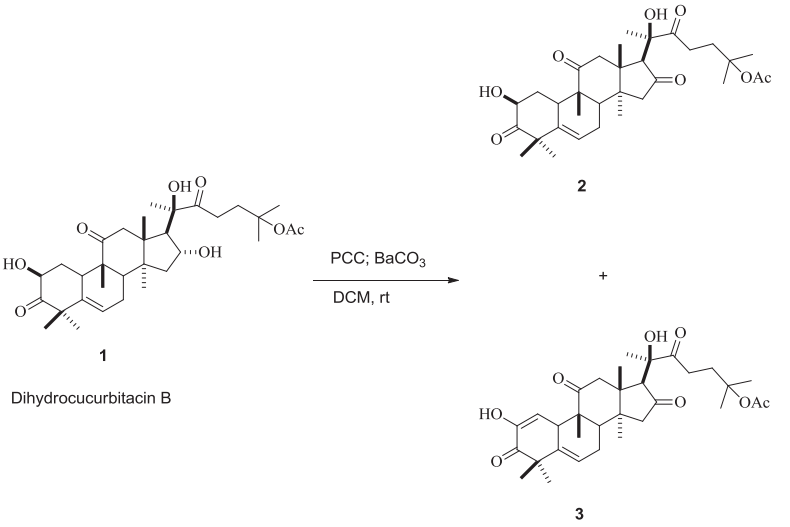


Fig. 7.1 Oxidation reaction of dihydrocucurbitacin B

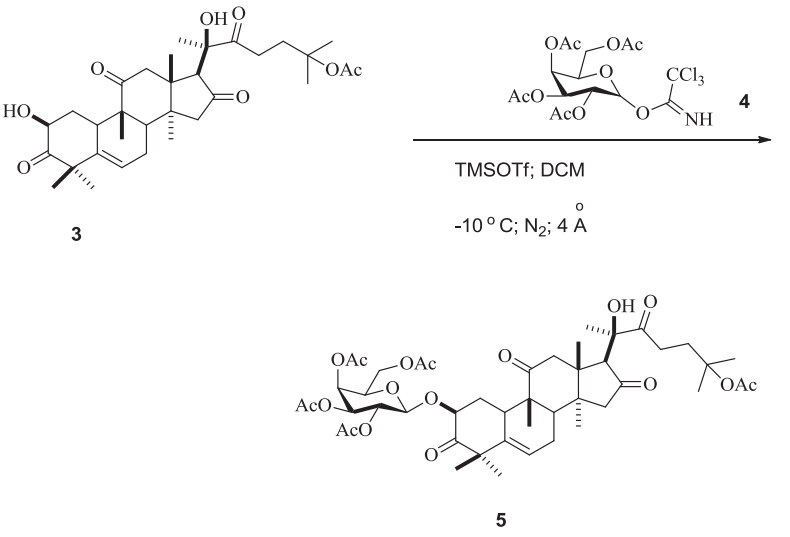


Fig. 7.2 TMSOTf stimulated O-Glycosylation reaction between **3** and **4**

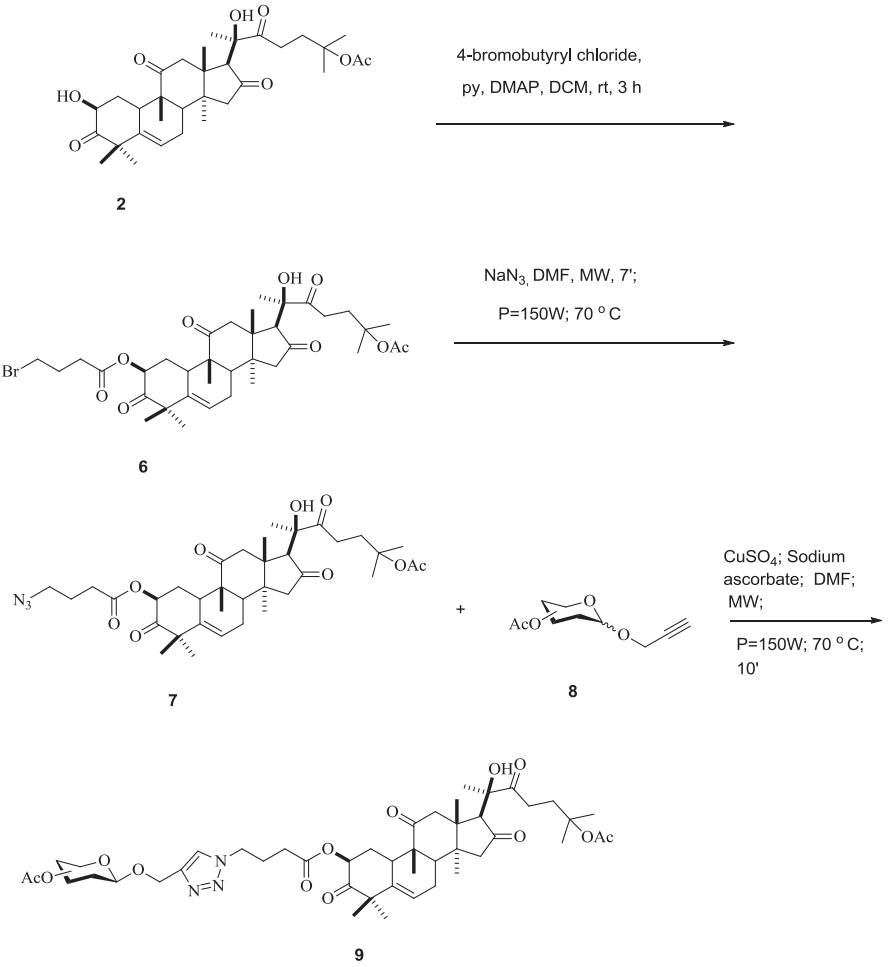


Fig. 7.3 Synthesis of triazole derivatives **9**, via Click Chemistry

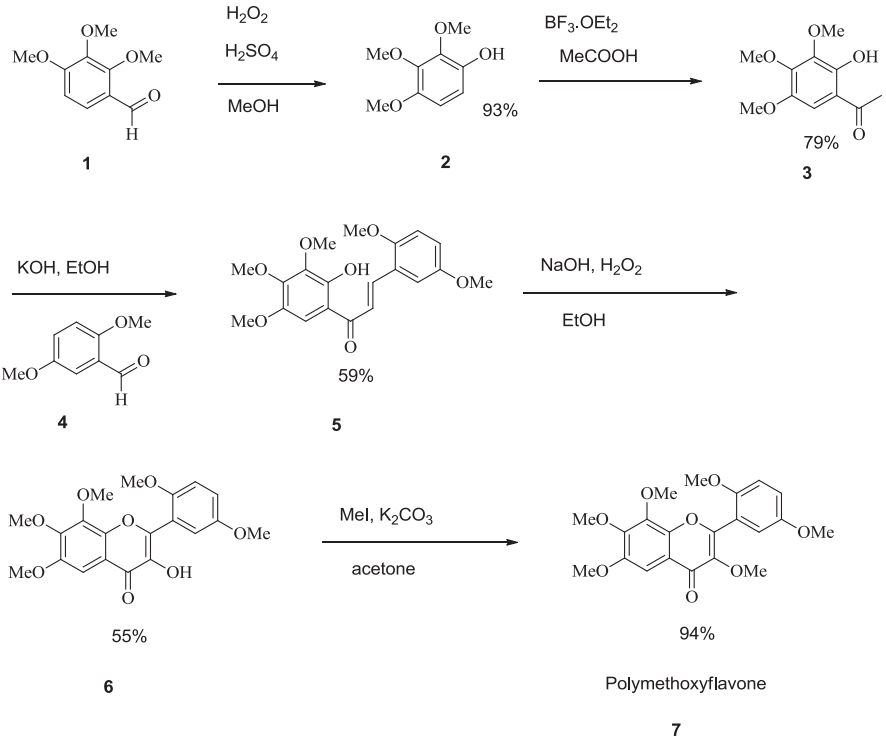
antitumor activity (Recio et al. 2004; Siqueira et al. 2009; Escandell et al. 2007; Escandell et al. 2008; Siqueira et al. 2009; Su et al. 2010).

7.6 Polymethoxyflavone

Polymethoxyflavones are being in various fruits, vegetables, nuts, tea, seeds and wine (Hollman and Katan 1999). The most common flavones such as tangeretin, nobiletin, hesperetin and naringenin are isolated tangerine peel (Citrus aurantium) (Kurowska and Manthey 2004), orange (Citrus sinensis) and grapes (Citrus paradise).

Polymethoxy flavones manifest various biological properties such as anticancer properties, anti-inflammatory, neuroprotective properties, antimalarial (Kumar et al. 2010), antibacterial (Solankee et al. 2010), decrease LDL cholesterol (Kurowska and Manthey 2004; Ballesteros et al. 1995), improved the immune system, antifungal (Nowakowska 2007; Kurowska et al. 2004; Silva et al. 2007), antidiabetics, antioxidant properties and antiproliferative effects.

1 underwent oxidation followed by acid hydrolysis to give phenol **2**. Orthoacylated compound **3** was attained by Fries rearrangement with $BF_3.OEt_2$, MeCOOH. Chalcone **5** was prepared by Claisen-Schmidt-condensation between **3** and **4.** Chalcone underwent Algar-Flynn-Oyamada oxidation to give **6** in 55%. **7** attained by methylated with MeI in acetone under reflux condition.



7.7 Anthocyanin

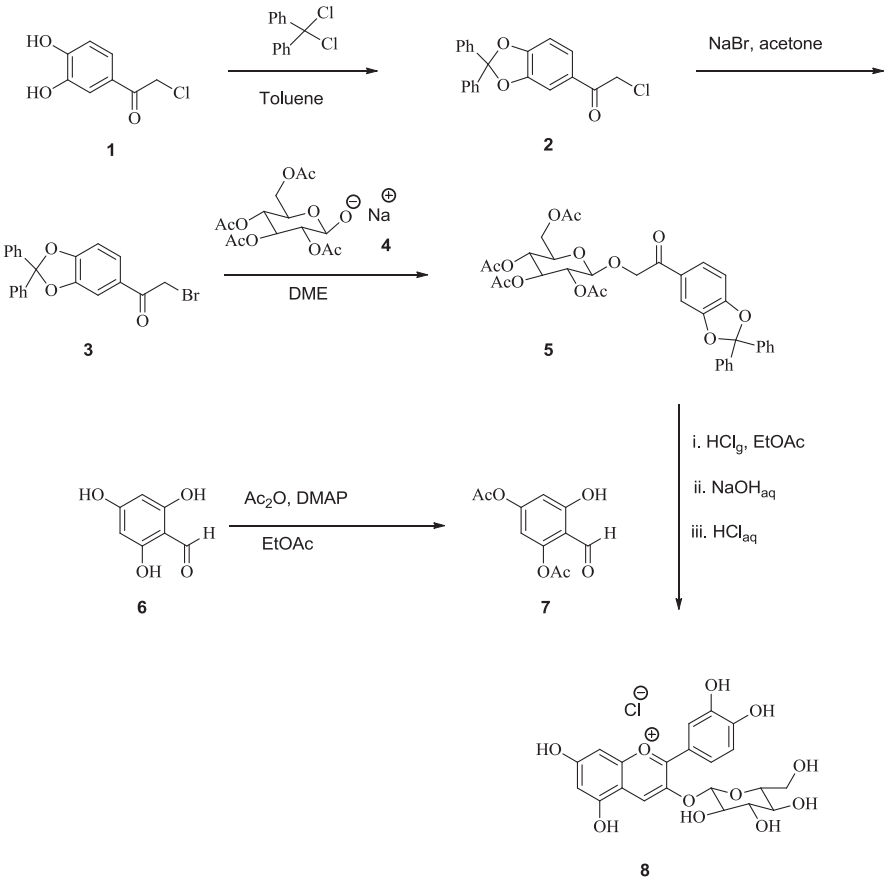
Anthocyanins are natural pigments (flavonoids) found in various fruits and vegetables. High level of anthocyanins found in fruits such as blackcurrant, bilberry, Black raspberry (Wada and Ou 2002), Queen Garnet plum, cherries (Wu et al. 2006), eggplant peel, raspberry, black rice, concord grape, muscadine grape, violet petals, red-fleshed peaches, banana, pea, fennel, potato, black soybean, chokeberry green gooseberries, blueberries, red currant, strawberries, grapes, cranberries, apples and vegetables such as red cabbage.

Fruits contain anthocyanins in the form of monosaccharides such as cyanidin, delphinidin, peonidin, pelargonidin, petunidin, malvidin with glucose, galactose and arabinose.

Anthocyanins manifest antioxidant activity (free radical scavengers). Anthocyanins protect plants from cold stress and abiotic stress (Van Breusegem and Dat 2006; Stapleton 1992) These have been used in the treatment type-II diabetes, decrease the cardiovascular problems, reduce the risk of adverse side effects of hormone replacement therapy.

Anthocyanins can be used in the dye-sensitized solar cells rather than p-n junction silicon cells because they have the ability to convert light energy into electrical energy (Cherepy et al. 1997). Anthocyanins are used as a food colorant and also used as P^H indicators because their color changes with P^H. They are red color ($P^H > 7$) in solutions, purple color ($P^H = 7$), greenish yellow ($P^H < 7$) in solutions (Michaelis et al. 1936).

I, 2 diols are protected in the form of acetals, ketals, and orthoesters to give **2**. Protected compound **2** worked (stirred) with sodium bromide and dry acetonitrile at room temperature overnight to give **3**. The resultant compound **3** underwent nucleophilic substitution followed by simultaneously reacted with an acylated compound **7** to give **8**.



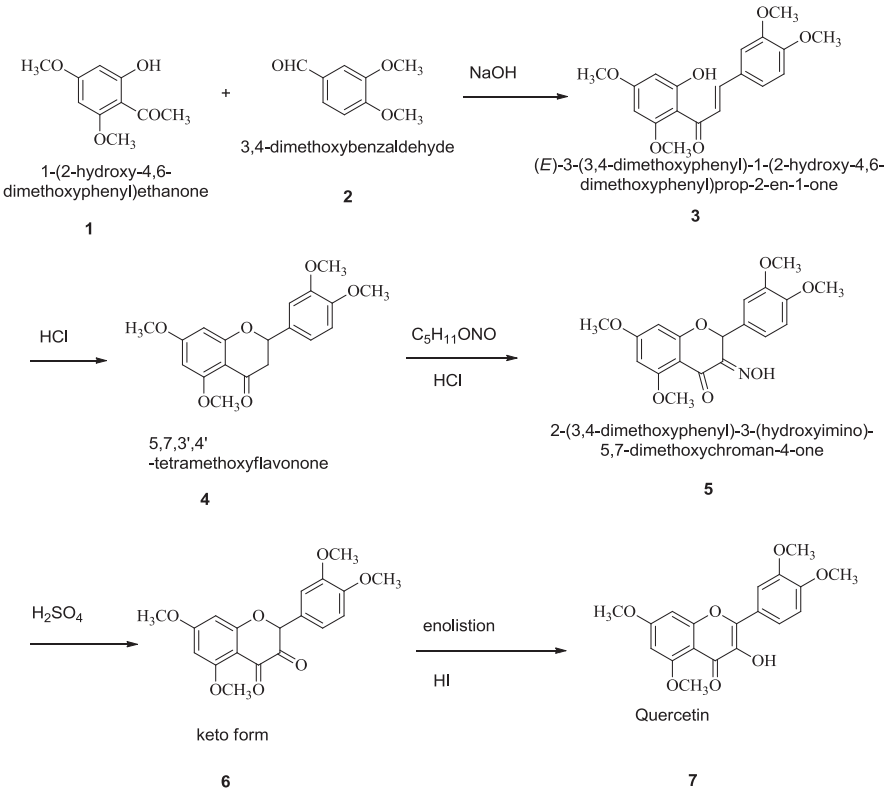
1 2 3 4 5 6 7 8

7.8 Quercetin

Quercetin is a flavonoid extensively scattered in various fruits, vegetables, leaves, and grains. Quercetin is used in beverages, food supplements. It is found in green tea, tea, black tea, bilberry, cowpeas, kale, cranberry, sweet potato, onion, broccoli, prickly pear cactus fruits, apples, sea buckthorn berry, blueberry, plum, chokeberry, watercress, buckwheat, radicchio, fennel leaves, Hungarian wax paper, dill (Justesen and Knuthsen 2001), cilantro, capers, lovage, radish leaves, dock-like sorrel and citrus.

Quercetin show infinite biological activities (Du et al. 2004; Renaud and De 1992; Scalbert et al. 2005) such as antioxidant (free radical scavenger), anti-inflammatory, anticancer (Alrawaiq and Abdullah 2014), inhibition of breast cancer (Bentz 2009; Kelsey et al. 2010; Mattarei et al. 2011), human lung cancer, nasopharyngeal carcinoma cells, prevention of Parkinson's disease, Alzheimer's disease (Aliev et al. 2008; Pryor 2000; Seifried et al. 2007).

1-(2-hydroxy-4, 6-methoxyphenyl) ethane was coupled with 3,4-dimethoxybenzaldehyde in the being of a base to give chalcone **3**. Chalcone transformed into flavone skeleton through reacted with acid. Keto form of quercetin was attained by simultaneously **4** reacted with amyl nitrite to generate analogous oxime derivative **5** followed by acid hydrolysis. Keto form of compound **6** enolized with HI to generate Quercetin.

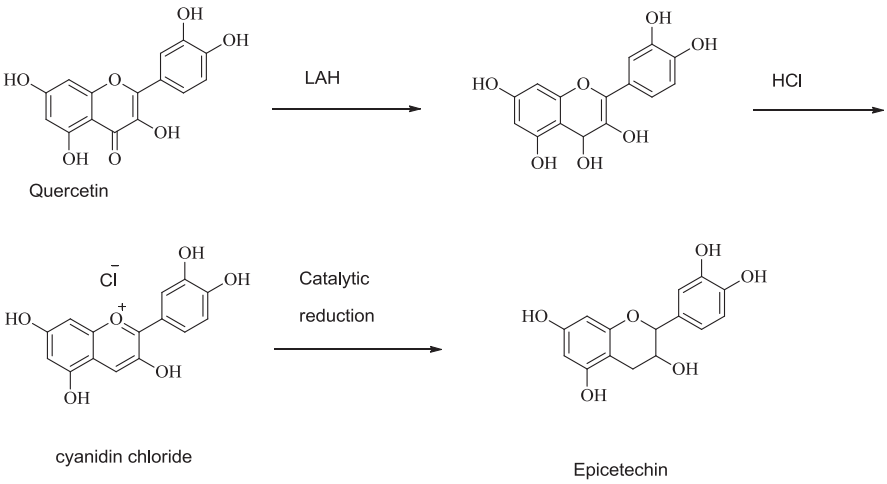


7.9 Epicatechin

Catechin and epicatechin are extensively scattered in cocoa, argan oil. Catechin being in the broad bean, prune juice tea (Chun et al. 2007).

Catechin can be applied as chemopreventive agents in various diseases like cancer, cardiovascular diseases, neurodegenerative diseases. It acts as a free radical scavenger (antioxidant property).

Quercetin was reduced with LAH, followed on reaction with HCl to give cyanidin chloride. The resultant compound underwent catalytic oxidation to generate epicatechin.



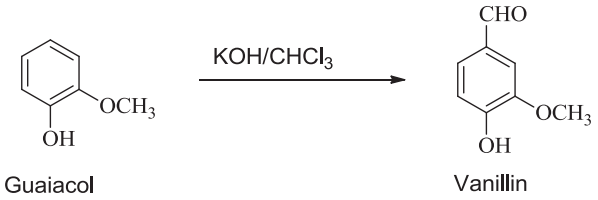
7.10 Vanillin

Vanillin is the crucial flavor and aroma compound in vanilla as alter as ras berry, lychee fruit. It is present in Leptotes bicolor is a species of orchid, vanilla beans. It is synthetically originated from lignin and guaiacol is a by-product of sulfite process for wood pulp (Hocking 1997) in the paper industry.

Vanillin has been used as a flavoring agent in the food industry (in baked goods, cookies, chocolates, and cakes), beverages, cosmetic additives, cleaning products and pharmaceuticals. Vanillin can be used in perfumery products, in pharmaceuticals to avoid the unpleasant smell or taste, and applied as strain in thin layer chromatography for visualizing purpose. It gives a range of colors for different compounds. Vanillin-HCl strain can be applied for identifying the presence of tannins in cell Vanillin has antioxidant, antimutagenic, antifungal properties versus Cryptococcus neoformans, Cryptococcal meningitis in immunocompromised patients due to the presence of hydroxyl or alkoxy group.

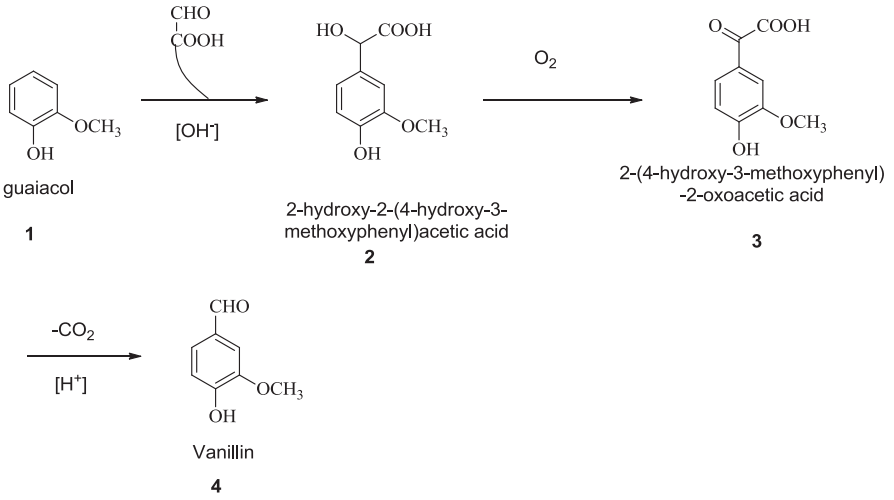
Vanillin is used as an intermediate in the production of pharmaceuticals, in the synthesis of rare chemicals (Sinha et al. 2008) Vanillin can be used to trigger the allergic reactions migraine headaches. Scolytus multistriate is applied as vectors for Dutch elm disease, vanillin can be used as a signal to find oviposition of the host tree (Meyer and Norris 1967).

Guaiacol (Reimer 1876) subjected to formylation reaction with potassium hydroxide and chloroform to give vanillin.



Guaiacol Vanillin

Guaiacol **1** underwent electrophilic aromatic substitution (Fatiadi and Schaffer 1974) when it reacted with a glyoxylic acid to give compound **2**. 2-hydroxy-2-(4-hydroxy-3-methoxyphenyl) acetic acid **2** underwent oxidative decarbonylation via 2-(4-hydroxy-3-methoxyphenyl)-2-oxoacetic acid **3** to give vanillin **4**.



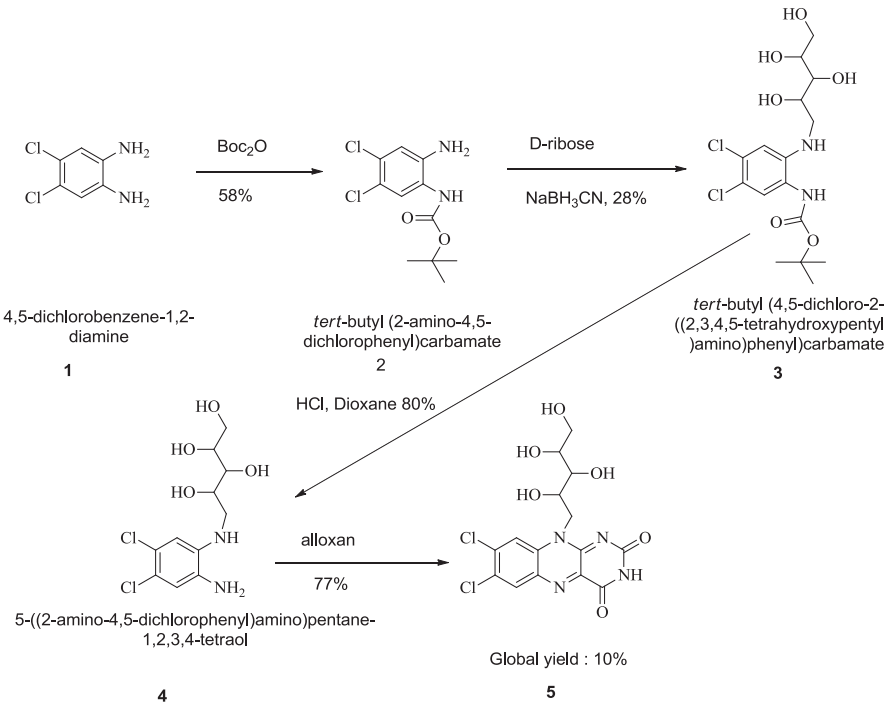
7.11 7, 8-Dichloro-Riboflavin

Riboflavin is also turms as vitamin B_2. It is being in milk, meat, green vegetables, cheese, liver, kidney, legumes, mushrooms, eggs, almonds, bread, brown rice, cereals, bovine milk. Riboflavin is vital for cellular respiration in the body.

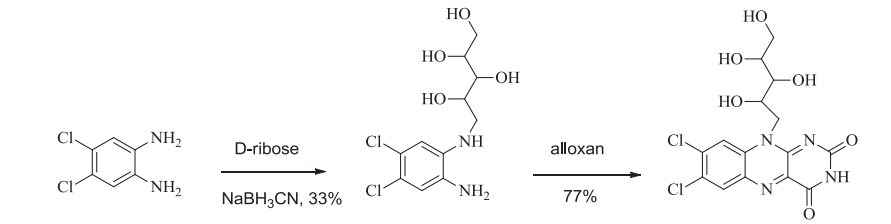
Riboflavin can be applied as the color for food. Riboflavin deficiency arises along with other vitamins deficiency (water-soluble vitamins).

Riboflavin can be applied to clean the blood (Yonemura et al. 2017) from the donor (elimination of pathogens), acts as a coenzyme. It is applied to cure corneal ectasia thinning of the cornea, then with UV light.

We should protect one of the amine groups present in the compound **1** with BoC_2O. Monoribitylation (Losi 2007) of compound **3** was attained by reacting the compound **2** with D-ribose and sodium cyanoborohydride in methanol. Product **5** obtained by simultaneous hydrolysis with acid followed by cyclisation with alloxan.



4,5-dichlorobenzene-1,2-diamine **1** reacted with D-ribose and sodium cyanoborohydride in methanol to give compound **2**. Dichloromethane was used to clean the crude product. Product yield gradually increased with increase in the concentration of D-ribose. Cyclisation of compound **3** was attained by reacting the compound **2** with alloxan (Kuhn et al. 1943) in the being of boronic acid in glacial acetic acid. Total yield is 25% whereas 10% in the above synthesis.



4,5-dichlorobenzene-1,2-diamine

1

5-((2-amino-4,5-dichlorophenyl) amino)pentane-1,2,3,4-tetraol

2

7,8-dichloro-10-(2,3,4,5-tetrahydroxypentyl)benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione

3

Global Yield : 25%

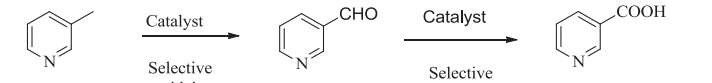
7.12 Niacin

Niacin is existence in various food sources such as seafood, spices, roasted sunflower seeds, dried apricots, ginger, tarragon, dried sweet peppers, portable mushrooms, cooked turkey, meat, pork, venison, veal, potato, grain flour like wheat rice, barley, pasta, and corn.

Because of the precursor of NAD, NADP, niacin is involved in DNA repair (Kirkland 2012). Niacin alone can decrease the coronary or cardiovascular deaths (Duggal et al. 2010).

'Pellagra' (Wendt 2015) is due to the deficiency of niacin in the diet, it is symbolized by hyperpigmentation, casal's necklace lesions on the lower neck, dementia, delirium, the thickness of skin, inflammation, amnesia, diarrhea, inflammation of mouth and tongue, death, if not dieted (Prakash et al. 2008). Psychiatric symptoms of niacin deficiency coupled with irritability, anxiety, fatigue, poor concentration, restlessness, apathy, and depression (Prakash et al. 2008). Pandemic deficiency disease is due to the deficiency of major vitamins such as niacin, thiamine, vitamin A, vitamin C, vitamin D. Adverse effect (warmth, diarrhea, redness, itching, rash) is also caused by the deficiency of niacin.

3-picoline underwent careful oxidation in the being of a catalyst to give pyridine-3- carbaldehyde. The resultant compound again oxidized under controlled catalytic conditions.

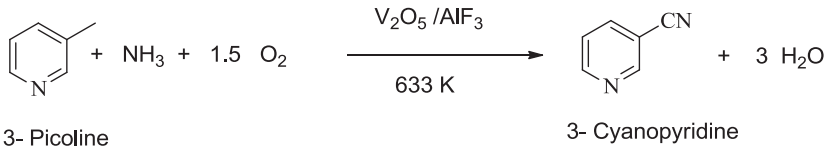


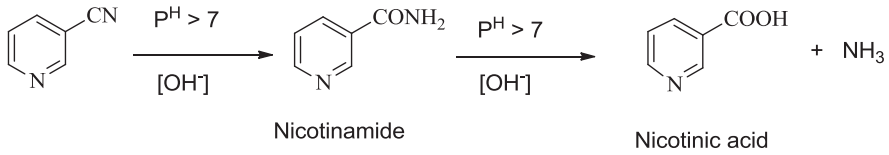
3- Picoline

Nicotinic acid

0000

3-picoline underwent ammoxidation step with ammonia and oxygen in the presence of V_2O_5/AlF_3 to generate 3- cyanopyridine. Nicotinic acid is formed as a result of enzymatic catalytic hydrolysis of 3-cyanopyridine.



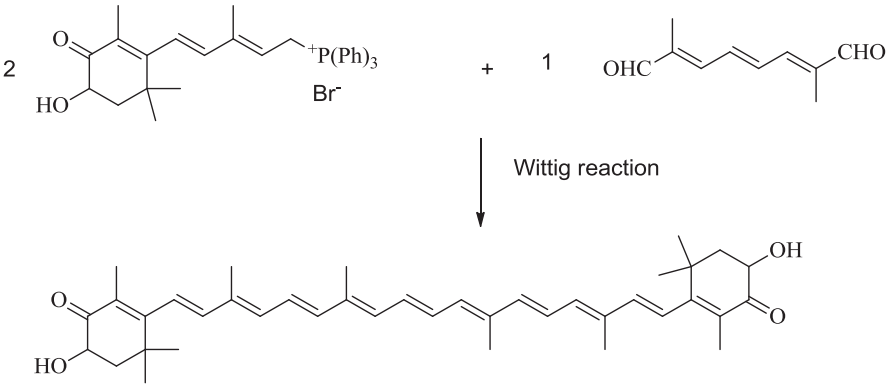


7.13 Astaxanthin

Astaxanthin is an unsaturated keto compound (Margalith 1999; Choi and Koo 2005). Astaxanthin is being in Euphausia pacifica, Euphausia superba. Haematococcus Pluvialis (Margalith 1999), Pandalus borealis, Phaffia rhodozyma, Salmonids, Plankton, Krill, Arctic shrimp, crustaceans.

Astaxanthin can use as food for crabs, shrimp, salmon, chicken for egg production. Astaxanthin shows antioxidant activity (free radical scavengers), it is fruitful for vision, skin health, inflammatory, immune, neurodegenerative (Fassett and Coombes 2009; Kidd 2011) cardiovascular diseases.

Astaxanthin can attain by the Wittig reaction. Phosphene yields reacted with a carbonyl compound to give astaxanthin.

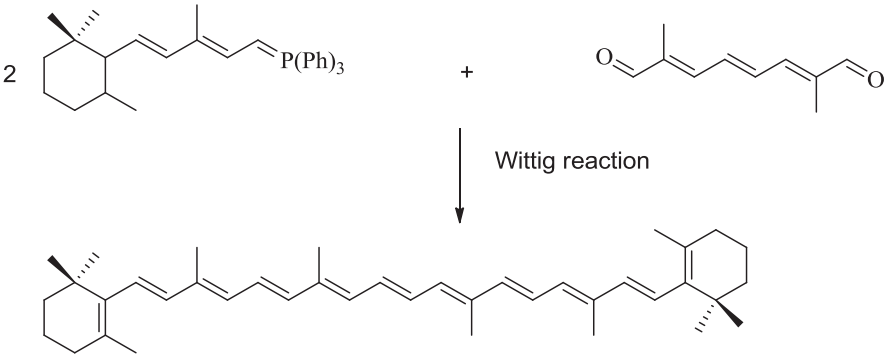


7.14 Carotene

The Orange color of carrots is due to the presence of carotene. These are unsaturated compounds existence in fruits, in some animals also. Carotenes are present in carrots, sweet potatoes, wolfberries (Ajila and Prasada 2008), cantaloupe melon, mangoes, apricots, chard, kale, turnip greens, dandelion greens, beet green, collard greens, watercress, cilantro, fresh thyme, broccoli, parsley, romaine lettuce, ivy gourd, rose hips, winter squash, pumpkin, cassava (Adewusi and Howard 1993).

Carotene is used as food additives (gives color to the food). These are important photosynthetic pigments in photosynthesis. The optical property of carbon nanotube can be increased by encapsulated the carotene into the carbon nanotubes. Chemical and thermal stability of carotene can be increased by encapsulation.

Carotenes can synthesize by Wittig reaction. Phosphene yield reacted with a carbonyl compound to produce to give carotene (Ballesteros et al. 1995).



7.15 Conclusion

Total synthesis of natural products occur from fruits and vegetables is useful in many fields like pharmaceuticals, beauty care industry etc. These shows several biological activities against to several diseases, its control and gives good health. Natural products occur in less quantity, and its demand also high for the current generation. So this book chapter scrutinizes the total synthesis of natural products synthesis in industry levels.

Acknowledgement The authors thank Vellore Institute of Technology, Vellore for providing infrastructure, library and research facility.

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Chapter 8
Phytochemical and Pharmacological Importance of Plant Secondary Metabolites in Modern Medicine

Gnanavel Velu, Veluchamy Palanichamy, and Anand Prem Rajan

Abstract The practice of treating various disease using medicinal plants are as older as an ancient civilization. Secondary metabolites present in the plants are predominantly responsible for treating various ailments. Secondary metabolites are also called as plant constituents or natural compounds which exert significant pharmacological and toxicological effects in humankind. The chemical compounds present in the plant sources are categorized as primary and secondary metabolites based on the chemical structure and biosynthetic derivation. Secondary metabolites exhibit different series of pharmacological activity which can be further classified based on their chemical structure and functional groups present in it. The most important secondary metabolites include terpenoids, phenolics, flavonoids, alkaloids and glycosides which act as an important source for single bioactive ingredients in nutraceuticals and modern medicines. Secondary metabolites have a very good antioxidant property which can be used as an effective natural antioxidants source in nutraceuticals. Most of the secondary metabolites have a broad range of their therapeutic activity and they directly interact with the receptors, cell membranes, and nucleic acids. This review evaluates the meticulous report of secondary metabolites, their classification, phytochemistry, pharmacological activity and its application in modern medicines which may pave the way for knowledge to identify and isolate the desired pharmacologically active lead compound in the drug discovery.

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_8

Keywords Alkaloids · Flavonoids · Glycosides · Phenolics · Secondary metabolites · Terpenoids

8.1 Role of Natural Products in Ancient Medicine

Ever since the primeval period, mankind has used the natural yields such as plant life, animals, microbes and aquatic organism, in medicine for the treatment of diseases. The practice of traditional medication has continued as a most reasonable and effortlessly accessible primary source of treatment for the humans since the prehistoric time in the effective management of disease and others various ailments (Hosseinzadeh et al. 2015; Manivel et al. 2009; Madhumitha et al. 2016; Roopan and Khan 2010). As per fossil documentation, the application of medicinal plants as medications accredited over 60,000 years ago (Shi et al. 2010; Fabricant and Farnsworth 2001). Sumerians have documented medication from the plant sources for the various illnesses. The primary treatment for the heart and circulatory disorders were clearly documented over 3500 years back in the papyrus. The plant-based medication accomplished by the primeval China provided a greater source of medicinal information for the treatments numerous diseases (Xiao 1988). The practice of traditional medication still exists in China. Nearly half of the total population of China indirectly depends upon the traditional medication for treating diseases predominantly in rural areas of China. There are almost five thousand different traditional medications available for the prevention and treatment of diseases throughout the China which account over one-fifth of the total pharmaceutical market of China (Li 2000). India is renowned for its greater and larger biodiversity which provided abundant valuable medicinal plants for the treatments involved in the preventive and curative medications to the mankind.

The history of Indian traditional system is as old as humankind and the extensive systematic information regarding the biochemical and pharmacological properties of important medicinal plants are clearly documented in the Rig Veda, ancient Hindu holy verses (Arash et al. 2010; Hemalatha et al. 2013; Hemalatha et al. 2015). The natural resources based medications were widely used by the ancient people around the world for the treatment and prevention of all types of diseases. These natural resources based medicines were predominantly obtained from the plant sources. The affluent diversity in plant resources supplied different kinds of natural drug materials for the curative and therapeutic effect of various kinds of infections and diseases. The other important natural resources based medicines were obtained from the marine and animal sources (Newman et al. 2000; Newman and Crag 2007). The make use of plant materials as natural medicines have resulted from the remarkable confront to earlier mankind by overcoming the difficulties in differentiating the medicinal plants from the non-edible plants (Haidan et al. 2016; Gao et al. 2007). Later the therapeutic properties of medicinal plants were classified broadly to configure definite herbal pharmacopeias which form the basis for the

indigenous remedial structure of medicinal plants based traditional medication throughout the world. The ethnobotanical study of medicinal plants provides comprehensive acquaintance of plant nature and inimitability of selective pharmacological characteristics of medicinal plant materials (Farnsworth 1990).

In current scenario, the applications of traditional knowledge on plant materials for the treatment and prevention of disease have received wide attention among the plant-based research community which resulted in the augmented exceptional attention among the drug discovery researchers towards the plant-based drug discovery research in phytochemistry and natural products (Newman and Crag 2007; Madhumitha and Saral 2009; Anupama et al. 2014). This increased wave of attention towards the plant-based natural product chemistry research in modern drug discovery accredited to numerous factors. The most important factor includes, the unchallenged therapeutic requirements, for many a dreadful diseases like Cancer, HIV, Alzheimer's diseases etc., there are no current available treatments to cure or prevent these diseases. Hence, the modern drug discoveries have turned their interest towards the plant-based drug discovery as an alternative source for the drug discovery to meet the unchallenged therapeutic requirements for this modern world. The other important factor includes the availability of wide variety of natural secondary metabolites in plant sources which act as potent curative medicines. The secondary metabolites thus obtained from these medicinal plant sources have a significant broad sequence of the inimitable chemical structure with different therapeutic activity. The novel bioactive lead compound derived from the secondary metabolites of medicinal plant sources can be easily developed as a bioactive probe into drug moiety because of the rapid advancement of modern science with wide range of modern analytical development technique availability to identify and isolate the particular desired bioactive phytocompound from the plant materials to exert the targeted pharmacological activity with minimal toxic effect (Clark 1996).

The importance of the role of traditional medicine based drug discovery was accepted by World Health Organization (WHO 1993) and documented the guiding principle for the strategic methods employed in the standardization and drug discovery development process from the medicinal plant materials (WHO 1993). The secondary metabolites rich medicinal plant materials are widely available throughout the terrestrial and aquatic world which acts as an alternative source for the novel drug discovery in the modern medicines. The large number phytocompounds were predominantly listed in the modern pharmacopoeias due to the accessibility of high efficient screening methods available to isolate the bioactive phytocompound from the medicinal plant materials and the advancement of combinatorial chemistry to modify the isolated novel bioactive phytocompound into semi-synthetic compound with improved structural activity relationship for the better efficacy of drug moiety for its targeted therapeutic pharmacological action with no or less toxic effects. So far, the very small proportional of plant materials have been systematically studied by the researchers from the total number of 500,000 existing plant species around the world. The further extensive research on the medicinal plant materials will pave the way for more isolation of novel bioactive phytocompounds that will

bring more future drug discoveries in the modern medicines (Ngo et al. 2013; Fowsiya and Madhumitha 2017).

8.2 Primary and Secondary Metabolites

Based on the biological requirements in plants, the naturally occurring phytochemicals can be broadly classified into primary metabolites and secondary metabolites. The primary metabolism process in the plants produces primary metabolites like carbohydrates, fats, amino acids and nucleic acids (Weinberg 1971). These primary metabolites are primarily important for the indispensable biological functions in plants which include the growth, development, and reproduction of plant cell (Fraenkel 1959). The secondary metabolism process in plants produces secondary metabolites which are generally important for the protective and self-defence function in plant cell caused by the ecological imbalance or harmful infections (Stamp 2003). These secondary metabolites are very specific and found great in numbers among the several groups of plants. The diverse combination of plant secondary metabolites produces unique chemical feature among the classes of plant species which plays an important tool for the taxonomical researchers to classify the taxonomy of plant species (Thrane 2001). The primary metabolites are generally produced from the plants species for the regular biological function of plant cells whereas the secondary metabolites are usually synthesized in different chemical configurations from primary metabolites by regulating the primary pathway metabolism of plant species based on the secondary metabolites requirements appropriate to the ecological influenced genetic code adaptability in plant cells (Waterman 1992).

8.3 Biosynthesis of Secondary Metabolites

The primary metabolites and secondary metabolites responsible for the biological functions of plant cells are chiefly produced through the biosynthetic pathways process (Nicolaou et al. 2011; Herbert 1989). The biosynthetic pathway process is an energy necessity process which is supplied through the energy released during citric acid cycle and glycolysis of carbohydrates (Kabera et al. 2014). Adenosine Triphosphate (ATP) is the chief energy molecule produced from the catabolic process of the primary compound and by the oxidation of amino acids, fats, and glucose. Coenzyme A is an important catalyst responsible for the hydrogen donor or hydrogen acceptor in anabolism and catabolism reaction (Michal and Schomburg 2013). Pentose pathway is responsible for the biosynthesis of glycosides and the Shikimic acid pathway is responsible for biosynthesis of phenols as mentioned in the Fig. 8.1 Similarly, Mevalonic acid and acetate malonate pathways are responsible for steroids and alkaloids biosynthesis (Dewick 2002). The acetyl coenzyme A

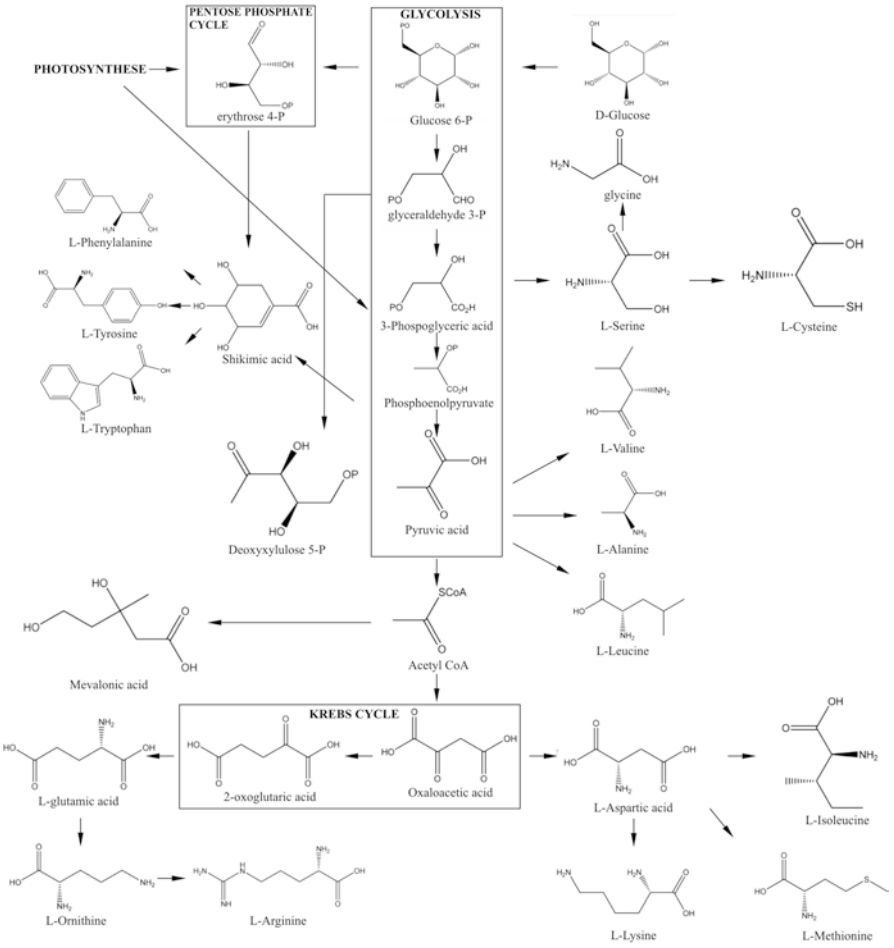

Fig. 8.1 Schematic design of plant secondary metabolites biosynthesis (Giweli et al. 2013)

is the chief important unit for the biosynthesis of secondary metabolites through the various pathways like Shikimic acid pathway, Pentose pathway, Acetate malonate pathway and Mevalonic acid pathway (Giweli et al. 2013).

8.4 Classification of Secondary Metabolites

The plant-derived phytochemicals or secondary metabolites can be further classified into different types of natural compounds based on their definite chemical structure in nature. The most important classification of secondary metabolites includes alkaloids, glycosides, flavonoids, terpenoids, phenolics, and saponins.

8.4.1 Alkaloids

Alkaloids are the most important prevalent natural group of secondary metabolites among the other chemically classified secondary metabolites. Alkaloids are made up of protein molecules containing an amino acid structural moiety which essentially holds nitrogen atom with it which are commonly occur by replacing the hydrogen atom of peptide structure with different radicals along with oxygen. Most of the alkaloid compounds are made up of carbon, oxygen, and hydrogen along with nitrogen but on the odd occurrence, further elements like phosphorus, chlorine, sulfur and bromine may also exist in the alkaloid structures (Nicolaou et al. 2011). The chemical properties of most of the alkaloids are basic in nature which turns red litmus paper into the blue. The primary, secondary and tertiary amines responsible for the basic nature present in the alkaloid groups are classified depending upon the number of nitrogen atom present in the alkaloid group. The extent of basic nature of alkaloids depends upon the variation in the chemical configuration of the molecular structure and the presence of a number of functional groups at a different location in the alkaloid molecule (Sarker and Nahar 2007). Most of the alkaloids are in solid forms but fewer alkaloids containing carbon, hydrogen, and oxygen are in liquid form also. The alkaloids produce their respective crystalline salt when treated with acids without formation of water molecule (Firn 2010). Most of the alkaloids are easily soluble in alcohol but few are sparsely soluble in water and the salt forms of alkaloids are not soluble in water. The solutions prepared from the alkaloid chemical substances are usually bitter in taste. The nitrogen atom present in the alkaloids act as a defence driving force which protects the plant cells against the bacteria, virus or microorganism infection and also from the damages caused by the other factors like herbivores attacks, ecological disturbances, and climatic modifications. These nitrogenous based alkaloids have very good pharmacological activity which can be effectively used in the modern medicinal research for the identification and drug discovery of potent drug moiety. Alkaloids are predominantly occupied in the roots and seeds of medicinal plants and found to have significant pharmacology activities like stimulation of central nervous system and anaesthesia effect (Madziga et al. 2010). Above 12,000 natural alkaloids are recognized throughout the 20% of the existing plant species around the world and most of the alkaloid compounds usually have the suffix *–line* at its end. The alkaloids from the plant origin have important medicinal application. Morphine is used as analgesics, berberine as antibiotics, vinblastine as anticancer and atropine as anti-cholinergic as discussed in the Table 8.1. The further significant alkaloids include codeine, coniine, cytisine, nicotine, quinine, solanine, strychnine and tomatine as mentioned in the Fig. 8.2. The preliminary screenings methods available for the identification of alkaloids includes the formation of cream precipitate with Meyer's reagent (Solution of Potassiomercuric iodide), formation of reddish-brown precipitate with Wagner's reagent (Potassium iodide with Iodine), formation of yellow precipitate with Hager's reagent (Picric acid solution), formation of reddish-brown or orange precipitate

Table 8.1 List of Important Alkaloids with blrPharmacological Activity

S. No.	Alkaloids	Plant Sources	Pharmacological Effect	References
1.	Atropine	Atropa belladonna, Darura stramonium, Mandragora officinarum	Muscarnic antagonist, anti-cholinergic, anti-myopia effects	McBrien et al. 2013; Gu et al. 2011
2.	Berberine	Argemone Mexicana, Xanthorhiza simplicissima, Phellodendron amurense,	Anti-inflammatory, antibacterial, antiviral, anti-cancer.	Kim et al. 2010; Zha et al. 2010; Zhang et al. 2010; Agyapong et al. 2013
3.	Codeine	Papaver somniferum	Analgesic, antitussive, anti-depressant	Simera et al. 2010; Smith et al. 2006; Vree et al. 2000; Mody et al. 1976
4.	Coniine	Conium macularum, Sarracenia flave	Neurotoxin	Panter et al. 2013; Hajek et al. 2013
5.	Cytisine	Cytisus laborinum	Acetylcholine agonist	West et al. 2011; Porreca et al. 1983
6.	Morphine	Papaver somniferum, poppy derivatives	Act on myenteric plexus, reduces shortness of breath	Rozov et al. 2014; Takita et al. 2000; Clarke et al. 1998
7.	Nicotine	Solanaceae plant family	Stimulant, insecticide, anti-inflammatory	Gandhi 2013; Melton 2006; Rhoades and Cates 1976; Achan et al. 2011
8.	Quinine	Cinchona succirubra, Cinchona calisya, Cinchona ledgeriana	Antimalarial, antipyretic, anti-inflammatory.	Adnyana 2013; El-Tawil et al. 2010; Mwita et al. 2012; Fewell and Roddick 1993
9.	Solanine	Solanum tuberosum, Solanum lycopersiam, Solanum igrum	Antifungal, sedative, anti-inflammatory, anticonvulsant	Lu et al. 2010; Kenny et al. 2013; Mohsenikia et al. 2013; Bonjoch and Sole 2000
10.	Strychnine	Loganiaceae plant family, Strychnos nux-vomica,	Anticonvulsant, pesticide	Buckingham and Nemesis 2010; Jensen et al. 2006; Umukoro et al. 2013; Dopham et al., 2014
11.	Thebaine	Papaver bracteatum	Analgesic	Fist et al. 2000; Jeong et al. 1990; Lee et al. 2011; Heal and Taylor Robinson 2010
12.	Tomatine	Solanum lycopersicum	Immune effects, anticancer, antifungal.	Morrow et al. 2004; Tomsik et al. 2013; Gao and Hu 2010.

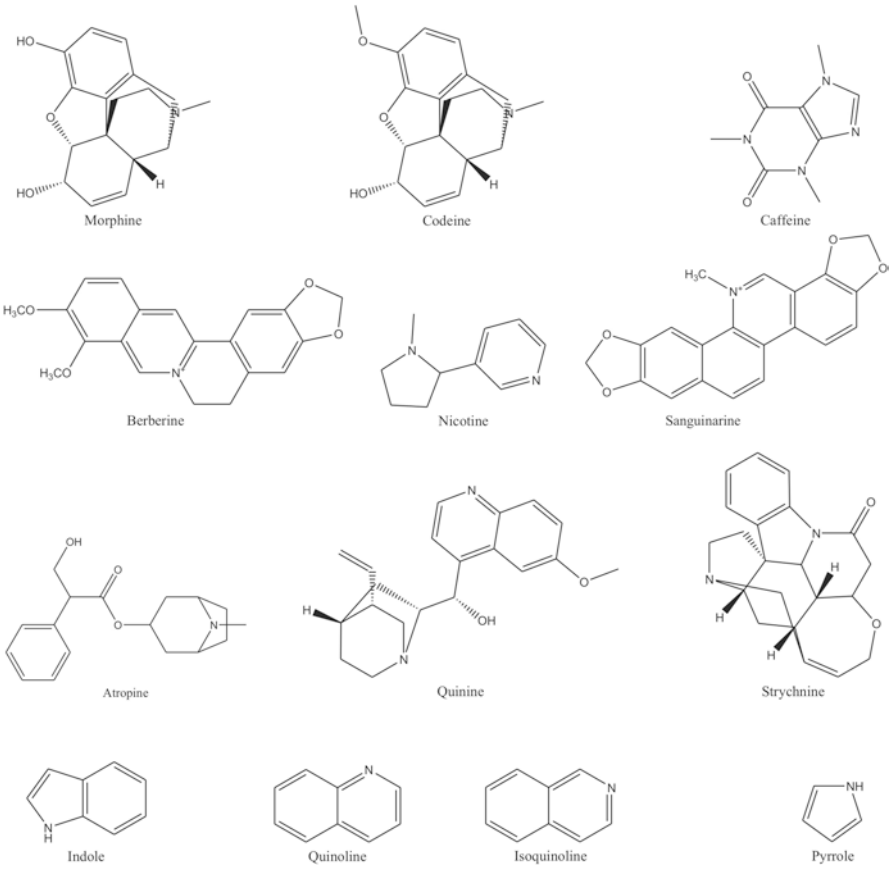

Fig. 8.2 Examples of alkaloid compounds

with Dragendorff's reagent and the formation of pink colour in Murexide test for the identification of caffeine alkaloids.

8.4.2 Glycosides

Glycosides compounds are the plant secondary metabolites compounds regularly formed by the bond attachment of condensed form of sugar moiety or glycone mostly polysaccharides with the other non-sugar moiety or aglycone (Kar 2007; Firn 2010). Glycosides are colorless alkaloid compounds with crystalline structure generally composed of carbon, hydrogen, oxygen, sulfur, and nitrogen. Most of the glycosides accumulated in the plants are inactive compounds. The enzyme hydrolysis on the inactive glycosides resulted in the formation of active glycosides which are potentially useful for the defense mechanism of plant cells (Polt 1995).

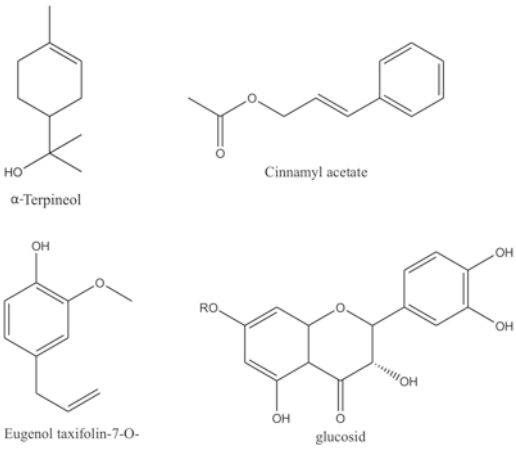

Fig. 8.3 Examples of glycoside compounds

Glycosides are also known as prodrug because the pharmacological activity of glycosides becomes active only when the aglycone part of glycosides separates from glycone part of glycosides during hydrolysis. The various hetero structure attachments of phenols, terpenes, and steroids in aglycone part of glycosides makes diverse in the classification of glycosides. The attachment of glycone and aglycone in glycosides are made up of the unique glycosidic bond which amalgamates multiple monosaccharides into different oligosaccharides and polysaccharides (Levy and Tang 1995; Newman et al. 2008). Most of the glycosides are extremely bitter in taste due to the presence of lactones group which acts on the gustatory nerves results in the excess secretion of salivary so as to increase the appetite and digestion. Cardiac glycosides are chiefly responsible for the heart disorders whereas chalcone glycosides are mainly used for anticancer activity. The important glycoside responsible for the pharmacological action includes α-Terpineol, cinnamyl acetate, eugenol taxifolin-7-O-, β-glucoside as mentioned in the Fig. 8.3. Similarly, anthracene glycosides are chiefly responsible for the management of skin infection whereas the cyanogenic glycosides are largely utilized in pharmaceutical industry as a flavour agent. The preliminary phytochemical analysis for the identification of glycosides includes addition of plant sample with hydrochloric acid and water for O-glycosides and with ferric chloride and hydrochloric acid for C-glycosides to produce violet or pink colour indicates the presence of both O-glycosides and C-glycosides.

8.4.3 Flavonoids

Flavonoids are the significant groups of polyphenols among plant secondary metabolites which are abundantly found in wide range of plants. Flavonoids are usually water-soluble compounds and are classified into flavones, flavonols and

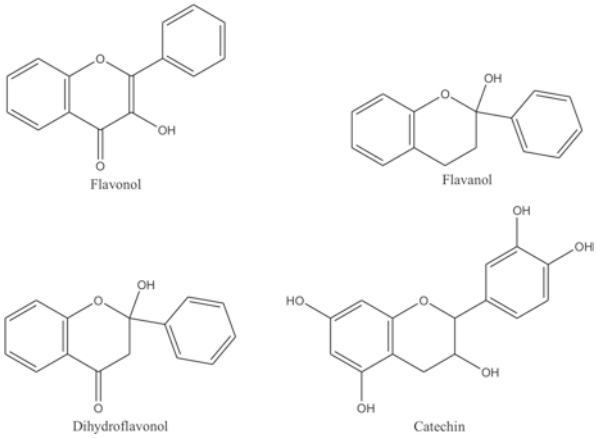

Fig. 8.4 Examples of flavonoid compounds

anthocyanins. Flavonoids play a major role in plant pollination by producing the beautiful colour over the petals of flower by filtering the ultraviolet rays which attracts the insect for pollination. Flavonoids are also act as a chemical messenger in plants which regulates the physiological function of plant cell through the inhibition of plant cell cycle. The major important flavonoids includes quercetin, quercitrin and kaempferol which are widely distributed almost over 70% of the total plant species and other class of flavonoids compounds includes flavans, flavonols, flavones, dihydroxyflavone, catechin and anthocyanidins as mentioned in the Fig. 8.4. The majority of the flavonoids have very good antioxidant property (Karr 2007) and other important therapeutic application includes anticancer, antiallergic and antiviral (Guardia et al. 2001; Hertog et al. 1995).

8.4.4 Phenols

Phenolic compounds are the most important plant secondary metabolites widely available in the all kinds of fruits, vegetables, tea leaves and other green plants. Phenolic compounds have significant pharmacology properties like antioxidant, anticancer, antimicrobial, antiseptic and anti-inflammatory activity (Pengelly 2004). Phenolic compounds are active against the oxidative stress and in the management of other diseases (Pengelly 2004). Phenolic compounds can be classified on the following basis: (1) based on the number of hydroxyl functional group, the phenolic compounds are classified as 1-, 2-, 3- and polyatomic phenols. Polyphenols are the phenolic compounds containing above one hydroxyl functional group in aromatic compounds; (2) based on the chemical configuration, the phenolic compounds are classified as mono-, di-, tri-, oligo and polyphenols; (3) based on the substitution in skeleton of carbon, the number of available carbon atom and aromatic rings in the side chain. Phenolic compounds with one aromatic ring, phenolic compounds with two aromatic rings, polymers and quinones are the four major classes of phenolic compounds. Phenolic chemical compounds with one aromatic ring are large

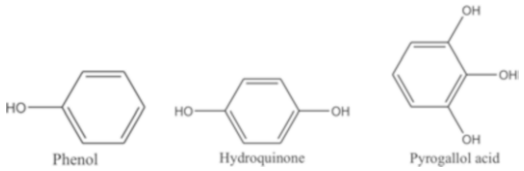

Fig. 8.5 Examples of C_6 phenolic compounds

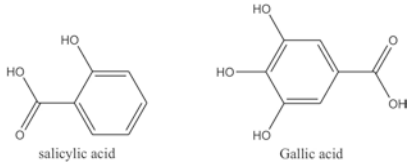

Fig. 8.6 Examples of C_6-C_1 phenolic compounds

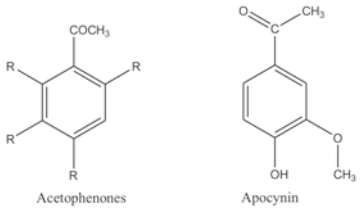

Fig. 8.7 Examples of C_6-C_2 phenolic compounds

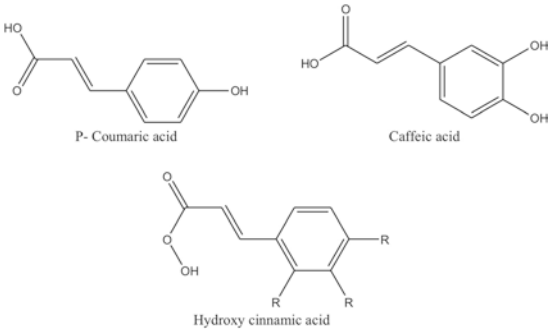

Fig. 8.8 Examples of C_6-C_3 phenolic compounds

number of phenolic compounds includes simple phenolic compounds C_6 as mentioned in the Fig. 8.5, phenolic compounds with attachment of one carbon atom C_6-C_1 as mentioned in the Fig. 8.6, phenolic compounds with two carbon atom as mentioned in the Fig. 8.7 and the phenolic compounds with attachment of three carbon atom C_6-C_2 as mentioned in the Fig. 8.8. A phenolic chemical compound with two aromatic rings includes two aromatic ring phenolic compounds linked by single carbon atom as in the case of xanthones and benzoquinones C_6-C_1-C_6 as mentioned in the Fig. 8.9. More than 8000 polyphenolic compounds are documented until now from the different plant sources and based on the characteristic features; these polyphenols are further subclassified into different groups as flavonoids along with non-flavonoids (Somasegaran and Hoben 1994).

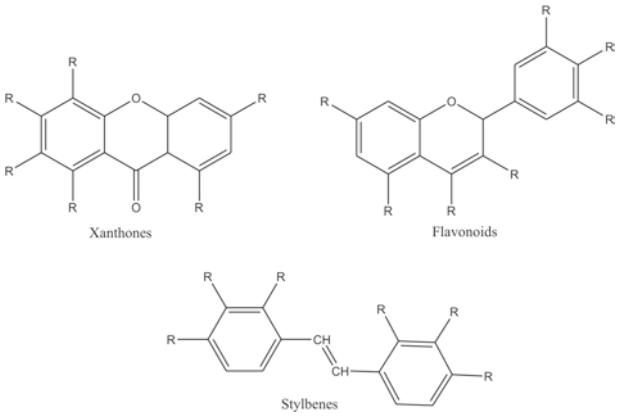

Fig. 8.9 Examples of phenolic compounds with two aromatic rings

Table 8.2 Different types of terpenoids (Kogan et al. 2006)

S. No.	Types of terpenoids	Number of carbon atoms	Number of Isoprene units	Example
1.	Hemiterpene	5	1	Isoprene, prenol
2.	Monoterpenes	10	2	Limonene, pinene
3.	Sesquiterpenes	15	3	Abscisic acid
4.	Diterpenes	20	4	Forskolin
5.	Triterpenes	30	6	Squalen, lanosterol
6.	Tetraterpenes	40	8	Carotenoids, lycopen
7.	Polyterpenes	Several	Several	Vitamin E, ubuquinones

8.4.5 Terpenoids

Terpenoids are the most important and widely available plant secondary metabolites among the major types of plant species throughout the world. Chemically, terpenoids are unsaturated hydrocarbon in liquid form mostly available in resins and essential oils (Firn 2010). Terpenoids are usually made up of isoprene units which are produced from acetate through the Mevalonic acid pathway. The different number of isoprene units unite together to form the large terpenoids which makes diverse in the structural classification of terpenoids as mentioned in the Table 8.2. All the terpenoids have a general formula $(C_5H_8)_n$ which is categorized as monoterpenoids, diterpenoids, triterpenoids and sesquiterpenoids depending on the number of carbon atom present in it. The important monoterpenoids includes menthol, eugenol and camphor reportedly having very good antioxidant property and the resins and taxol are the groups of diterpenoids having significant anticancer activity. The triterpenoids includes cardiac glycosides, ursolic acid and steroids have cytotoxic, sedative and

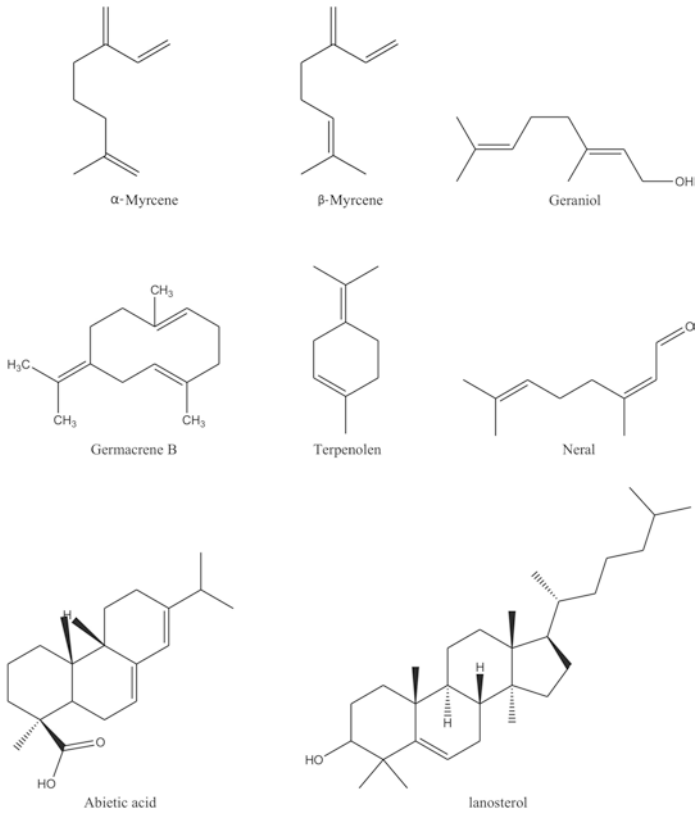

Fig. 8.10 Examples of terpenoid compounds

anti-inflammatory activity as mentioned in the Fig. 8.10. Monoterpenes are important sesquiterpenoids which forms the larger components in essential oil (Martinez et al. 2008). The recent developments in the phytochemical research on terpenoids have proved the significant pharmacological activities of terpenoids molecule for the treatment and management of disease.

8.4.6 Saponins

Saponins are the class of plant secondary metabolites which generates foam on shaking with water. The development of foam is due to the formation of colloidal solution when aglycone parts of the saponins join together with water. Sapogenin is the product formed when the aglycone of saponins hydrolysis with water. The two main types of sapogenin includes triterpenoidal and steroidal. Most of the saponins occur in glycoside form having triterpene or steroidal structure at its aglycone

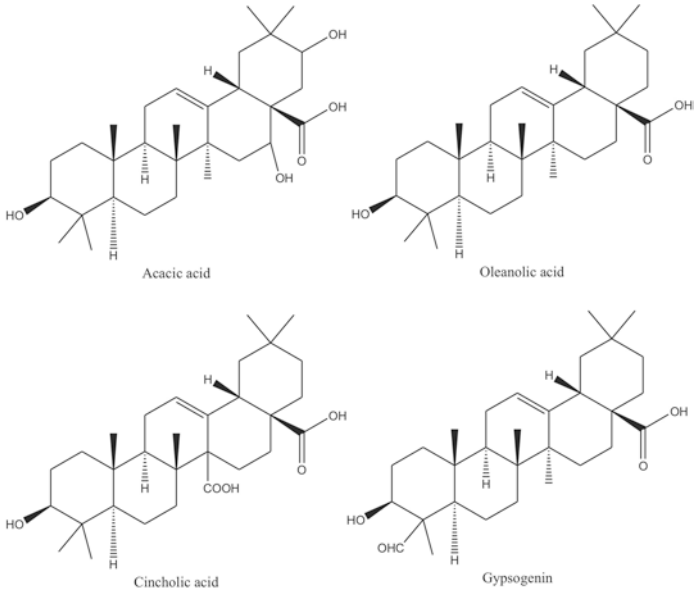

Fig. 8.11 Examples of saponin compounds

component. Diosgenin, cincholic acid, gypsogenin, oleanolic acid, acetic acid and hecogenin are the important types of saponins responsible for the hypolipidemia and anticancer activity as mentioned in the Fig. 8.11. The lowering of surface tension by the reason of grouping lipophilic sugar moiety resulted in the formation of foam over the surface (Guclu- Ustundag and Mazza 2007). Saponins are usually found in all types of plant throughout the world. Saponins have diverse physiochemical properties which makes its application significant in the preparation of pharmaceutical products. Saponins are widely used for the emulsification, altering sweetness, foam formation, increasing solubility and as surfactants by increasing critical micelle concentration.

8.5 Mechanism of Action of Plant Secondary Metabolites

There are different types of mechanism of action postulated for the plant secondary metabolites. Secondary metabolites may possibly act upon the disease-causing organism by altering the essential metabolic process and signal transduction pathway or by altering the gene expressions (Manson 2003; Surh 2003; Kris-Etherton et al. 2002).

8.5.1 Antioxidants

Antioxidants are responsible for protecting the healthy cell against the oxidative stress causing factors. These factors include the free radicals like superoxide, hydroxyl radicals and singlet oxygen which produce reactive oxygen species responsible for the destruction of the nucleus of the healthy cell (Mattson and Cheng 2006). Antioxidants obtained from the secondary metabolites play a major role in the prevention of diseases like a neurodegenerative disease, cerebral ischemia, and atherosclerosis (Uddin et al. 2008; Jayasri et al. 2009). The free radicals which are not chemically scavenged exist in metastable forms which are chemically unstable in nature and they tend to obtain the electron from the surrounding nuclear level like lipid membranes, mitochondria, DNA and another protein molecule in the cell nucleus to get the stable form leads to the disruption of cellular pathways and ultimately causing the cell death (Uddin et al. 2008). The cellular pathway disruption caused by the reactive oxygen species results in the various diseases like Alzheimer's disease, diabetes, asthma, gastrointestinal infections and meningitis (Chen et al. 2006; Uddin et al. 2008). The fewer amount of antioxidants are naturally synthesized in the human body by its own defense mechanism which is helpful in scavenging the free radicals produced in the human body (Sen 1995). The secondary metabolites obtained from the plant sources like β-carotene, vitamin E, ascorbic acid and other phytochemicals help to scavenge the remaining untreated free radicals (Diplock et al. 1998; Madsen and Bertelsen 1995; Rice-Evans et al. 1997).

8.5.2 Anti-ulcer

Plant secondary metabolites are effective against the infection of *Helicobacter pyroli* and it also inhibits the *in-vitro* anti-ulcer activity in addition to urease activity. The efficiency of anti-ulcer activity against the gastric ulcer can be improved by lowering the pH of secondary metabolites in a liquid state. It helps to reduce the Na+/K+ ATPase activity in the gastrointestinal tract and transfer of alanine in the small intestine (Jakhetia et al., 2010).

8.5.3 Anti-inflammatory

The secondary metabolites obtained from *Cinnamomum osmopholeum* have significant anti-inflammatory activity and it is also effective against the liver cell lines (HepG2). The mechanism of action of anti-inflammatory activity involves lessening the formation of inflammation causing factors like nitric oxide through the stimulation of macrophages by plant secondary metabolites like lipopolysaccharides (Jakhetia et al., 2010).

8.5.4 Anti-diabetes

The plant secondary metabolites like cinnamaldehyde play an important role in the treatment of diabetes. The phytocompound cinnamaldehyde significantly reduces the triglycerides and cholesterol level (James 2012). It also effectively increases the high-density lipoproteins cholesterol level in the streptozotocin-induced rat models. The other important plant secondary metabolites like cinnamaldehyde and polyphenols from cinnamon extracts and other plant extracts are effective in the treatment of diabetes and are widely used as oral antidiabetic and hypolipidemic agents (Jakhetia et al., 2010).

8.5.5 Anti-microbial Activity

The most important application of plant secondary metabolites is to protect its own from the fungi, insects, bacteria and other disease-causing organisms. These secondary metabolites are also effective in the prevention or treatment of various diseases in the humankind. It helps to protect the mankind from disease-causing organisms and found important application in the modern medicine (Nascimento et al. 2000; Park et al. 2001). The secondary metabolites like phenolic acids are primarily responsible for the treatment of microbial infection near the bladder, teeth and urinary tract infection. Most of the plant secondary metabolites have significant bacteriostatic and bactericidal activities. The gas phase of clove oil and cinnamon oil are used to inhibit the bacterial and fungal growth on mid-level moisture food materials with a customized atmospheric gas level of oxygen and carbon dioxide (Jakhetia et al., 2010).

8.5.6 Neuroprotective Activity

The various pharmacologically active secondary metabolites obtained from the different plant sources have significant neuroprotective activity against the neurodegenerative disorders. The neurodegenerative disorder can be described as an irreversible gradual loss of neuronal cell which is essential to perform the normal brain functions and the continuous loss of neuronal cell ultimately leads to brain death. The neurodegenerative disorder includes Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic lateral sclerosis (Marcello et al. 2010). The secondary metabolites obtained from plant sources like Physostigmine, Galantamine, Huperzine A, Resveratrol, and Curcumin plays an important role in the treatment of Alzheimer's disease as mentioned in the Fig. 8.12. Physostigmine is a bioactive alkaloid compound obtained from *Physostigma venensosum* act as an important drug for the short-term treatment of Alzheimer's disease (McCaleb 1990; Sitaram et al. 1978; Julian and Pikl, 1935). The mechanism of action involved in the treatment of

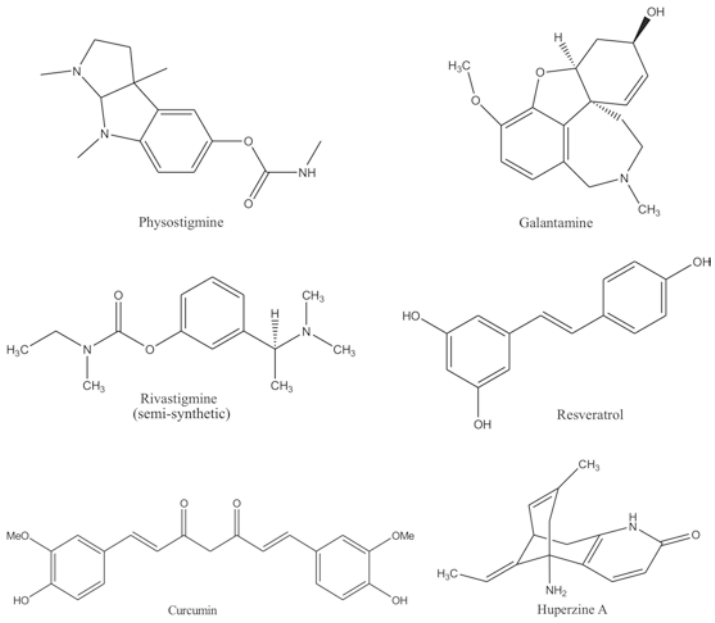

Fig. 8.12 Examples of neuroprotective compounds

Alzheimer's disease includes the reversible inhibition of cholinesterase enzymes which eventually prevents the breakdown of brain enzyme acetylcholine and also helps to restore the declined acetylcholine for the treatments involved in memory disorder (Kamal et al. 2000; Howes and Houghton 2009). Galantamine is an alkaloid type of bioactive compound obtained from *Galanthus nivalis* which is widely used in the treatment of moderate stage of Alzheimer's disease (Bores et al. 1996; Howes and Houghton 2009). Huperzine A is a bioactive alkaloid compound isolated from the *Huperzia serrata* which is widely used for the treatment of moderate stage of Alzheimer's disease by a selective inhibitor of acetylcholinesterase enzyme (Skolnick 1997; Houghton et al. 2006). Resveratrol is a bioactive polyphenol compound obtained from *Vitis vinifera* which is also widely used for the treatment of Alzheimer's disease (Marambaud et al. 2005). Curcumin is also another type of bioactive compound obtained from *Curcuma longa* is widely used for the treatment of mild stage of Alzheimer's disease by inhibiting an enzyme called cholinesterase which prevents the breakdown of brain enzymes acetylcholine (Goutam 2011; Ng et al. 2006).

8.6 Conclusion

The secondary metabolites obtained from different plant materials have diverse pharmacological activity against various diseases. This review helps to understand the classification of bioactive secondary metabolites in a systematic approach based

on the chemical nature which provides detailed information related to physiochemical and therapeutic properties of individual phytocompounds. The bioactive compounds isolated from the different plants have significant therapeutic activity in the management and treatment of many dreadful diseases with minimal side effects. Nowadays, researchers have focused more attention towards the plant-based drug discovery for the management of many diseases which are immensely challenging to the modern healthcare system. The drugs derived from the plant secondary metabolites have a wide choice of application in the management or treatment of various diseases by modifying the structural activity relationship of isolated phytocompound parent nucleus to the desired pharmacological activity with no or very minimal side effects. With more positive conclusions from the phytocompounds based drug research in recent times, the medicinal plant's based drug discovery have become a promising scope in the field of natural products drug research for the further isolation and drug development of newer bioactive phytocompounds from the secondary metabolites of medicinal plants.

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Chapter 9
Anti-Diabetic Effect of Fruits on Different Animal Model System

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Abstract Fruits have important bioactive and dietary components ingredients of our everyday life that plays a major role to cure diseases. Inadequate intake of antioxidant and improved reactive oxygen species is associated with diabetes mellitus. Many of the components were proved to be succeeding to treat several chronic diseases like cancer, cardiovascular, obesity, and diabetes. Fruits which have listed here have dietary fiber which reduces diabetes and cardiac and other diseases also. Fruits like *Momordica cymbalaria, Pongamia pinnata, Diospyros peregrina, Xylopia aethiopica, Ficus deltoidea, Prunus avium, Trapa natans, Terminalia pallida* and *Punica granatum.* The fruit aqueous extract of *M*omordica cymbalaria exposed significant antihyperlipidemic as well as antihyperglycemic administered orally at 0.5 g/kg for six weeks by alloxan-induced diabetic rats. In Pongamia pinnata fruits, compounds called pongamal and karanjin was administered using streptozotocin diabetic rats which decreases the blood glucose level at the dosage of 50 mg/kg for 11.7 and 12.8%, 20.7% at 100 mg/kg individually post oral administration of six hours. An edible fruit of *Diospyros peregrina* streptozotocin-nicotinamide induced type 2 diabetes was achieved in aqueous extract decreases the blood glucose level at the dosage of 50 and 100 mg/kg body weight for twenty-eight days. *Xylopia aethiopica* acetone fraction of ethanol extract was investigated for type 2 diabetes. Streptozotocin was induced by single intraperitoneal injection and animals were treated orally at the dosage of 150 or 300 mg/kg body weight for 4 weeks reduces blood glucose level. *Ficus deltoidea* fruit was carried out with crude aqueous extract and fractions were estimated for sugars, phenol, protein and

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_9

flavonoid content. Antidiabetic activity was carried out in water fraction using alpha-glucosidase assay reveals the highest amount of protein 73.33 ± 4.99 μg/mg. Ethanol extract (200 mg/kg) of *Prunus avium* fruit was administered orally by single intraperitoneal injection using alloxan induced (120 mg/kg) rats which decrease blood glucose level. *Trapa natans* fruit peel of methanol extract was evaluated for antidiabetic activity by streptozotocin (100 and 200 mg/ kg body weight) induced a diabetic rat which decreases blood glucose level. *Terminalia pallida* ethanol fruit extract was given intraperitoneal injection using alloxan (150 mg/kg body weight) monohydrate induced for diabetic rats model. Blood glucose levels were significant to at the dosage of 0.5 g/kg body weight. The aqueous ethanol extract of *Punica granatum* juice sugar for diabetic rats for ten days. Significantly reduces the blood sugar level, total peroxide level, and peritoneal macrophages. The aim of this book chapter reveals that fruit is considered as one of the important dietary ingredients. It has a vital significant role to control and to treat type 1 and type 2 diabetes mellitus. Henceforth, encouraging adherence of mentioned fruits was considerable significance to public health.

Keywords Anti-diabetic activity · *Terminalia pallida* · *Punica grantum* · Extraction · Medicinal plants

9.1 Introduction

Diabetes mellitus is one of the metabolic disorders, which is continues to elevate the numbers and its importance due to increased obesity and decreased physical activity because of lifestyle changes (Wang et al. 2013). Diabetes is a chronic disease which is characterized by impairment in insulin; consequences are hyperglycemia, glycosuria, and hyperlipidemia (Anupama et al. 2014; Fowsiya and Madhumitha 2017; Madhumitha and Saral 2009; Tripathi and Verma 2014). This chronic hyperglycemia, hyperlipidemia, and insulinemia would lead to many complications in different organs such as cardiomyopathy, neuropathy, nephropathy, and retinopathy (King 2012). The diabetes is a non-communicable global disease; the prevalence is increasing day by day all over the world, but occurrence rate of diabetes varies from country to country (Asif 2011). Danaei et al., suggests that the occurrence of diabetes in the worldwide during 2008 is calculated as in women (9.2%) and in men (9.8%) around it is 347 million people suffered from diabetes (Danaei et al. 2011). It is calculated that people suffer from diabetes worldwide would increase to double in subsequently 25 years (Asif 2011). In between 2010 t0 2030 it is expected to increase 69% in developing countries and 20% in developed countries (Shaw et al. 2010). Diabetes is a complicated condition to treat and valuable to manage it (Wild et al. 2004).

The nature of food and quantity of food we are consuming is the major determinant of human health. Diet plays an important role in many metabolic disorders inclusive diabetes. The supervision of diabetes is either through diet alone or diet

along with hypoglycemic drug or diet with insulin. Based on the individual diet would play an important role and includes the criteria such as age, weight, occupation etc. The reality of dietary guidelines would maintain nutritional value, glycemic control and impediment of diabetes. This maintenance of diet with the healthy lifestyle (low energy diet and increased physical activity) would prevent from chronic damage to eyes, kidney, heart, nerves and other major complications. The research elucidating the nutritional composition is vigorously increasing in the field of diabetes (Foltran et al. 2010). The bioactive components present in the foods would act as a complementary or alternative medicine for the management of diabetes (O'Connell 2001). One of the major components of our daily diet is fruits which contain various bioactive nutraceuticals, which elevates strength in the body and fight against various illnesses. Different ethnic and geographically explicit fruit is utilized for the treatment of various metabolic disorders including diabetes (Babio et al. 2009). Earliest Chinese medicine includes local fruits has more antioxidant properties which are known to protect against various metabolic disorders including diabetes (Ceylan-Isik et al. 2008; Hemalatha et al. 2013; Hemalatha et al. 2015; Liu et al. 2008). In India and Bangladesh, ayurvedic medicine plays an important role in the prevention of diabetes against various disorders with the help of locally identified fruits (Mirunalini and Krishnaveni 2010). The fruits in India such as *Garcinia indica* also have effective against various metabolic disorders including diabetes (Baliga et al. 2011). There is various fundamental research is conducted in different countries in which all these fruits are growing mainly in developing countries would be utilized for treatment of diabetes. There are different types of diabetes; most common among them are type 1 and type 2 diabetes.

9.2 Type 1 Diabetes

Type 1 diabetes or insulin-dependent diabetes or childhood-onset diabetes is not as much as type 2 diabetes (Asif 2011). Approximately 10% of the people with diabetes have type 1 diabetes. It is a multifactorial autoimmune disease leads to depletion of insulin-generating beta cells in the islets of Langerhans which is mediated by T-cell and macrophage (Mathis et al. 2001). Type 1 diabetes is mostly determined in children and young adults in which the patients are found to have less production of endogenous insulin (King 2012). Insulin acts as a regulatory hormone for both glucose and the lipid metabolism. These metabolisms are improper in the individuals who have type 1 diabetes (Cefalu 2006). The major consequence of type 1 diabetes is diabetic ketoacidosis, which would be critical without management. The complications of chronic vascular type 1 diabetes would affect various organs and tissues further lead to decrease in a lifetime (Chatzigeorgiou et al. 2009). Insulin therapy is found to be commencement for the type 1 diabetes. The aggravation of glucose deregulation is associated with a pre-diabetic state which leads to the development of type 1 diabetes (Cefalu 2006).

The type 1 diabetes is connected with other common autoimmune diseases such as thyroid disease, Addison disease, and celiac disease. There are other syndromes associated with these diseases are autoimmune polyendocrine syndrome I and II, immuno-dysregulation-polyendocrinopathy-X-linked syndrome (Barker 2006). There is no ambiguity that susceptibility of type 1diabetes is dependent on MHC genes and 50% of MHC genes would donate to diseases. The genes which are used to determine the disease at the genetic level are HLA-DR and HLA-DQ, the consequence of this individual allele would be modified by the haplotypes through which it is agreed (Fernando et al. 2008). The genetic influence and environmental factors also play an important role in the progression of this disease, for instant 27% of identical twins are with this type 1 diabetes (Hyttinen et al. 2003). The occurrence of type 1 diabetes would range up to 100 fold depends on the countries, in UK 15–20/100000 and doubling of the children who are under the age of 5 by 2020 in Europe would be estimated. The treatment for it is a subcutaneous injection of insulin regularly and monitoring glucose level in the blood habitually to manage hypoglycemic condition (Patterson et al. 2009). The other treatment would include diet i.e., diabetic meal plan and regular exercise i.e., physical exercise also suggested (Asif 2011).

9.3 Type 2 Diabetes

The most general type of diabetes is type 2 diabetes or non - insulin dependent diabetes (NIDD), which is a complex metabolic disorder and it is influenced by both genetic and environmental factors. Both are interacting with each other and involved in concern of disease (Chatzigeorgiou et al. 2009). Though it is genetic, risk factors are determined by calculating body mass index (Lehtovirta et al. 2010). It is highly found in middle age adults, with elevated levels of obesity (Pinhas-Hamiel and Zeitler 2005). 90–95% of the people are type 2 diabetes among diabetes patients. Type 2 diabetes is associated with insulin resistance, hyperinsulinemia, hyperglycemia and beta cell dysfunction (either with a beta cell mass increase or without) (Srinivasan et al. 2005). Weight reduction and exercise would result in insulin sensitivity (Solomon et al. 2008). The decreased level of circulating insulin would lead to the condition called insulin resistance and it is the more regular feature of type 2 diabetic patients. Insulin resistance acts as an important role in developing type 2 diabetic condition (Reaven 1988). This insulin resistance would elevate insulin secretion in a beta cell with compensatory hyperinsulinemia (Taylor 1999). The dysfunction of a beta cell would lead to impairment in glucose homeostasis, insulin resistance and glucose intolerance further cause's type 2 diabetes (Lebovitz and Banerji 2004). Clinical studies in humans are limited due to the ethical issues, thus we are using various different rodent model system in animals with comparable results to the human (Lin and Sun 2010). Based on the size, generation interval would be small, economic consideration and depends on the availability the rodent model acts as an appropriate model system to study type 2 diabetic conditions (Srinivasan and Ramarao 2007).

9.4 Gestational Diabetes

Gestational diabetes or impaired glucose tolerance is the third type of diabetes, which occurs only in pregnant women (Association 2004). This affects approximately 14% or 135,000 of pregnancy women/year in U.S (Kim et al. 2002). The symptoms and management are imitating of type 2 diabetic condition. This condition will fade away after childbirth (Kim et al. 2002).

9.5 Five stages of Progression of Diabetes – Changes in Beta Cell Function, Phenotype, and Function

The 5 stages have been described for progression of diabetes based on the changes in beta cell dysfunction, phenotype, and function.

Stage 1: (Normal or compensated)

In stage 1, secretion of insulin would be elevated to maintain the normal glycemic condition in order to control the insulin resistance or impaired beta cell mass which is the outcome of obesity, physical idleness, and genetic predisposition. In this stage, it would sustain the differentiated function with proper glucose-stimulated insulin secretion (GSIS) (Weir and Bonner-Weir 2004).

Stage 2: (Adaptation)

In this stage 2, elevation of glucose level approximately 5.0 to 6.5 mmol/l i.e., 89-116 mg/dl. This stage is stable for adaptation of beta cell with decreased beta cell mass and impairment of function through decreased GSIS and beta cell dedifferentiation process. This would lead to pre-type1 diabetic condition (Weir and Bonner-Weir 2004).

Stage 3: (Early decompensation)

In this stage 3, it is an unstable stage, in which glucose level would be elevated comparatively quickly to stage 4. This stage acts as a borderline stage and shows transient beta cell mass (Weir and Bonner-Weir 2004).

Stage 4: (Decompensation)

Stage 4 represents as a very stable decompensation with added rigorous beta cell dedifferentiation. This stage shows type 2 diabetes and early type 1 diabetes with reduced beta cell mass(Weir and Bonner-Weir 2004).

Stage 5: (Severe decompensation)

Stage 5 involves in stable beta cell mass reduction with the succession of diabetic ketosis.

The treatment with proper diet, exercise, and oral agents would remission type 2 diabetic people from stage 4 to stage 2. In case of type 1 diabetic also it would return form stage 4 to stage 2 (Weir and Bonner-Weir 2004).

9.6 Rodent Studies in Diabetic Research: A rodent model of type 1 diabetes

9.6.1 Induction of Type 1 Diabetes Using Chemicals

In this chemically induced type 1 diabetes, there is more destruction of pancreatic beta cells and causes loss of endogenous insulin production which leads to increased glycemic condition and loss of weight. This chemically induced diabetes is the cheapest model in inducing type 1 diabetes in rodents as well as higher animals (Dufrane et al. 2006). The chemicals have to be given 5 to 7 days before starting the experiment to make certain secure hyperglycemia condition. Since these chemicals such as streptozotocin and alloxan are similar to the structure of glucose (Bansal et al. 1980), it lowers the blood glucose level through non-beta cell action with proper treatment (Jederström et al. 2005). One of the disadvantages of using this chemically induced diabetes would cause toxicity in other organs such as liver, testis, kidney, brain, lung with P450 isozymes changes (Lee et al. 2010).

(a) **Streptozotocin**

Streptozotocin (STZ) is a chemical which occurs in nature, which is used to produce a model system for type 1 and type 2 diabetes with multiple low dosages are utilized in animal rodent models. Metastatic cancer of islets of Langerhans would be treated by using STZ. The derivative of monofunctional nitrosourea is streptozotocin i.e., 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D –glucopyranose is isolated from *Streptomycetes achromogenes.* It can be administrated either through i.p or i.v., Glut-2 transporter helps to enter the chemical into the pancreatic beta cells and causes DNA alkylation (Szkudelski 2001). STZ would trigger PARP and nitric oxide release which causes depletion of NAD^+ decreased ATP level further cause's cell death through necrosis and inhibition of insulin production finally causes insulin depended on diabetic condition (Patel et al. 2006; Sandler and Swenne 1983).

(i) Streptozotocin (High dosage)

One time high dosage of streptozotocin to mice ranges from 100 to 200 mg/kg depends on the strain of the mice. In case of rats, it ranges form 35-65 mg/kg. This is sufficient to disturb beta cell and cause hyperglycemic condition (Srinivasan and Ramarao 2007). STZ treatment would regenerate the pancreatic islets. STZ with high dosage is utilized in transplantation models in which islets (Deeds et al. 2011) or putative stem cells (Song et al. 2010) would be transplanted beneath the kidney capsule. Lymphopenia is one of the cause for a high dosage of STZ which would elevate T-regulatory cells and it is involving in interference of studies i.e., immunotolerance studies (Muller et al. 2011).

(ii) Streptozotocin (Low dosage)

Multiple dosages of STZ at a low dosage ranging from 20 to 40 mg/kg dependent on the strain for 5 days would cause dysfunction in a beta cell further mediates insulitis either in mice or rats (Like and Rossini 1976; Lukic et al. 1998; Wang and Gleichmann 1998). There is an impediment of insulin secretion level correlates with the number and function of beta islet cells (Bonnevie-Nielsen et al. 1981). The first immune cells to infiltrate the islets is macrophage and depends on the production of cytokine, the diabetes condition would progress (Lukic et al. 1998).

(b) **Alloxan**

Alloxan is an important chemical induced model using in diabetogenic research to induce type 1 diabetes. This is a derivative of urea which destroys beta cells and pancreatic islets by causing necrotic cell death (Etuk 2010). Alloxan, the chemical name is 2,4,5,6-tetraoxypyrimidine; 5,6-deoxy uracil would be quickly uptake by beta cells and there by involves in free radical formation (Nerup et al. 1994). Dialuric acid is formed by reducing alloxan and which re-oxidized to form alloxan by forming a redox cycle to produce superoxide radicals. These radicals would undergo dismutation to yield hydrogen peroxide formation and further causes DNA fragmentation in a beta cell through hydroxyl free radicals (Szkudelski 2001). The reducing agent such as glutathione (GSH), sulfhydryl (-SH) group bound to the protein, cysteine, and ascorbate are involving in reduction process in pancreatic beta cells (Lenzen and Munday 1991; ZHANG et al. 1992). This –SH group is oxidized, particularly glucokinase (Im Walde et al. 2002) and impairs calcium homeostasis at intercellular level by alloxan through beta cell damage (Kim et al. 1994). The dosage is fixed depends on the strain and administration route with i.p and sc but for high dosage through i.v. 3 times are mandatory. In mice the dosage varies from 50 to 200 mg/kg, in case of rat the dosage ranges from 40 to 200 mg/kg and incase of rabbit the dosages vary from 100 mg/kg for induction of chronic diabetes (Szkudelski 2001; Wang et al. 2010). If the alloxan is not given in proper dosage it would cause toxicity in different organs especially in the kidney (Szkudelski 2001).

9.6.2 Spontaneous Autoimmune Diabetes Type 1

For studying spontaneous autoimmune disease, there are 5 different animal models are utilized. They are NOD (non-obese diabetogenic) mice, BB (Bio breeding) rats, LEW.1AR1/– idmm rats, LETL rats, and KDP rats.

(a) **NOD mice**

The NOD mice are the majority preferential mice for researchers to study autoimmune diabetes. It is developed in Shionogi Research Laboratories in Osaka (1974), in Japan by inbreeding the strain Jcl: ICR (Hanafusa et al. 1994). The impairment in insulin is started within 4 to 5 weeks in NOD mice. During development of diabetic stage, the infiltration of pancreatic islets is mainly

through the lymphocytes like $CD4^+$ and $CD8^+$, though the cells like B and NK cells are present (Yoon and Jun 2001). The beta cell impairment would disturb more than 90% of the pancreatic insulin in 10 to 14 weeks, though it would take 30 weeks to develop completely. The occurrence of diabetes found to be more in female (60 to 90%) in most of the colonies and 10 to 30% in male in most colonies (Hanafusa et al. 1994; Pozzilli et al. 1993). The class 2 MHC is similar in its structure both NOD mice and human. This similar gene would be functional to determine the pathways in type 1 diabetes (Todd and Wicker 2001; Wicker et al. 2005). These mice should protect from pathogen-free condition to continue diabetic condition (Atkinson and Leiter 1999). This model is utilized in obstruction studies where we aimed to protect or impede from autoimmune diseases.

(b) **BB rats**

Outbred Wistar rats are used to isolate BB rats. In 1974, spontaneous autoimmune diabetes was found in Canadian colonies. Form this, two founder colonies were produced which leads to isolation of two sub-strains such as BBDP/Wor (one inbred) and BBdp (one outbred). BB rats generally progress diabetes just subsequent to the puberty and have similarity in both male and female rats. This rat needs 8 to 16 weeks of age to develop the diabetic condition. During pancreatic beta cell dysfunction, there is a rigorous reduction of $CD4^+$ T cells and deficiency of $CD8^+$ T cells, although there is an appearance of T, B, NK cells and macrophages (Mordes et al. 2004). This model would be useful for genetic studies and diabetic neuropathy (Zhang et al. 2007).

(c) **LEW.1AR1/−idmm rats**

The colonies of congenic lewis rats with the distinct haplotypes of MHC (LEW.1AR1) are utilized for the spontaneous autoimmune diabetic condition. This causes beta cell dysfunction within 8 to 9 weeks of age but the frequency of diabetes would be 20% but further inbreeding would increase into 60% for both the genders (Jörns et al. 2005; Lenzen et al. 2001). Before forming hyperglycemic condition, this model would involve in an infiltration of islets. Form this we can establish different stages of infiltration mediated by immune cells. This model is utilized for elucidating the mechanism for developing diabetes (Jörns et al. 2005).

(d) **LETL rats and KDP rats**

The Long Evans Tokushima Lean (LETL) model is the earliest rat model revealed for the spontaneous autoimmune diabetes condition. It mediates beta cell disruption and causes the diabetic rate to 20%. The sub-strain of LETL rats is KDP rats which produce a good progression of this disease at the rate of 70–80% in both the gender without lymphophenic (Kawano et al. 1991; KOMEDA et al. 1998). This model is similar to the human disease but still, only some studies are done in this model particularly genetic study (Yokoi et al. 2007).

9.7 Type 1 Diabetes-Induced Genetically

(a) **AKITA mice**

From C57BL/6NSlc mouse, AKITA mouse was isolated in Akita, Japan with a spontaneous gene mutation in *insulin 2* which would protect from the accurate dispensation of proinsulin. This would be the reason for forming misfolded proteins further it causes ER stress. For 3 to 4 weeks of age, this would cause insulin dependent diabetes (loss of beta cell) condition with the symptoms such as hypoglycemia, polyuria, hypoinsulinemia and polydipsia (Mathews et al. 2002). This model is utilized for the studies like a macrovascular disease, neuropathy, ER stress and transplantation studies (Chen et al. 2011; Drel et al. 2011; Zhou et al. 2011).

9.8 Virally Induced (Coxsackie B Virus, Encephalomyocarditis Virus, Kilham Rat Virus and LCMV under Insulin Promoter)

The virus would have been also mediating condition of type 1 diabetes. There are different animal models have been identified using a virus to disturb the beta cell function. This disruption is either through beta cell dysfunction directly or commencement of autoimmune reaction adjacent to the beta cell (Jun and Yoon 2004). Some of the virus which is used to mediate type 1 diabetic condition is Coxsackie B virus (Jaidane et al. 2009), Encephalomyocarditis virus (Shimada and Maruyama 2004) and Kilham rat virus (Ellerman et al. 1996).

Apart from this virus, there is a development of transgenic virus model such as lymphocytic choriomeningitis virus (LCMV) in which insulin promoter has to be expressed, it acts as a viral antigen (Von Herrath et al. 1997). This doesn't cause beta cell destruction immediately but when we administrated LCMV it would cross-reacts with the antigen which is articulated in the pancreatic beta cells. This would lead to disruption of pancreatic beta cells. This model is little problematical because the conclusion depends on the replication of virus and infection timing (Von Herrath et al. 1997). Human type 1 diabetes is associated with the virus but it still needs to elucidate that to what scope this virus is mediating type 1 diabetic condition (Richardson et al. 2009).

9.9 Rodent Model of Type 2 Diabetes

Type 2 diabetes is distinguished by resistance in insulin secretion and incapability of pancreatic beta cells to adequately compensate it. In this animal model of type 2 diabetes, either it would cause insulin resistance or disruption of beta cell in the

pancreas. Since obesity and type 2 diabetes are interlinked with each other. Most of the diabetic model system is obese in nature. The outcome of obese animal would be obviously happening genetic mutation or manipulation. Some of the obese models for diabetes development are given below.

9.9.1 Obese Models (Monogenic)

The monogenic mutation in a human would be due to the obesity, monogenic obesity models are frequently used in type 2 diabetic research. This model is characterized by the impairment in leptin signaling. Leptin would mediate satiety condition if there is a deficient in of leptin function in monogenic obese models leads to hyperphagia and consequent obesity. Depend on the mutation on leptin gene or its receptor, these monogenic obese models are determined such as $Lep^{ob/ob}$ mouse (Leptin gene mutation) and $Lepr^{db/db}$, Zucker Diabetic Fatty rat (Leptin receptor mutation) (Gault et al. 2011; Yoshida et al. 2010).

(a) **Lep $^{ob/ob}$ mice**

The ob/ob (Lep $^{ob/ob}$) genotype mice have appeared with the strain C57BL/6 (Zhang et al. 1994). This model is distinguished by elevated body weight with hyperglycemia at 2 weeks, hyperglycemia at 4 weeks of age and augmented blood glucose concentration at 3 to 5 months. The other consequences include hyperlipidemia, impairment in thermoregulation, elevated pancreatic islets volume and decreased physical activities (Lindström 2007). Moreover, it causes infertile in mice (Chehab et al. 1996). This model can't act as a complete model system of human type 2 diabetes because of deficient in beta cell failure. This mouse would cause severe diabetes with regression of islets when it is exposed to C57Bl/KS strain (Coleman 1978).

(b) **Lepr $^{db/db}$ mice**

Lepr $^{db/db}$ mice (autosomal recessive mutation in leptin receptor) discovered in Jackson Laboratory in 1966 with the strain C57BLKS/J (Chen et al. 1996). These mice are characterized with hyperphagic, hyperinsulinaemic, obese with a hyperglycemic condition. At 3 to 4 weeks of age-mediated obese condition, hyperinsulinemia at 2 weeks of age, 4 to 8 weeks for apparent of hyperglycemic condition due to the failure of beta cells. There is an evidence of ketosis in this model along with the diminutive life span (Srinivasan and Ramarao 2007).

(c) **ZDF Rats**

The Zucker (fa/fa) fatty (obese) rats were originated form M-strain and Sherman rats in 1961 (Phillips et al. 1996). It has comparable characteristic features with db/db mice as well as an obese human model with hyperlipidemia and high blood pressure. This has the characteristic feature of hyperphagia leads to 4 weeks of age

and also other feature like hyperinsulinaemic, glucose intolerance, hyperlipidaemic and high blood pressure (Srinivasan and Ramarao 2007). The strain mutation in ZF rats would originate Zucker Diabetic Fatty rats (ZDF). These rats would decrease body weight comparable to the ZF rats with high insulin resistance with augmented apoptotic levels in pancreatic beta cells (Pick et al. 1998). It causes hyperinsulinemia at the age of 8 weeks after that it would decrease the level of insulin (Shibata et al. 2000). Insulin resistance would reach at the age of 8 weeks in case of male but in a female doesn't mediate noticeable diabetes (Srinivasan and Ramarao 2007).

9.9.2 Obese Models (Polygenic)

The obese polygenic model would provide the similar model equal to the human condition. The characteristics of the obese polygenic model are impairment in glucose tolerance, obesity, and diabetes. This model doesn't require any wild-type control (Leiter 2009). Polygenic obese model is more utilized to recognize the link between obesity and proper glucose homeostasis (Kluth et al. 2011) or any complication in the diabetic model (Buck et al. 2011).

(a) **KK mice**

KK (Kuo Kondo) mice are originated from wild-type ddY mice in 1957 in Japan by Kondo (Clee and Attie 2007). They expand the insulin resistance, hyperleptinaemia and slightly obese. The characteristic feature of this is hypertrophic and degranulated pancreatic islets (Ikeda 1994). KK-A^Y is the derivative strain and it is originated from yellow obese A^Y gene to the strain (KK). This model progresses the hyperinsulinemia condition at the age of 8 weeks along with the disruption of pancreatic islets. This condition is because of melanocortin receptor 4 (MCR4) antagonizing with the agouti protein expressed on the ectopic region (Chakraborty et al. 2009). This mouse model would be useful to study obesity-induced type 2 diabetes model and new anti-diabetic drugs.

(b) **OLETF rat**

The OLETF (Otsuka Long Evans Tokushima Fatty) rats are derived from the Long Evans rats (outbred colony) and male rats which are prone to a progression of type 2 diabetic condition at the age of 18 to 25 weeks. These animals are identified by having features of polyphagia, insulinemia, elevated triglyceride, cholesterol level and hyperglycemia with increasing age (Kawano et al. 1992). The degeneration and infiltration at the cellular level have been found at the age of 6 to 20 weeks, hyperplasia at 20 t0 40 weeks. Thus degenerative cells are becoming fibrotic and this would be replaced by connective tissue (Kawano et al. 1994). This drug is utilized to test antidiabetic or hypertensive drugs (Harada et al. 1999; Kosegawa et al. 1996).

(c) **NZO mice**

The NZO mice is a polygenic obesity model, this would increase the weight in first 2 months of age but depends on the strain the frequencies of diabetic would vary. It has the characteristics of hyperphagic and obese due to the leptin resistance (hyperleptinaemic) at 9 to 12 weeks of age (Leiter and Reifsnyder 2004). This mouse is characterized by the insulin resistance, hyperleptinemia, and hyperphagia (Thorburn et al. 2000). The concentration of blood glucose would be augmented with impaired glucose tolerance in this model which would aggravate the diabetic condition (Haskell et al. 2002).

(d) **TallyHo/Jng mice**

TallyHo/Jng mice model is obviously phenomenon for obesity and types 2 diabetes and it is originating from mice with selective breeding with hyperglycemia and hyperinsulinemia Theiler mice (outbred colony) (Kim et al. 2005). Hyperglycemia is comprised to male mice in the age of 10 to 14 weeks. Still, the characterization is completely determined but the pancreatic islets would be hypertrophied, hyperinsulinemia and degranulation (Leiter 2009).

(e) **NoncNZO10/LtJ mice**

The loci form two strains of mice such as NZO and nonobese diabetic mice would produce the NoncNZO10/LtJ mice (Cho et al. 2007). This mouse has progression of insulin resistance in both the liver and skeletal muscle at 8 week and chronic hyperglycemia at 12 weeks. In this, initially beta cell mass would elevate before a loss of beta cell (Leiter 2009).

9.10 Induced Obesity

(a) **High-fat feeding (mice or rats).**

High-fat diet feeding would lead to the condition like obesity, impaired glucose homeostasis due to inadequate compensation by islets of the pancreas. The elevated body weight gain in high-fat diet feeding rats compared to the normal chow diet rats. This would take more weeks to induce weight gain by using a high fat diet. Increase in weight of the animals would cause insulin resistance, impaired glucose tolerance due to lack of compensation of beta cells (Winzell and Ahrén 2004). This obesity-induced diabetic model is due to manipulation in the environment rather than the changes in genes. So this would be the proper model to correlate the results with the human diabetic condition (Almind and Kahn 2004).

(b) **Desert gerbil**

The desert gerbil (*Psammomys obesus*) would be derived for developing a diabetic condition. This condition has hyperglycemia in mild condition with hyperin-

sulinemia to rigorous hyperglycemia with hypoinsulinemia and ketoacidosis condition. To this animal, we would give high energy nutrition to in the laboratory to induce the condition hyperinsulinemia, obesity, and type 2 diabetic conditions. Due to excessive nutrition, there is a pitiable adaptation so this model would cause metabolic syndrome and insulin resistance. The studies which are involving nutritionally diabetes and its prevention, this model would be quite needed (Bödvarsdóttir et al. 2010).

(c) **Nile grass rat**

Nile grass rat (Arvicanthis niloticus) has been identified recently during 2010 by Noda et al., and recommended to utilize for the metabolic syndrome includes diabetes. With one year of age under normal diet, these rats would develop dyslipidemia, hyperglycemia and obesity, reduction in mass of the beta cell and liver steatosis (Noda et al. 2010).

9.11 Non-obese Models

All types of diabetes patients are not obese. So this is significant to study about the lean model of diabetes. In this model, there is an insufficient beta cell further causes type 2 diabetes(Weir et al. 2009).

(a) **GK rat**

GK (Goto–Kakizaki) rats are originated from a breeding of Wister rats repetitively with reduced glucose tolerance (Goto et al. 1976). These model rats are characterized by intolerance in glucose level and insufficient glucose-mediated insulin production. Not depends on the insulin resistance, hyperglycemia would develop but this is due to the glucose metabolism disruption with a disturbed mass of the beta cell and its function (Östenson and Efendic 2007; Portha et al. 2001). This mouse is utilized to study the dysfunction of a beta cell during type 2 diabetes (Portha et al. 2001).

9.11.1 Genetically Induced Models of Beta Cell dysfunction (hIAPP Mice)

Form islet amyloid polypeptide (IAPP), type 2 diabetes would forms amyloid within the tissue of islets (Höppener et al. 1994). For diabetic condition, rodent won't depend on the IAPP because it is not amylogenic in nature. The transgenic mice have been formed using human IAPP (hIAPP) with insulin promoter. This creates amyloid within the tissue of islets. This model would elevate the toxicity in beta cells of the pancreas (Matveyenko and Butler 2006).

9.12 Fruits in Different Rodent Model System

9.12.1 Prunus avium *(L.) (Cherry)*

The species of cherry (*Prunus avium)* universally called sweet cherry, wild cherry which belongs to flowering plant in the rose family (Databases 2009). Scientific classification of cherries comes under the Kingdom: Plantae, Order: Rosales, Family: Rosaceae, Genus: *Prunus*, Species: *avium.* Habitat includes Anatolia, western Asia, from British Isles, Europe, and Maghreb (Claridge and Wilson 1982). Plant pigments were strongly packed in cherries known as anthocyanin. A fruit looks like bright red color due to anthocyanin's which reduces blood sugar level. Antioxidant and anthocyanins were the wealthy source in cherries, which can abolish free radicals and damaging molecules in the body (Lukivskaya et al. 2004). In avoiding everyday life- correlated diseases like cardiovascular, cancer, diabetes and neurological disorders can be prevented by intake of anthocyanin-rich fruits (cherry) which plays a major significant role (Kim et al. 2006). The color of the fruit is bright red when turns to dark purple and sweet in taste. Fruits can be cheerfully eaten by means of several kinds of mammals and birds (Mitchell 1974). It has played a major important role in averting diseases like neurological diseases, cancer, cardiovascular and diabetes (Konczak and Zhang 2004).

Extraction and Solvent Used Sample was preserved in a freezer until use at 18 °C. One kilogram of the samples was used for the extraction process. Fruits were crushed using a mixer with ethanol acid solvent then extracts were filtered using Buchner funnel vacuum. Ethanol-acid solvents of the filtered products were separated using vacuum evaporator at 35 to 38 °C to isolate the solvent. Finally, pure cherry fruit extracts were collected and preserved for the treatment (Vijayvargia et al. 2000).

Model of the Study Various experiments confirmed that selection of medicinal plant extracts efficiently lowers the blood glucose level in alloxan (animal) model (Vijayvargia et al. 2000). Antihyperglycemic activity has shown in ethanol extracts of cherry. Study exhibited that 150–200 grams of male Wistar rats were used. Six groups of animals were divided and used for this study by giving an intraperitoneal injection of alloxan monohydrate was dissolved in freshly prepared saline at a dose of 120 mg/kg. Study exhibited that cherry fed groups decrease levels of plasma marker in oxidative damage parallel increases antioxidant capacity in blood.

9.12.2 Terminalia Pallida

Terminalia pallida is a small evergreen widespread tree (Rao et al. 2003) which belongs to the family of Combretaceae. Tellakaraka is a local name for *T.pallida*. The Scientific classification includes Kingdom: Plantae, Phylum: Tracheophyta,

Class: Magnoliopsida, Order: Myrtales, Family: Combretaceae, Genus: *Terminalia* Species: *pallida.* Tribal people used the fruits of *Terminalia pallida* for the treatment of diabetes (Nagaraju 1992; Nagaraju and Rao 1989; Rai 1995). Fruit powder (maceration) can be given orally as a drink for 25 days (twice in a day) to treat diabetes (Thammanna and Nagaraju 1990; Thammanna et al. 1994). Ethanol fruit extracts of *T.pallida* has antihyperglycemic and anti-ulcer activities (Gupta et al. 2005; Rao et al. 2003). It can also use to apply externally on the affected part of the body and also given orally to treat diabetes and dried fruits can be used as dry pickles (Palani et al. 2009).

Extraction and Solvent Used In this extraction process *T. pallida* fruit ethanol (95%) were used. Fruits were soaked in 95% of ethanol for 2 days in a glass jar at normal room temperature. Extraction was repeated for 3 to 4 times and solvents were filtered. Extracts were concentrated using Buchi rota vapor under reduced pressure. The yield of the extract is 6.7% (Rao et al. 1999).

Model of the Study Male Wistar albino rats were used for this study. Four months aged with 180 g body weight of the rats was used. Aqueous alloxan monohydrate was administrated for 150 mg/kg body weight by intraperitoneal method (Rao et al. 1999).

9.12.3 Punica granatum *L. (Pomegranate Flower)*

Punica granatum Linn, pomegranate which belongs to the *Punicaceae* family inborn to Middle East (Johanningsmeier and Harris 2011). The scientific classification of the plant occurs under Kingdom: Plantae, Order: Myrtales, Family: Punicaceae, Genus: *Punica*, Species: *granatum*. It is commonly called as Anar and Pomegranate. Flowers are terminal and rest marginal, small or without peduncle. The color of the flower is hardly yellow, white and red. A native of the plant belongs to Asia regions of Himalaya, Iran, Middle East, and Mediterranean regions. Cultivation of pomegranate includes the regions like Spain, Afghanistan, America, India, Russia, Morocco, Uzbekistan and Greece. World's leading producers of pomegranate is Iran (Al-Said et al. 2009). In Unani and Ayurvedic folk medicines pomegranate flowers were used to cure diabetes (Wang et al. 2012) antioxidant activity (Aviram et al. 2002; Gil et al. 2000).

Extraction Process Pomegranate 400 mg/kg aqueous ethanolic (50% v/v) of flower extract were administered to animals (Jafri et al. 2000).

Model of the Study Pomegranate flower extract was used to induce in alloxan-induced diabetic rats which decrease blood glucose level.

9.12.4 Momordica Cymbalaria

Momordica cymbalaria it's generally known as gourds, melons or cucurbits which belong to the family of Cucurbitaceae. The taxonomy of the plants comes under the Kingdom: Plantae, Superdivision: Spermatophyta, Division: Magnoliophyta, Class: Magnoliopsida, Order: Cucurbitales, Family: Cucurbitaceae, Subfamily: Curcurbitoideae, Tribe: Jolifficae, Subtribe: Thladianthinae, Genus: *Momordica*, Species: *cymbalaria Hoof.* The synonyms of *Momordica cymbalaria* are *Momordica tuberosa* Roxb.Cogn. Or *Luffa tuberose* Roxb. This plant is a perennial climber and it's available throughout the monsoon season and habitat of the plant found in South Indian states of Maharashtra, Madhya Pradesh, Andhra Pradesh, Karnataka and Tamil Nadu (Parvathi and Kumar 2002). It has Antihyperglycemic and antihyperlipidemic activity reports have been found in fruit powder of *Momordica cymbalaria (*Rao et al. 2001*)*. Therapeutic uses of the plant were considered as the stimulant, stomachic and alterative. Rheumatism and gout can be treated using fruit. Leaf tea and fruit juice of Momordica cymbalaria was used for colic, sores, wounds, malaria, parasites, and diabetes. For the treatment of diabetes mellitus, *Momordica* species have been used as therapeutic agents and hypoglycaemic effects have been reported on other species of the genus are *M.Charantia* and *M. Foetida (*Fernandes et al. 2007*;* Osinubi et al. 2008*)*.

Extraction and Solvent Used Aqueous extracts of *Momordica cymbalaria* dried fruit yield was 9.4% (Rao et al. 2001).

Model of the Study *M.cymbalaria* fruit has hypoglycaemic and antidiabetic activity has been reported (Rao et al. 1999). Fruit powder of *M.cymbalaria* possesses hypoglycaemic was estimated in alloxan-induced diabetic rats. Blood glucose level was decreased in diabetic rats by giving the continuous treatment of *M. cymbalaria* fruit powder at the concentration of 0.25 g/kg body weight for a period of 15 days.

9.13 Streptozotocin-Induced Diabetes

9.13.1 Pongamia pinnata

The synonyms of *Pongamia pinnata* are *Pongamia glabra* (Vent); Pongamia pinnata (Merr.); *Derris indica* (Lam.). The genus of the plant Pongamia which belongs to the Leguminosae family (Meera et al. 2003). The Scientific classification comes under Kingdom: Plantae, Division: Magnoliophyta, Class: Magnoliopsida Order: Fabales, Family: Leguminosae, Genus: *Pongamia*, Species: *Pinnata*. The plant is the medium-sized glabrous fast-growing tree, which can grow up to forty feet in

height and enough shade (Allen and Allen 1981). It's commonly called as Pongam, ponga in Tamil, Karanja in Hindi, Indian beech in English and Naktamala in Sanskrit. Native belongs to Myanmar, Nepal, Thailand, India, and Bangladesh. It is predominantly found in the Western Ghats and tidal forests area in India. In tradition medicine, different parts of the plants have been used for a whooping cough, rheumatic joints and diabetes (dipsia) (Kirtikar and Basu 1999). In *P.pinnata* flowers has stated for Antilipidperoxidative and antihyperglycemic activity(Punitha and Manoharan 2006) alloxan-induced diabetic rats was found to have hypoglycemic activity (Mandal and Maity 1986).

Extraction and Solvent Used Ethanolic extract with the yield of 12.5% was obtained from *Pongamia pinnata* with successive solvent (n-hexane, chloroform) extraction (Yadav et al. 2004). The chloroform extract was subjected for column chromatography to obtain compound based on the TLC fractions. Finally, they got Karanjin and pongamol from ethanolic extracts of chloroform soluble fraction in *P.pinnata* fruits (Yadav et al. 2004).

Model of the Study A Sprague Dawley rat was intraperitoneally induced by Streptozotocin to make diabetic (0.1 M citrate buffer pH 4.5, 60 mg/kg body weight). STZ, Single dose 100 mg/kg body weight reduces blood glucose level (Szkudelski 2001).

9.13.2 Diospyros Peregrina

Diospyros peregrina belongs to Ebenaceae family. Scientific classification of the plant consists of Kingdom: Plantae, Order: Ebenales, Family: Ebenaceae, Genus: *Diospyros* Species: *peregrina.* The tree is evergreen which can grow up to the fifteen meters in height which can raise all parts of India especially in the river banks and coastal regions in India. In Tamil, it is called Tumbika, Pannicai, and Benchu Maram. Leaves were distichous, alternate and simple. Petiole can grow up to 1.5 cm in long and glabrous. Flowers are unisexual, female flowers axillary and male three to seven axillary cymes flowered. The immature *Diospyros peregrina* fruits can be used acrid, oleaginous, astringent and bitter (Anjaria et al. 2002a). From ancient times such as Traditional Chinese Medicine, Indian traditional medicine, Ayurveda, and African folklore were used (Laloo et al. 2006; Lewis and Elvin Lewis 1977). A mature fruit plays a significant role as aphrodisiace and tonic (Kirtikar and Basu 1975). *D.peregrina* secondary metabolite soluble tannins, betulinic acid, lupeol, sitosterol and Furano-(2″, 3″, 7, 8)-3′, 5′-dimethoxy-5-hydroxyflavone, 4′-hydroxy-3, 6, 3′5′-tetrameth-oxy-7, 8-pyranoflavone (Chopra et al. 1956; Jain and Yadava 1994; Jain and Yadava 1997; Misra et al. 1971). The ripened fruits of *D.peregrina* were effectively used for the treatment of diabetes by local peoples and traditional healers in India.

Extraction and Solvents Used Collected fruits were powdered using mixer grinder and macerated for 48 h with double distilled water on shaking. The yield of 6.2% of aqueous crude extract was obtained by lyophilization (Misra et al. 1971).

Model of the Study A Wistar male rat with the age of 2 to 3 months (180-200gms) was used for the study. Streptozotocin 65 mg/kg and nicotinamide 110 mg/kg was given to rats by intraperitoneal injection to induced diabetes (Masiello et al. 1998). 140–200 mg/dl fasting blood glucose level rats were used for type 2 diabetes. Streptozotocin with nicotinamide which gives insulin responsiveness to glucose (Shirwaikar et al. 2005). Study exhibited that diabetic rats suggestively elevated triglycerides and cholesterol level associated with normal rats. Fruit extract of *Diospyros peregrina* lowers triglycerides and blood glucose level in experimental type 2 diabetic rats.

9.13.3 Xylopia aethiopica

Xylopia aethiopica is an aromatic and perennial tree. It is an Original spice also known as Ethiopian pepper distributed throughout Africa. Taxonomy of the plant comes under Kingdom: Plantae, Order: Magnoliales, Family: Annonaceae, Genus: *Xylopia*, Species: *aethiopica*. The tree can grow up to the twenty meters in height, pod is twisted bean, dark brown in color, cylindrical in nature and 1.5–6 centimeter in long and four to seven millimeter in thick (Iwu 2014; Orwa et al. 2009). It is known also called Negro pepper, Kani pepper and West African pepper tree in English (Nwangwa 2012). In Africa and Asia fruit of *X.aethiopica* generally used as in several local dishes (Freiesleben et al. 2015). For, various diseases *X.aethiopica* fruit is extensively used for the treatment (Soladoye et al. 2012). In traditional medicines system, *X.aethiopica* fruit decoction is extensively used for the treatment of diabetes in Nigerian, Togolese and Senegalese and Guinean (Diallo et al. 2012; Dièye et al. 2008; Karou et al. 2011; Kuete et al. 2013) anticancer (Kuete et al. 2011; Nwangwa 2012), antifertility (Uwakwe 2013), anti-sickling (Esekhiagbe et al. 2009), antimicrobial (Nwozo et al. 2011), hypercholesterolemic and antioxidant activity.

Extraction and Solvents Used Three kilograms of the fruits were extracted with hexane to remove defatt and to carry out sequential extraction in ethanol solvents by means soaking 48 h and filtered using filter paper (Esekhiagbe et al. 2009). By using Buchi Rotavapor II extracts were evaporated and condensed. The yield 7.05% was obtained from 40 grams of crude (ethanol) extracts.

Model of the Study SD (Sprague-Dawley) 6 week old (male) rats were made diabetic by streptozotocin-induced diabetes single intraperitoneal injection with a low dosage of 40 mg/kg body weight.

9.13.4 *Ficus Deltoidea*

'Mascotek' is locally called as *Ficus deltoidea* belongs to Moraceae family. The taxonomy of the plant comes under the Kingdom: Plantae, Order: Rosales, Family: Moraceace, Genus: *Ficus*, Species: *deltoidea. Ficus deltoidea* is broadly distributed all over Thailand, Sumatra, Malaysia, Kalimantan and Sulawesi (Berg 2003). Moreover, twenty-five kinds of species obtainable from the areas of western Malesia and Sino-Himalayas (Adam et al. 2011). The plants have leafy-twigs, midrib dichotomous and milky latex. The dried leaves were considered as an herbal tea and marketed in Malay traditional medicine. It has antioxidant, aphrodisiac and antidiabetic activity which helps to improve blood circulation (Aminudin et al. 1970; Choo et al. 2012; Sulaiman et al. 2008). *F.deltoidea* has been revealed to exhibit blood glucose-lowering effects (Adam et al. 2007; Adam et al. 2012), ulcer healing (Fatimah et al. 2009), antioxidant (Abdullah et al. 2009; Hakiman and Maziah 2009), anti-inflammatory (Zakaria et al. 2012), antimelagonic (Oh et al. 2011), and antinociceptive activity (Sulaiman et al. 2008).

Extraction and Solvents Used The fruit (1 kg) of *Ficus deltoidea* was powdered and used for crude ethyl acetate solvent was evaporated using a rotary evaporator to obtain an extract.

Model of the Study *Invitro* studies have carried out for diabetes like yeast alpha-glucosidase inhibition assay.

9.13.5 *Trapa natans*

Trapa natans are generally known as water caltrop and Water Chestnut in English, Bengali it is commonly called as *Paniphal.* The Scientific classification which comes under *Kingdom*: Plantae, Order: Myrtales, Family: Lythraceae, Subfamily: Trapoideae, Genus: *Trapa,* Species: *natans. T. natans* is yearly water floating herb arising lakes and ponds all over the Indian subcontinent (Joshi et al. 2017). This plant has been used for numerous important medicinal properties in India. *T. natans* used as diuretic, astringent, aphrodisiac, nutritive and tonic. Fruits of *T. natans* were used in making creams to cure sunburns, sores and rheumatism (Anjaria et al. 2002b). It also has psychopharmacological and analgesic activity from roots (Panda et al. 2010). Fruit peel extract has antifungal and antibacterial activity (Parekh and Chanda 2007; Parekh and Chanda 2008).

Extraction and Solvents Used Powdered sample of 450 grams was macerated with methanol by maceration on shaking. The macerates extracts were filtered and evaporated by vacuum desiccator. The yield of the crude extract was 6.35 percentages.

Model of the Study Healthy adult male Wistar albino a rat was with 170–200grams was used for the model. Streptozotocin was induced by an intraperitoneal method with 65 mg/kg body weight was injected at the low concentration. Results were exhibited that STZ induced diabetes rats revealed at the dose of 100 and 200 mg/ kg body weight effective for normoglycemic, antihyperglycemic and hypoglycemic.

9.13.6 Pomegranate Seeds

Pomegranate which belongs to Punicaceae family. Protecting antioxidant compounds pomegranate juice contains protecting antioxidant compounds(Panda et al. 2010).

Extraction and Solvent Used Pomegranate seed was extracted using methanol solvents to obtain an extract.

Model of the Study Streptozotocin was induced by giving a single intraperitoneal injection. Oral administration of seed extract was administered orally at 300 and 600 mg/kg decreased blood glucose level by 42% and 47%, observed after 12 h (Parekh and Chanda 2007).

9.13.7 Pomegranate Juice

The fruits are red in color leathery rind and seed is enclosed in pulp and partitioned by walls. The size of the fruits ranges from the width 2.25 to 5 inch wide. The taste of Pomegranate juice is acid in nature due to the presence of two kind of acids contain phenol and non-phenolic acid. Phenol acids like chlorogenic, gallic, caffeic and coumaric acids. Ascorbic, oxalic, citric, malic and succinic acid come under nonphenolic acids. Bioactive compounds also present in fresh pomegranate juice (Parekh and Chanda 2008). Pomegranate juices can be used for anticipation and treatment for many diseases like male infertility, brain ischemia, arthritis, obesity, dental diseases and diabetes (Aviram et al. 2002; Das et al. 2001), anti-carcinogenic, anti-infective, antioxidant, anti-infective anti-inflammatory and anti-hyperglycemic (Jurenka 2008; Krueger 2012).

9.14 Conclusion

In this chapter, a study indicates that *Momordica cymbalaria* was observed lower the blood glucose level in diabetic treated rats. A change was observed in aqueous extract of *M.cymbalaria* fruits in the liver, plasma, kidney glycogen and hemoglobin. In *P.pinnata fruits* ethanol extract on streptozotocin induced reduces blood glucose

level at 9.2% at 250 mg/kg body weight. *Diospyros peregrina* aqueous stated that extract lowered the blood glucose level in type 2 diabetes mellitus. The maximum reduction was observed in 27 and 33% for 28 days when compared with standard drug (Glibenclamide) 45% of reduction was observed on the 28 day. In *Xylopia aethiopica* reduction of blood glucose level was observed in 4 weeks treatment which gives a significant value of $p < 0.05$ compared with metformin (standard drug). The fruits of *Ficus deltoidea* crude extract showed phenol content of 121.62 ± 4.86 mg/g of extract. Antioxidant activity has lost in crude extract fractions. The cherry (*Prunus avium)* fruit lowered the blood glucose level significantly. *Trapa natans* which reduce blood glucose level and gives a significant value of *<0.001* glibenclamide were used as a standard. *Terminalia pallida* ethanol extract showed decreases in blood glucose level in 31.1% of diabetic rats at the dosage if 0.2 g/kg body weight in glibenclamide. *Punica granatum* fruits, flowers, and seeds have been used for the diabetes study which revealed lower the blood glucose level. Pomegranate flower aqueous ethanol (400 mg/kg) extracts lower the blood glucose level in alloxan (500 mg/kg) monohydrate induced diabetic model and also lower contents of cardiac triglycerides (TGs) as well plasma and total cholesterol.

Acknowledgement The authors thank to Vellore Institute of Technology, Vellore, Tamilnadu, India for supporting this work. The author Papitha R, Kaviyarasi Renu is grateful to Vellore Institute of Technology for providing the financial assistance during this tenure. The authors wish to greatly acknowledge the editor and reviewers for the suggestions and critical evaluation of the manuscript.

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Chapter 10
Potential Applications of Nanotechnology in Agriculture: Current Status and Future Aspects

Ravichandran Rathna, Asaithambi Kalaiselvi, and Ekambaram Nakkeeran

Abstract Globally, agriculture and its related sectors are facing major challenges. The bountiful applications of several agro-chemicals led to environmental pollution, eco-system imbalance, climate change and other ecological impacts. Ultimately, resulted in exacerbation of water resources, soil quality and uneven distribution of rainfall. Therefore, precision agricultural practices are essential to employ recent advancements such as nano based agricultural technologies to overcome huge demands of agro-based products in the near future. This chapter discuss about various nano-assisted technologies to improve the crop production using several formulations like nano-pesticides, herbicides and fertilizers to enhance their effects on germination, growth and protection of crops and other live stocks from farm to fork.

Keywords Agro-nanotechnology · Nano formulations · Crop-protection · Water management · Nano-assisted livestock production

10.1 Introduction

Agriculture forged a great suit for manufactures and commerce, which ultimately had a significant impact on the economy. The historiographical perspective of Edward Gibbon, that "Agriculture is the foundation of manufactures, since the productions of nature are the materials of art". From this perspective, it may be inferred that agriculture and society are entirely intertwined. From ancient times to the modern era, the agriculture is considered as the basis to solve the socio-economic issues. In the present era, agriculture and related sectors are facing major global challenges such as ecological imbalance, rapid urbanization, environment pollution,

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_10

climate change, global warming, resource management and other environmental impact caused as the result of improved crop production. As per The World Population Prospects: The 2017 Revision, published by the UN Department of Economic and Social Affairs, current world population of 7.6 billion is expected to reach 8.6 billion in 2030, 9.8 billion in 2050 and 11.2 billion in 2100. Therefore, exacerbate the demand for sustainable agricultural and food products. Moreover, world is pivoted on renewable sources in order to replace future diminishing petroleum resources. Ultimately, agricultural sources and related products would be considered as inexpensive energy support for enormous development in the nation. The development of agriculture and related sector eventually purge the poverty, impoverishment, food paucity and starvation.

Agriculture is considered as the backbone of the developing country's economy; more than 60% of the population depends directly or indirectly on agriculture and its related activities. Taking into consideration of global climate change, water scarcity, erratic magnitude of rainfall and its distribution and transformation of the agricultural area to non-agricultural activities are major challenges of today's global agriculture. The recent advancement in science and technology has touched all the facets in the agriculture sector. The advent of agri-genomics and bioinformatics offers opportunities to transform obstacles into component traits. However, adoption of molecular biology found to be effective in overcoming the major challenges faced by agricultural sector. However, this technology is underutilized in developing nations due to high cost, lack of skilled personnel, unavailability of analytical tools, inadequate high-throughput facilities, penurious infrastructure, paucity of information system and incapacitated regulatory framework (Helmy et al. 2016). It is pivotal to support molecular breeding in spite of advantageous outcomes because of risk factors and public opinion. The risk factors and regulatory aspects increase the disparity between the developed and developing countries for using the advances in science and technology.

The rapid evolution in technological innovations led to potent structural shift in the agricultural sector from cultivation to product development. Contemporary developments not only augment the crop production, but also alleviate the environmental and cost related issues in agronomics. One such example is hybrid rice varieties with enhanced yield, robustness and resistance towards insects/diseases. Thus, new technologies are developed to conserve water, land and resources, by improving the yield and economy without defiling the ecological balance. The innovative technologies offer solution for the challenges and add values to the commodities production system (Sekhon 2014; Bharathi et al. 2014; Roopan et al. 2014). Thereby, profusion of critical challenges like poverty, food scarcity, malnutrition, lack of fertile soil etc., could be obliterated from the society. It is also noted that not all new agricultural innovative technologies may be effective to solve existing issues of global food production, distribution and consumption. In this vein, it is indispensable for developing nations to dynamically participate in research and development based on their needs and potential.

In recent years, nanotechnology has added impulse to technical innovations that led to the development of unique materials targeted towards specific applications.

Nano mediated materials are potentially used and engrossed in several fields such as medicine, pharmaceuticals, electronics and environmental sciences (Elango et al. 2015; Madhumitha et al. 2016). Nevertheless, the use of nanotechnology towards agriculture is still considered as an under explored area by researchers. Nano mediated science and technology is found to be the most important tool towards modern agriculture for the production and protection of plants by improving nutrient absorption ability. Nano based kits are developed and used to prevent various plant diseases through rapid detection. These crop pathogens are detected and destroyed through smart delivery systems such as nano bio-sensors. In near future, nanotechnology can change the entire scenario of agriculture and food industries. It is assumed that even nanocatalyst will be available in future to reduce the dosage level of pesticides and insecticides required for crop plants (Rai and Ingle 2012; Elango and Roopan 2016).

The Agri-food Nanotechnology cynosures on production, protection and sustainability of agri- based food crops produced for human consumption and animal feeding. Agri-food Nanotechnology, a broad scientific frontier is converged to become as driving economic force globally in near future. Precision farming techniques along with nano based formulations, kits, sensors and devices improves the yield of crop production without damaging the soil, water with minimal usage of pesticides and fertilizers and enhances the retention of nutrients in the soil through long term incorporation using soil microorganisms. Nano-technology also helps in the development of insect-resistant varieties through DNA transfer or by nanoparticle mediated gene transfer into crop yielding plants and increases the shelf life of the produced food crops. Advanced agrochemical agents and new mode of delivery mechanism is introduced through nanotechnology to boost agricultural production and protection by increasing the crop yield with minimal pesticide usage. Several Nano based agricultural applications are illustrated in the Fig. 10.1.

10.2 Nanotechnology in Agriculture

10.2.1 Nano Guarded Pesticides

To improve the efficiency, quality and yield of food crop pesticides are commonly used. Recently nano-formulated pesticides are used to overcome synthetic pesticides (Sasson et al. 2007). Nano-pesticides are small particles of active ingredients having beneficial pesticidal properties engineered with small nano range structures. These agricultural formulations are efficiently dispersed in water and acts as a barrier to decrease unwanted movement of pesticides (Bergeson 2010). Nano-pesticides are delivered through several techniques such as nano based emulsions, encapsulations, nano cages and nano containers. These nano-formulated pesticides have increased affinity to the specific target site due to their large surface area (Yan et al. 2005). Nano based materials are potentially used in agricultural sector as nano-pesticides

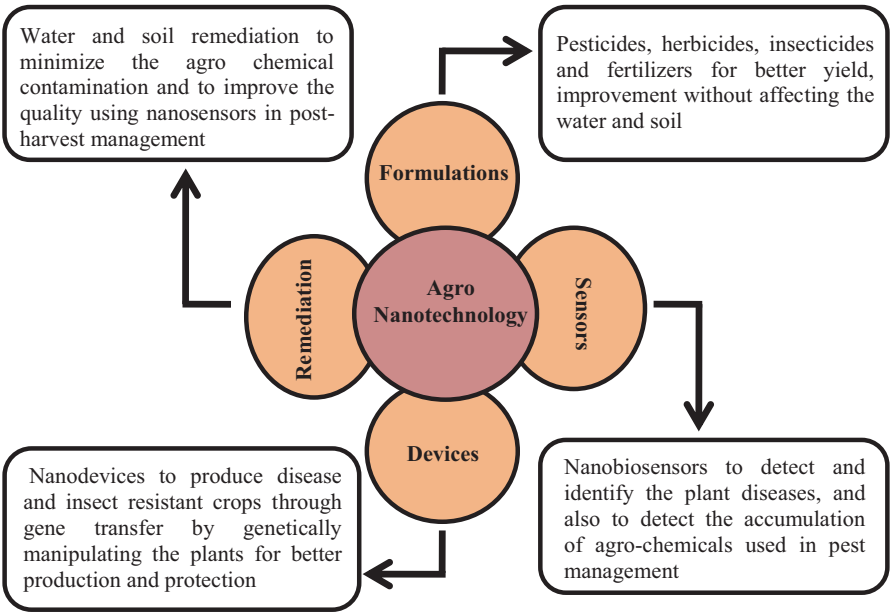

Fig. 10.1 Applications of Agro-Nanotechnology

with enhanced properties such as dispersion, biodegradability, crystallinity, permeability, stiffness and thermal stability (Bouwmeester et al. 2009).

These crop- protecting agents developed using nano formulations are immiscible in water due to combination of various organic polymers with inorganic metal nanoparticles along surfactants within nanometer range (Perlatti et al. 2013). Nano formulated pesticides are often in the form of microencapsulation with increased hydrophobicity. This versatile tool enhances the active compounds dispersion effectively in aqueous phase with controlled release. Nano encapsulated pesticide such as ethiprole has its encapsulation with polycaprolactone and poly lactic acid in the form of nanospheres. Due to its nano range size, it effectively penetrates the plant than commercially available classical suspensions but they lack controlled release of active core ingredients (Boehm et al. 2003).

Variety of nano formulated agro based chemicals are studied on chitosan, which is a polysaccharide derived from chitin (Kashyap et al. 2015). Novel fungicide nano formulations were developed with solid lipid polymeric nanocapsules loaded with active compound such as carbendazim and tebuconazole. The study revealed that these nanocapsules releases its active compounds gradually and decreases the adverse effects of fungus and promotes the plant growth by voiding the fungal interruptions comparatively than available commercial agro chemical products (Campos et al. 2015). Pesticides such as validamycin and the herbicide 2,4-dichlorophenoxyacetate are evaluated and reported for their controlled gradual

release of active compound from porous hollow silica nanocapsules (Liu et al. 2006b). Beta-cypermethrin with surfactant based nanoemulsions was formulated and evaluated to understand the controlled delivery system of active pesticides (Wang et al. 2007).

Fruit pests are controlled by a cost effective commercially available agro chemicals such as pheromone methyl eugenol which is formulated into nanogels. These nanogels prevents the fruit pest even in lower dosage without altering its property and efficacy, it controls the pest deteriorating fruits (Bhagat et al. 2013). Inorganic metal nanoparticles and nano sized ashes that occur in free state in nature are studied extensively and evaluated for its anti-microbial, fungal and insecticidal properties (Sonkar et al. 2012). Nanoparticles formulated garlic essential oil loaded with polyethylene glycol are studied for its controlled release core compound against pest that affects the shelf-life of the stored agro-food products (Yang et al. 2009). These nano formulations based agro-chemicals not only protect the food crop from various pests and fungus (Kole et al. 2013) but also boosts up the quality and yield of crop produced. Therefore, nano formulations potentially utilize low quantity of fertilizer and pesticide compared to commercially available products (Pandey et al. 2010).

Nano based formulations with imidacloprid (1-(6 chloro-3-pyridinyl methyl)-N-nitro imidazolidin-2-ylideneamine), synthesized from polyethylene glycol and various aliphatic diacids along with active compounds are used in several crops for efficient pest management (Gogos et al. 2012). Stem fly, *Melanagromyza sojae* (Zehntner) and white fly, *Bemisia tabaci* (Gennadius) are the major pests found in soybean (Adak et al. 2012). These flies exhibited better pest resistance with controlled release of bio active ingredient imidacloprid formulations than commercially available formulations. These poly (oxyethylene-1000)-oxy suberoyl) amphiphilic polymer-based formulations exhibited higher yield and control over commercial formulations (Adak et al. 2012). Researchers have explored several nano based particles for formulating nanopesticides such as gold, silver, iron and polymer nanoparticles.

Nano formulated (NF) carbofuran and imidacloprid had better pesticidal effect against aphid, *Aphis gossypii* and leafhopper, *Amrasca biguttula* Ishida on potato crop (Kumar et al. 2011). An aqueous leaf extract of *Tinospora cordifolia* mediated silver nanoparticles exhibited potential pediculocidal and larvicidal mortality against *Pediculus humanus* (head louse). Also possess excellent anti-lice and mosquito larvicidal effect against *Anopheles subpictus* (fourth instar larvae) and *Culex-quinquefasciatus* (Jayaseelan et al. 2011). Amorphous nanosilica is used as an excellent biopesticides (Barik et al. 2008). Nano copper suspension known as Bouisol, a commercial fungicide product used for better protection and production of grapes and fruit yielding trees (Hatschek 1931).

The insect and pest resistant nano pesticide or nano herbicides are produced by several companies as uniform suspensions, either oil based or water based formulations in size range of 200–400 nm (Pérez-de-Luque and Rubiales 2009). Herbicides prepared using nano capsules gradually allows the active ingredient to enter the cuticles and tissues with specific controlled release. Mutagenic alterations

on viral capsids in order to achieve different configurations against parasites are investigated to deliver specific nucleic acids, enzymes and antimicrobial peptides (Lamsal et al. 2011). The mycelial growth and conidial germination of powdery mildew on cucurbits and pumpkins are inhibited when 100 mg/kg silver nanoparticles used (Afrasiabi et al. 2012). Ethanolic suspension of hydrophobic alumina–silicate nanoparticles is used in treatment of *Bombyx mori* leaves. This suspended formulation significantly reduces the viral load and treats grasserie disease (Goswami et al. 2010). DNA-tagged gold nanoparticles are significantly effective in pest management strategy on development of viral diagnostics nano based kits to detect diseases and identify strains of viruses (Chakravarthy et al. 2012).

Copper nanoparticles with soda lime glass powder exhibited excellent antimicrobial property against gram-positive and negative bacteria (Esteban-Tejeda et al. 2009). Polymer-based copper nanocomposites act against pathogenic fungi (Cioffi et al. 2004). Silica–silver nanoparticles are potentially effective against *Botrytis cinerea*, *Bipolaris sorokiniana*, *Colletotrichum gloeosporioides*, *Magnaporthe grisea*, and *Rhizoctonia solani* (Jo et al. 2009). Also, nano silica has been widely used in agricultural sector as insecticides and pesticides and as ectoparasites in animals. These particles when administered on leaves and stem surfaces through physisorption cuticular lipids are absorbed and causes death (Ulrichs et al. 2005). Compared to commercially available classical and conventional pesticides, nanoencapsulated pesticides have the ability to cause death to specifically targeted insects effectively even at low dosage facilitating controlled release with prolonged duration (Scrinis and Lyons 2007). Alumina nano based structures when exposed on wheat crops, significant mortality was reported against *Sarocladium oryzae* and *Rhyzopertha dominica* insects. Halloysite nanotubes are potentially used in agro medicines and pesticides (Stadler et al. 2010).

10.2.2 Nano Guarded Herbicides

Nano herbicides are economically viable alternative, has essential needs to increase the yield of the crop and remove weeds that interrupts the crop growth. Conventional herbicides are highly effective but lack of moisture limits its efficiency and usage. Therefore, silicon nano-carriers comprised with diatom frustules are used in controlled delivery of pesticides and herbicides with specific release in plants and wastewater treatments (Lodriche et al. 2012). Several herbicides are evaluated and reported by researchers based on hybrid nanocomposites functions, an anionic intercalation of two herbicides 2,4-dichlorophenoxy acetate and 4-chlorophenoxy acetate with zinc–aluminum-layered double hydroxide (Bashi et al. 2011).

Core-shell manganese carbonate nanoparticles loaded with programmed pendimethalin (pre-emergence herbicide) released smartly to plant based on its plant systems requirement (Kanimozhi and Chinnamuthu 2012). Plant diseases are managed effectively with silver and titanium dioxide nanoparticles (Soni and Prakash 2012). Sulfur nanoparticles effectively acts against fungal strains *Fusarium solani* from

tomato leaf (Fusarium wilt fungal disease) responsible for early blight and apple scab disease caused by phytopathogen *Venturia inaequalis* has been reported (Rao and Paria 2013).

10.2.3 Nanogels Formulation

Nanogels are used in agrochemical industries especially in fruit producing orchards. Pheromones an eco-friendly, semiochemical, volatile compound acts as a pest controlling agent. This active compound is immobilized in nanogels and exhibits effectively in open orchards with increased residual activity and reduces the undesirable fruit fly and pest populations that minimizes the quality and yield of the fruit production (Sekhon 2014). Nanogels are produced due to self-assembly of gelator molecules by using all-trans tri (p-phenylene vinylene) bis-aldoxime. Nano based gels are used in agrochemical sectors for its reduced evaporation, sustained release of the pheromone, easy handling, transportation without refrigeration and stability at ambient atmospheric condition with minimal frequency and recharging of active compound pheromone in orchards (Bhagat et al. 2013).

These nanogel pheromone deleterious effect on prevalent harmful pest such as *Bactrocera dorsalis* that harm number of fruits yielding trees. Nanostructured alumina acts against *Sarocladium oryzae* (L.) and *Rhyzopertha dominica* (F.) insects, that exists in the stored food supplies throughout the world. Significant mortality of insect was observed by the exposure of alumina nanoparticles continuously for 3 days. Nano structured alumina nanoparticles are reliable and cost effective compared to commercially available conventional pesticides used for pest/insect control management (Stadler et al. 2012).

10.2.4 Nano Guarded Fertilizers

Fertilizers formulated with nanostructured particles have created a profound opportunity by increasing the impact on economy and reducing the environmental nitrogen loss that occur due to long term contact with soil microorganism, emission and soil leaching (DeRosa et al. 2010). Recent study as proved that the efficiency of nitrogen usage by plants have become very low and about 50 to 70% of the nitrogen is supplied only through commercially available conventional fertilizers. Through nanoencapsulated fertilizers, new nutrient delivery system is formulated to reduce the nitrogen loss in plants. Nanoformulated fertilizers are triggered and their controlled release based on environmental condition (Liu et al. 2006a). Gradual release with prolonged duration increases nutrient uptake efficiency of the plant and helps to improve soil nutrients by reducing the toxic effects due to over usage of fertilizers and prevents autrification and polluting water resources (Moaveni and Kheiri 2011).

Nanofertilizers are prepared with natural material as soluble fertilizers with coating and cementing granules. Promising growth was observed in wheat crops treated with TiO_2 nanoparticles but found negligible when treated with bulk TiO_2. SiO_2 and TiO_2 nanoparticles facilitate increase of nitrate reductase activity with intensified plant absorption capacity especially in soybean cultivation (Lu et al. 2001). Nano organic environmentally sustainable iron-chelated fertilizers are produced by Iranian researchers. These nano based fertilizers have unique configurations such as ultrahigh absorption, increased photosynthesis with significant expansion on surface area of leaves (Council 2009). Pot study using foliar spray on tomato plants with 20 mg/ mL of ZnO nanoparticles formulation exhibited efficient biomass production, growth and yield potentially surpasses conventional fertilizer usage (de la Rosa et al. 2013). Nano fertilizer encapsulated and coated by thin film facilitates controlled slow release of fertilizer. Nano based engineered particles helps agro-food sector to mitigate various chronic problems such as retention of moisture content in arid soil, to enhance crop yield by increasing the efficiency and bioavailability of nutrients in rhizosphere (Raliya et al. 2013).

Several researchers have reported that formulations designed with nanostructures consisting of required micro and macro nutrients, nitrogen, phosphorus, potassium, amino acids and mannose promotes the growth and yield of cultivated grain crops due to enhanced uptake and effective utilization of active composites (Guo 2004). Agro-chemical nanocomposite Zinc–aluminium layered double-hydroxide is used as regulators for plant growth. Sustained slow release of nitrogen in three varied pH values was reported using urea-modified hydroxyapatite encapsulated nanoparticles on *Gliricidia sepium* (Kottegoda et al. 2011). To improve the efficacy of nitrogen usage in crop productivity nitrogen based fertilizers such as nanoporous zeolites were used as an alternative to conventional fertilizers (Manik and Subramanian 2014). Nanofertilizers are delivered through three possible modes such as encapsulating active core nanoporous material, thin film polymer coatings, nanoscale dimension delivery either as particles or emulsions (Rai et al. 2012).

Nanocoated urea and phosphate promotes and fulfills the requirement of food crops by sustained release of micronutrients specially nitrogen. Prolonged and sustained release of NPK fertilizer mediated through Kaolin, biodegradable polymeric composite and chitosan nanoparticles (Corradini et al. 2010). Silicon based fertilizers such as silicon dioxide nanoparticles increases the resistance of plant, promotes the development and growth of seed and root systems (Ghormade et al. 2011). TiO_2 nanoparticles are non-toxic additives used in precision agricultural farming as fertilizers to increase the potency of water retention (Corradini et al. 2010). Nanoclay adsorbents such as zeolite, montmorillonite, bentonite and halloysite are nano formulated to develop nitrogen fertilizers with controlled release and cost effective except zeolites (Manik and Subramanian 2014). Hydrophobic silica nanoparticles have improved viability of cells and reduced the sedimentation of cells by thickening the oil phase during crop storage (Vandergheynst et al. 2007). Silver and gold nanoparticles are effectively used as growth promoters in development of horticulture crop especially fabaceae by limiting land and water usage (Dikshit et al. 2013). Combinations of eco-friendly microorganisms such as

Pseudomonas fluorescens, *Paenibacillus elgi* and *Bacillus subtilis* with nanoparticles have exhibited good growth development under in-vitro conditions as nano biofertilizers (Shukla et al. 2015). They are cost effective compared to commercialized conventional fertilizer; also several hectares of crops can be managed even with one liter of nano-bio fertilizers. Therefore, precision agricultural farming and crop cultivation with high quality and increased yield can be produced.

10.2.5 Seed Germination and Plant Growth

Nano based composites and formulations are potentially used in seed germination and plant growth technology to achieve the goal in promoting precision agricultural farming applications. TiO_2 nanoparticles and bulk metal oxide TiO_2 was treated with naturally aged spinach seeds to understand germination and growth (Zheng et al. 2005). It was reported that nano TiO_2 treated spinach seeds produced plants with 73% dry weight and 45% increased chlorophyll content along with 3 times increased photosynthetic rate compared to bulk TiO_2 exposed for 30 days. Therefore, the growth rate of spinach seeds is inversely proportional to nano size. Smaller size exhibits better photo-generation, photo-sterilization and germination. TiO_2 nanoparticles also promote oxygen and water intake for fast germination of seeds and effectively acts as stress resistant.

The penetration of nano based material and formulations into seeds are considered as an important key to increase the rate of seed germination and growth at faster rate. Researchers have reported that water and oxygen uptake by tomato seeds was increased; further germination and growth efficiency was found higher up to 90% on 20 days of exposure (Khodakovskaya et al. 2009). Study on metal nanoparticles such as palladium, gold at lower concentrations and copper, silica at higher concentrations and combination of gold and copper treated with lettuce seeds exhibited positive influence on seed germination (Shah and Belozerova 2009). Silica nanoparticles labeled with fluorescein isothiocyanate (FITC), Cadmium-Selenide (CdSe) quantum dots was used as bio labels, they are photostable and promotes seed germination. Nano aluminum facilitates and promotes the root growth of radish and rape. The rate of root growth depends on the type and concentration of nanoparticles used (Lanthanum (III) oxide, Gadolinium (III) oxide, Ytterbium oxide) on several crop yielding vegetative plants such as radish, rape, tomato, lettuce, wheat, cabbage, and cucumber.

10.2.6 Detection of Residual Pesticides

Food and Drug Administration (FDA) has reported, detection of more than 1045 residual pesticides in various food crops globally. Earlier gas or liquid chromatography mass spectroscopy techniques were used in the detection of

residual pesticides. Due to the recent advancements of nanotechnology in agricultural sector, nanosensors are used as a precised alteration in the detection of accumulated pesticides in various food crops (Stan 2000). Using Pesticide Data Program (PDA) analysis, U.S. Department of Agriculture (USDA) has evaluated more than 10,000 samples every year, which reported the accumulation of several organophosphates such as organochlorines, carbamates, triazines, triazoles, pyrethroids, neonicotinyls, strobilurins. Pesticide detection assisted with nanosensors has increased sensitivity, selectivity, responses and small sizes with accurate evaluation. Biosensors with nanomaterials like carbon, gold, hybrid titanium, gold-platinum and lead dioxide nanostructures are immobilized on sensor substrate enzymes are used in detection of pesticides with increased sensor sensitivity (Khot et al. 2012).

Nanosensors also act as an alert system, indicate farmers in usage, dosage limits and frequency of pesticides (eg: alert on color change of soil indicates nutrient deficiency). Nanomaterials also facilitates the degradation of detected pesticides (organochlorine pesticides) using nano-TiO_2 film through photocatalytic degradation, Rhenium (Re^{3+})-doped nano-TiO_2 degrades organophosphorus and carbamate pesticides in soil as well from tomato leaves (Rui et al. 2010). Nano biosensors promote smart field system as an effective tool in detection of bacterial, viral and fungal plant pathogens in its preliminary stages. Nano-chips (microarray) probes labeled with fluorescent oligo nucleotide are used in detection of single nucleotide changes in bacteria and viruses. Antibodies conjugated with fluorescent silica nanoparticles detect bacterial spot disease in Solanaceae plants caused by *Xanthomonas axonopodis* (Yao et al. 2009). Surface plasmon resonance (SPR) based nano-gold immunosensors used in detection of Karnal bunt disease in wheat crops. Modified gold electrode with copper nanoparticles monitors and measures the level of salicylic acid in oil seeds (*Sclerotinia sclerotiorum*) for the detection of fungi (Wang et al. 2010).

10.2.7 Nano Based Technologies for Water Quality

Requirement of clean water for human, animal, farming and industrial usage globally has become the most daunting challenge. It is estimated that over next two decades, clean water can be availed as only one third than needed for a person. This particular situation of water scarcity may condemn millions of people into premature death. Agriculture needs fresh water but in turn due to usage of excess pesticides, fertilizers and other agricultural chemicals the groundwater system gets polluted. Therefore, an effective measure is required on use of continual basis by farmers with cost effective new technologies (Vörösmarty et al. 2010). Nano-technology based research towards agricultural sector has provided various measures which are economically feasible. Nano based technologies deals with various aspects in maintaining water quantity and safety, e-treatment, decontamination, reuse, and conservation that occur through various human activities and natural leaching (Diallo 2009). Water contaminants also includes tens of thousands contaminants

from agriculture, pharmaceuticals, personal care waste products with several pathogenic microorganisms such as Cryptosporidium, Coliform bacteria, virus, etc. Also groundwater is polluted by radioactive contaminants that are produced naturally or during oil, gas production and mining (Chen and Yada 2011).

10.2.8 Nanoparticles in Microbicidal Action

Microorganisms disinfected through chemical and physical mode of actions, such as chlorine dioxide, ozone, and ultraviolet rays are an effective microbial disinfection systems. As pathogenic microbes are tremendously increasing, it requires an efficient, cost effective, infrastructure and alternate technology. Oligodynamic metallic nanoparticles, such as silver nanoparticles act as a promising nanomaterials along with bactericidal and viricidal properties (Nangmenyi et al. 2009). It has the mode of mechanism by increasing the production of reactive oxygen species (ROS) that cleaves DNA. This microbial disinfection is facilitated with photo catalytic effects of transition metal oxide nanoparticles, nanoporous fibers, and nanoporous foams. The cell wall of the microbes are disrupted during tubular nanostructures entry and further collapses the structural integrity, results in intercellular compound leakages and cell death (Li et al. 2009).

10.2.9 Nano Based Desalination

Conventional desalination technology requires large amount of energy to convert seawater into fresh water using reverse osmosis (RO) membrane technology. To overcome large energy consumption, nanotechnology based methods such as thin film nanocomposite membranes, aligned-carbon nanotube membranes and nano protein polymer biomimetic membranes are developed. Especially, carbon nanotubes exhibits excellent permeability of water than other nanomaterials and integrates with other functionalities such as disinfection, deodorizing, self-cleaning and de-fouling actions. Scale-up, fabrication, effective desalination and long-term stability are some of the technical challenges that should be sorted before its commercialization (Hoek and Ghosh 2009).

10.2.10 Nano Based Heavy Metal Removal Systems

Heavy metal contaminants that exist in high concentration can be effectively adsorbed through functionalization of ligand based nanocoatings that are bonded to the matrix. The matrix used in the treatment is regenerated and further bio-functionalized nano coated media is used in removal of heavy metals contaminants

(Farmen 2009). Crystal Clear Technologies – a startup company have demonstrated and proven that even by using the same matrix multiple layers of heavy metals can be bonded and accumulated within the matrix. Also, functionalized dendrimers are used in removal of heavy metals and ions by adhering with anions and cations based on acidity. Therefore, removal of heavy metals through nanomaterials from water contaminants along with water treatment system can be a boon to avail abundant, clean and fresh water which is "an elixir of life" (Diallo 2009).

10.2.11 Nanocomposites for Water Conservation and Precision Agriculture

Due to scarcity of water even for human consumption in various regions globally, many regulations and limitations are implemented for the usage of water in agricultural sector. It is a well-known fact that production of crops require large amount of water supply. Taking into account, scientists and engineers with an elaborate research have improved several solutions to enhance food crop production with minimal usage of water. New nano based technologies along with innovative ideas, such as drip irrigation (precise water delivery systems), water delivery and distribution near roots when required, enhanced water holding capacity, nano encapsulated release of water on demand, field intelligence through nano sensor distribution systems (Mamadou et al. 2008).

10.2.12 Nano Detection on Various Water Contaminants

Over the last decades, various contaminants in water are detected with several physio-chemical analysis and evaluations in laboratory as well as field application studies. Using the field of nanotechnology, number of sensing and prototyping devices are developed under lab scale level in detecting pollution, pathogens and contaminants present in water. These innovative nano based technologies are expected to be availed commercially in the global market in the next decade (Nightingale 2008).

10.3 Nanotechnology Assisted Animal and its Feed Production

Animal husbandry assisted with nano based technologies are developed to improve the nutritional requirements, feeding efficiency, to overcome disease with minimal losses, to modify animal waste into value added by-products (fertilizers and pesticides). Pathogens and toxins are removed with nanosized surface functionalized

nano additives. Nano feeds are used as animal food supplements fortified with rich antioxidants that enhances the immune system, maintains healthy cell and self-healing force which indirectly builds in disease resistant capacity of the animal. Therefore, administration of antibiotics is reduced along with improved utilization of phosphate, bone growth and development. These nano based feeds helps in reducing the rate of mortality (Chen and Yada 2011).

10.3.1 Nano Assisted Pig Farming

Dry zinc oxide nanoparticles, Fra ZN C4 (nanoproduct from Framelco, Raamsdonksveer, The Netherlands) is administered to young piglets to prevent diarrhea, it has better action and prevents weight loss by arresting dehydration. This nano coated dry zinc has enhanced activity even with administration of minimal dosage and does not affect the environment because only very less evacuation of zinc was found in excretion. Hence, accumulation of zinc in environment is minimized. Silver nanoparticles (Ag-NPs) is also used as additives in diet formulations for weanling pigs to protect digestive tract, gut and small intestine by reducing the microbial load (Fondevila et al. 2009).

10.3.2 Nano Assisted Poultry Farming

Ag-NPs are also used in broiler chickens along with feed as potential antimicrobial agent (Fondevila 2010). Presence of aflatoxin B1 and zearalenone are recovered from animal feed by monoclonal antibodies utilization against these toxic agents (Pineda et al. 2012). Nanoclays such as modified montmorillonite nanocomposite reduces deleterious effects of aflatoxin developed on poultry (Kim et al. 2012). Bioactive polystyrene nanoparticles developed by the US Department of Agriculture and Clemson University is used in chicken feed, they bound with harmful microbes and promotes the reduction of foodborne pathogens. Anabolic activities increased with nanobiotic silver and influenza virus are diagnosed with gold nanoparticles based evaluation kits (Woodward 2009). Silica nanoparticles incorporated with poly (hydroxyethyl methacrylate)-500 were prepared into thin films by binding with starch nanoparticles. These thin films with surface incorporation were effective against listeria bacteriophage such as *Listeria innocua* (Shi et al. 2006).

10.3.3 Nano Assisted Livestock Production

Agriculture production is mainly influenced by live stock animals and their reproductive performance globally (Kuzma 2010). In recent decades, nanotechnology assisted artificial insemination has gained more attention to increase the live stock

reproductive efficiency. Several nano assisted procedures are followed in improving the live stock efficiency such as fertility testing, semen purification. Nano based trials were carried out in identifying biomarkers such as sperm proteins ubiquitin, post-acrosomal and bull semen nano purification for commercial usage (artificial insemination) (Sutovsky and Kennedy 2013). Also nanotechnology has become a modern magical weapon to achieve desired satiety to fulfill hunger based on each individuals need in forthcoming decades. Nanofoods (meat) are exclusively developed for vegetarians without sacrificing animals. It is developed as high proteinaceous food but in in-vitro form as cultured meat or lab scale grown meat. However, the freshness of value added product availed from livestock can be ameliorated by use of nanoparticles mediated or incorporated edible coatings, laminates and flexible pouches (Verma et al. 2012).

10.3.4 Nano Aquaculture and Fisheries Farming

Aquaculture and fish farming have gained much attention towards food production globally. Farming of fish, crustaceans and mollusks are highly integrated with fish farming industries. They are exhibited as first among the population for the use of commercialized nano based products in order to produce high yield (Can et al. 2011). Nano based products have potential promising effects, maintains healthy fish farming by incorporating fortified supplements in fish foods (granules) and protects against diseases caused by pathogens. Iron nanoparticles fed to young carp and sturgeon enhances the growth rate (Zhou et al. 2009). Administration of nano selenium as supplement diet improved glutathione peroxidase activity, antioxidant status, weight gain and muscle concentration of crucian carp (*Carassius auratus gibelio*) (Rather et al. 2011). Direct usage of Ag-NPs was found toxic in young trout but Ag-NPs coated on water filter for indoor farming prevented fungal growth and infection on rainbow trouts (Johari et al. 2013).

Nanosensors are used in detection of pathogens and nano purified water can be used for irrigation of fish cultures (Handy 2012). Iron–manganese oxide nanoparticles and Calcium–alginate nano polymer are effectively used as sorbent (Bezbaruah et al. 2014) in removal of arsenic (III) and arsenic (V) that are present in any form of water resources (Kong et al. 2013). Nutrient supplements such as vitamins, lycopene, and omega fatty acids required for healthy fish farming are efficiently delivered with nanocochleates (Jha et al. 2011). Researchers have successfully developed vaccines using nanoencapsulation technique against white spot syndrome virus in shrimp (Kumar et al. 2008) and bacterial infection in Asian carp by *Listonella anguillarum* (Rajeshkumar et al. 2009). An oral plasmid DNA vaccines are developed using chitosan nanoparticles as a promising nanocarrier system (Kumar et al. 2008). For example, chitosan/pDNA orally administrated against *Vibrio parahaemolyticus* to induce antibody immune response in fish (Li et al. 2013).

10.4 Regulations in Agro-Nanotechnology

The consideration of regulatory bodies decides the success of the nanotechnology in the agriculture and related vista. Regulatory approaches and assessments are not specific for nano-agriculture materials but it is certain for all the nano-based applications in food and related sectors. Legalized framework is essential to manage the potential impacts on safety, adverse effects, risk assessment and protects the consumers. Industries, governmental and non-governmental agencies are showing interest towards nano-based agriculture since nanotechnology has the potent to innovate the agronomics and food sector. Few nano-agricultural applications that are merchandised are shown in Table 10.1.

There are worldwide legislations, recommendations and guidelines to address and regulate the nano-based products. The regulatory bodies active in this vista are European Union Scientific Committees and Agencies (EUSCA), Joint FAO/WHO Expert Committee on Food Additives, Joint FAO/WHO Meeting on Pesticide Residues (JMPR), Organisation for Economic Co-operation and Development (OECD), The International Organization for Standardization (ISO), or The Food and Drug Administration (FDA or USFDA). According to OECD, European Union and Switzerland have successfully established legislative provisions for specific nanomaterials in agriculture while other countries have developed non-mandatory frameworks with non-legal guidance (Amenta et al. 2015). Regulatory bodies

Table 10.1 Merchandised Nano-agricultural products

Product name	Company name	Country	Area of application
NASCO Bio NPK fertilizer	Nano Agro Science Co-operative Society Limited	India	Fertilizer
Tag-Nano	Tropical Agro	India	Fertilizers, pesticides, insecticides
Karate with Zeon Technology	Syngenta Crop Protection, LLC	USA	Pesticides
Nano Metsulfuron Methyl 20% WP	Shri Ram Agro Chemicals	India	Herbicide
Nanozim Eco Granules	Biostadt India Limited	India	Plant growth regulators
Nano Reef fish food	Ripples Water lifes	UK	Fortified fish food
Dennerle Nano Granfish food	Pro Shrimp	UK	Growth and increased resistance to illness
JBL Chips Nano Crabs	Japankoi	Japan	Main food chips for dwarf crayfish
FRA® 2C4	FRAmelco	Netherlands	Stimulates gut development, reduces health problems and improves animal performance
NANOTEC® 5-in-1	Nano Silver Manufacturing Sdn Bhd.	Malaysia	Water purification

function is to define the terms for nano-based materials such as nanomaterials, nanoparticles, nanoencapsulation, nanoemulsion etc., and helps in registration, evaluation, and authorization of protocols, assess and manage the risk factors, and standardize the provisions to increase the transparency and traceability of nano-based products for its commercial usage. The main aim of the regulatory approaches are to regulate and ensure safety use of the products. These rules and regulations are highly stringent and open to consumers' opinions. These regulatory bodies not only focus on registration and authorization but also implements precautionary approaches based on the risks, economy, benefits and public interest. Since, the application of nanotechnology helps in evolving advanced new generation products in the market, existences of proper assessments based on scientific findings proving the safety and regulatory actions are of high priority. Already nano-based products are entering the international trade and most of them are available via interconnected networks. Moreover, regulatory bodies are coming under one roof for developing harmonized approaches, to define the nanomaterials, market the product, develop standardized protocol to assesses and manage the risk, harmonize the guidance and safe use of the product.

10.5 Health and Environmental Concern

Exposure to nano-based materials is an antediluvian problem because *Homo sapiens* are exposed to nano sized materials since the primeval times to modern era through forest fires, volcanic ash, ocean spray, the radioactive decay of radon gas and other anthropogenic sources. In general, consumers and research communities fear for nanomaterial toxicity, residue carry-over of nanomaterials and adverse side effects. This is due to insufficient knowledge of physicochemical properties, systemic pharmacokinetics, toxicokinetics and toxicodynamics of the nanomaterials. Nanomaterials enter the biological system via inhalation, ingestion and skin; many studies on the various mechanism of eliminating or filtering these nanomaterials are carried out (Mukherjee et al. 2016). The benefits of nano-based products countermand by the pitfalls, efforts that are made to evaluate the compatibility and suitability of integrated approaches of agri-nanotechnology. Currently, academia and researchers are enduring to fill the knowledge gaps regarding the toxicity kinetics and dynamics of nanomaterials towards the ecosystem. In general, when nanomaterials are released to the biospheres, they are subjected to interactions with abiotic and biotic systems and get transformed or modified. Based on the modifications, property, distribution, concentration, mobility, and effects in the environment will be determined. Figure 10.2 illustrates the perspectives of agro-nanotechnology.

Researchers are carried out to understand and scrutinize the interactions and functional knowledge of the nanomaterials released into biospheres and agricultural activities. These findings contribute to the permissible level and tolerable safety limits of the nanomaterials in the ecosystems. The main driving force for crop production in agriculture is plant-soil interaction, which is affected by the physico-

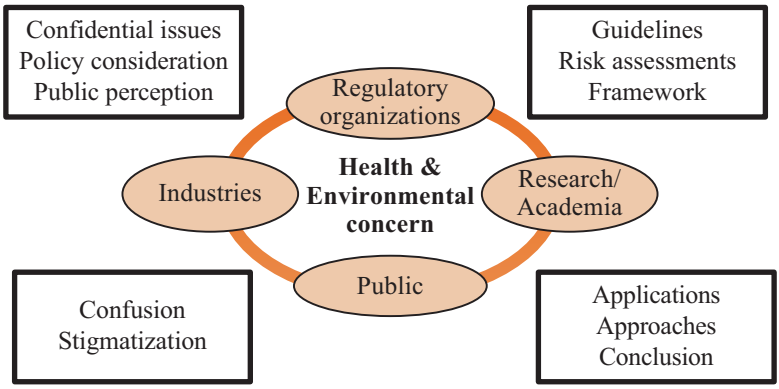

Fig. 10.2 Health and environmental perspectives of agro-nanotechnology

chemical nature of the soil. In agriculture, soil is the paramount component for the release of nanomaterials and hence, these nanomaterials will have subsequent interactions with biological system and other components which will have vigorous impact on the behavior, fate, and ecological effects of the nanomaterials. Therefore, the soil environment must be subjected to ecotoxicity studies with nanomaterials in order to determine the prolonged effects of the system. Indeed, it is necessary to analysis the basic risk assessment during the interactions of nanomaterials with plant, soil, and soil related biological system.

10.6 Future Recommendations

Nanotechnology has a promising application in all vistas, especially in agriculture and allied sectors. The negative perception and uncertainty in employing nanomaterials in agricultural sector has to be considered and necessary steps shall be taken to provide possible solutions. In this context, following key recommendations are suggested for future research:

- A comprehensive and standard international definition for nano-based materials is needed. Efforts are under progress to implement a perspicuous definition globally.
- Prove the validity or accuracy of the techniques to detect and characterize the nanomaterials in food and ecosystems. Permissible levels of nanomaterials concentration and dosage along with its safety profile is in need to be explored, clarified and validated.
- A comprehensive knowledge on nanotoxicity studies along with transgenerational epigenetic inheritance and interactions in food chain shall be understood since it could provide adequate safety assessments.

- Nanomaterials toxicity kinetics and dynamics differs from materials to materials. Therefore, its exposure and behavior in the agroecosystems is still unclear, further research is needed.
- The future research shall be emphasized towards the transport, transformations, and fate of nanomaterials in model agroecosystem and information regarding the release, distribution, modifications, and bioavailability of nanomaterials need to be envisaged.
- A collaborative and integrated research is needed to understand the effects of nanomaterials in the environment and human health at molecular and mechanistic level.
- Nano education programmers shall be organized by the industries and regulatory bodies to enhance the awareness of nanotechnology.

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Chapter 11
Bio-synthesized Nanoparticles as Photo-catalysts for Destruction or Degradation of Toxic Species

K. Anand, K. G. Moodley, and A. A Chuturgun

Abstract The biosynthesis of metal nanoparticles using plants has received considerable attention as a suitable alternative to using hazardous chemical and physical techniques. Plants are being exploited for their unique metal tolerance and effective production of metal nanoparticles. A single plant contains a multitude of chemical elements (e.g. proteins, vitamins, enzymes, amino acids, polysaccharides and other organic compounds) that are "environmentally benign, yet chemically complex" and therefore serve as ideal tools for enhanced medicinal and catalytic applications. It has been reported that polyols such as terpenoids, polysaccharides and flavones take part in the bio-reduction, stabilisation and bio-capping mechanisms to form stable metal nanoparticles. This chapter focuses on the photocatalytic activity of phyto-synthesised metal nanoparticles and their applications to degradation of toxic and potentially toxic organic compounds to benign by-products.

Keywords Green synthesis · Nanoparticles · Dye degradation · ZnO NPs · AuNPs · Pd NPs

11.1 Introduction

11.1.1 General Features of Nanotechnology

'Downsizing' is a term used family in circles to describe a change in mode of living which involves the move from large and spacious homes, with an array of amenities which require constant care and attention, to small living units requiring major adaptations from the occupants. The rationale for this choice is that smaller units

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_11

require less expenditure of energy to maintain. In other words less 'activity' will be displayed by the occupants of such small units. If we consider the concept of downsizing in the world of physics and chemistry, the 'activity' or more appropriately the 'reactivity' will generally increase quite tremendously. If we further restrict the concept to the size of metal particles, 'downsizing' has given rise to a revolutionary branch of science known as nanotechnology which has led to a fitting motto: 'the smaller the better'. The belief in this concept has been the driving force in motivating many researchers working in diverse fields to include an aspect of nanotechnology in their research projects. There may be a myriad reasons for the surge of interest in research involving nanoparticles. If one was asked to give a single fundamental reason for the ever-growing research based on nanotechnology, it has to be the relation between surface area and reactivity. Reactivity is also enhanced by the presence of catalysts which, in many instances, are 'precious' metals. Since nanoparticles of these metals can be more efficient as catalysts, very small amounts of these metals will suffice to provide the total catalytic activity required for any particular application. In view of the very high costs of most precious metals, their uses in nano forms is a win-win case for researchers who can use inexpensive methods of generating the nanoparticles from precious metal salts. A relatively low-cost method for generating nanoparticles from metal compounds involves the use of plants. If the appropriate conditions are used, nanoparticles capped with phyto-moieties can be synthesized. The following aspects of nanotechnology and related fields will be described and or discussed in this introduction: outlines of methods of generating metal nanoparticles of single metals, green chemistry approach to generating nanoparticles, catalysis by nanoparticles, pollutants in wastewater and degradation of dyes in wastewater.

11.1.2 Outlines of Methods of Synthesis and the Requirement of Green Chemistry

Nanoparticles can be generated by physical, chemical or biological methods (Iravani et al. 2014). Physical techniques involve inter alia, laser oblation and sputtering (Hatakeyama et al. 2011). Chemical methods (Manikam et al. 2011) employ reducing agents while biological reagents (Mokhtari et al. 2009) emanate from parts of plants including barks of trees (Bahram and Mohammadzadeh 2014), bacteria (El-Deeb et al. 2015) and fungi (Shaligram et al. 2009) to name a few sources. The robust nature of some physical methods implies that it may be difficult to get particles of the same or very similar sizes. Experimental results indicate that the opposite may be true in some cases (Song et al. 2011). Chemical routes may introduce undesirable by-products into the reaction vessel. Reductants from biological sources are likely to give 'clean' reaction and produce particles of similar shapes and sizes. Furthermore the use of plant materials as reducing agents incorporates the best features of 'green' chemistry practices. In a review article (Anastas and Eghbali 2010),

the 12 principles of green chemistry are listed. Since we did not seek permission from the publishers to reproduce them here, we offer two statements which, we believe, cover the main requirements of green chemistry:

- Use natural materials and reagents from nature, wherever and whenever possible
- Avoid actions which would pollute the different compartments of the atmosphere with materials which are toxic or potentially toxic or eco-unfriendly

With respect to the second point above, the dumping of over-ripe fruit which is not suitable for sale is a good example of eco-unfriendly action. However in the case of some fruits (Deokar and Ingale 2016), the so-called waste may be used as source of reductants for generating nanoparticles from metal salts. In illustration of this point, it may be stated that bananas, which are indigenous to several developing countries, tend to over-ripen or become 'mushy', soon after they ripen. They cannot be sold as fruit for human consumption. However they serve as an excellent source of reductant to produce nanoparticles from metal salts, for example.

A very noteworthy point about green synthesis of metal nanoparticles is that the potential exists for moieties from plants to adsorb onto the nanoparticles to yield species (Renata 2016) with enhanced catalytic power. This should be the case for species which incorporate metal particles with innate catalytic property. The future scope for isolating phyto-catalysts, for a variety of applications, is enormous because of the myriads of plant species which have the potential to be the sources of reductants and capping agents. In addition, different parts of a given plant may be used for the functions described above (Jobitha et al. 2012; Anupama and Madhumitha 2017). To give credence to these statements a small sample of the parts of plants for the synthesis of silver nanoparticles is shown in Table 11.1 below.

11.1.3 The Importance of Metal and Metal Oxide Nanoparticles as Photocatalysts

It is well-known that catalysts speed up reactions but it is not so well known that catalysts also kick-start some reactions and influence the pathways of some other reactions. Since contact with the starting materials is an important step in catalysis, the large surface area of nanoparticles is a highly helpful property. The application of nanoparticles in photo-catalysis is very important for solving domestic and industrial problems. To describe and discuss the properties and or suitabilities of selected nanoparticles as photo-catalysts, the following brief background is given:

11.3.1 First and foremost, the chosen material must have the capacity to absorb light or more specifically the energy from a light source.

11.3.2 The light source could be natural (sunlight) or artificial (so called white light from an incandescent source).

Table 11.1 Parts of plants used in producing Ag and Au nanoparticles

Name of plant	Part of plant used	Bio-Activity if reported	Ref. no.
Moringa oleifera	Flower	Anticancer	13
Arbutus unedo L.	Leaf	–	14
Cassia auriulata	Flower	Antimicrobial	15
Etelcardmomom L.	Seed	Antibacterial	16
Medicago sativa L.	Sprouts	–	17
Citrus sinensis	Peel	Free radical scavenger	18
Curcuma longa L.	Tuber	Bactericidal	19
Cocos musfera L.	Coir	Larvicidal	20
Ficus racemosa L.	Bark	Larvicidal	21
Rosa damascene	Petals	–	22
Smilax china L.	Root	–	23
Zingiber officinale	Rhizome	–	24
Jatropha curcas L.	Latex	Antimicrobial	25
Psoralea corylifolia L.	Resin	–	26
Euphorbia nivulia	Stem latex	Toxic	27
Triticum aestivum L.	Seedlings	Peroxide catalytic activity	28
Rhizophora mucronata Lam.	Leaf buds	Antibacterial	29
Shorea robusta Roth.	Stem bark	Antimicrobial	30
Solanum xanthocarpum L.	Berry	Anti-microbe & uriase inhibition	31

11.3.3 The absorption of light energy must result in the formation of energised electrons on the surface of the material and resulting holes with the body of the material. Stated differently this means that the electron is promoted from the valence band to the conduction band.

11.3.4 The duration of existence of the electron-hole pair is dependent on the size of the particle. The duration increases with decreasing size of the particles.

11.3.5 The ease of promotion of the electron from the valance band to the conduction band is dependent on the energy separation between the two levels known as the band gap.

11.3.6 The band gap may be decreased by doping; for instance, it is has been shown (Anand et al. 2015) that the band gap was lowered for TiO_2 nanoparticles which were doped with tungsten.

As an illustration of the application of nanoparticles as photo-catalysts, it is noted that nanoparticles of TiO_2 are used in air purifiers in the presence of UV light to convert organic pollutants into less harmful carbon dioxide and water (Han et al. 2009; Kandiel et al. 2010; Thiruvenkatachar et al. 2008). It is called photo-catalysis because a photon is needed to initiate the whole process. The photon is supplied by UV light which is a part of sunlight or it can come from an artificial source such as an UV lamp. The function of the photon is to cause the movement of an electron from the valence band to the conduction band of the metal oxide. When electrons collide with H_2O molecules (in the form of vapour) in air, the energised electron cause the water molecule to split to yield free hydroxyl radical with very high energy.

In air purification, these hydroxyl free radicals react with organic molecules to give relatively less toxic carbon dioxide and water and as products. If the nanoparticles used in photo-catalysis are synthesised by 'green chemistry principles' (Karpovich et al. 2015a, b; Yu et al. 2016; Xin et al. 2014; Ramakrishna et al. 2016; Devi and Ahmaruzzaman 2016) then it is a genuine 'win-win 'application of photo-catalysis. Green sources of reductants are, inter alia, parts of plants such as leaves and fruits. Another environmental problem, for which these types of catalysts are needed, is in waste water treatment (Konwarh et al. 2011).

11.1.4 Pollutants in Wastewater

Pollutants in wastewater are of myriad types; which makes classification a great challenge. To get a global idea of which pollutants are in wastewater, we may use broad categories. Taking solubility as a basis, the pollutants may be soluble, partly soluble and insoluble. The latter could be removed by filtration methods. The other two fractions have a range of polarities from very low to very high. In a general scenario, wastewater treatment involves, in the main: filtration, sedimentation / coagulation (to remove suspended matter) and disinfection (to destroy organisms and some chemical pollutants). Although ozone may be preferable, chlorine is more commonly used on account its lower cost. However, the by- products of chlorine with pollutants are regarded as carcinogenic (Sathishkumar et al. 2010). A group of pollutants which pose major challenge to treatment of wastewater are dyes and pigments (Roopan et al. 2013) which emanate from various activities. The major users of dyes are textile industries which also use relatively large volumes of water in their processes. Thus the wastewater from textile industries may have relatively small amounts of dyes. In the light of this, the degradation of small quantities of dyes appears to be easier than finding methods for removing the dye. Several methods may be used for the degradation of dyes; but the use of photocatalysts (Velayutham et al. 2013) appeals on the grounds of simplicity. Furthermore, catalysts of 'capped' nanoparticles, produced by reduction of selected metal salts utilizing reductants from parts of benign plants, are likely to effect the degradation in an eco-friendly manner.

11.1.5 Green Synthesis of Metal Nanoparticles by Using Extracts from Plants

The role of plants in synthesizing metal nanoparticles will be reviewed in this section. The applications of these nanoparticles will be described; with special emphasis on nanoparticles which catalyse reactions, in general, and those that catalyse the degradation of pollutants in water, in particular. Furthermore the review will be confined to three recent reports so that the reader may use the references therein to find

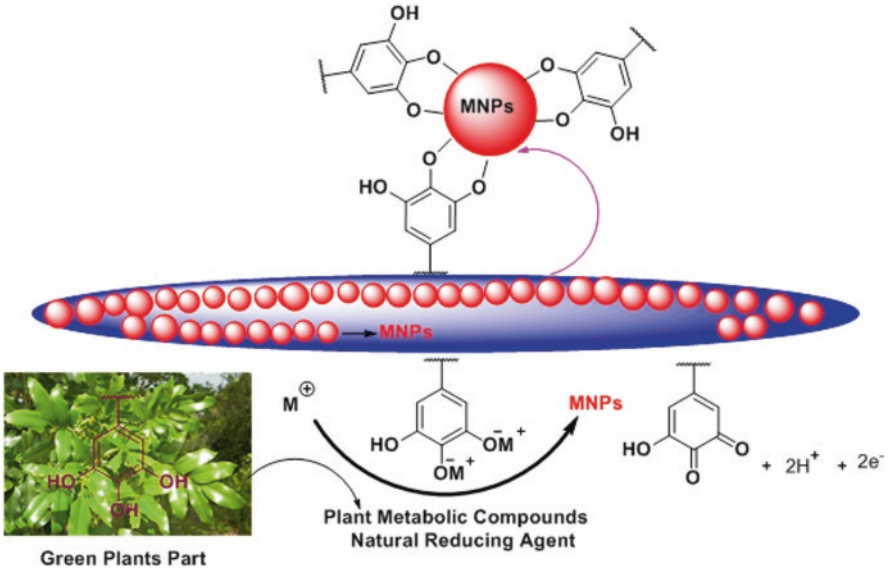

Fig. 11.1 Mechanism involved in the formation of metal nanoparticles

earlier reports. The metals and metal oxides selected for review are: Ag, Au, Pt, Pd, ZnO and TiO_2. The rationale for choosing these elements arises from their positions in the periodic table of elements as well as their wide use as catalysts, in their bulk forms, in many reactions. The oxides of zinc and titanium have been included in the light of their usefulness as photo catalysts for waste water treatment (Kalpagam and Kannadasan 2014; Kouvaris et al. 2012; Thema et al. 2016). The illustration below (Fig. 11.1) shows what happens in a typical case of phyto-mediated or green synthesis of nanoparticles:

11.1.6 Silver Nanoparticles

An aqueous extract of *Annona muricata* fruit was used to produce (Bar et al. 2009; Shaniba et al. 2017) silver nanoparticles. In vitro assays and determination of phenolic content led the reporting researchers to conclude that the nanoparticles, synthesized under these conditions, possessed anti-oxidant properties. They also reported that the nanoparticles showed photocatalytic properties; in that methylene blue was degraded by the nanoparticles in the presence of sunlight. An aqueous extract of leaf of *Coleus aromaticus* was used. (Ramkumar et al. 2016; Gardea-Torresdey et al. 2003; Jha and Prasad 2011) to generate silver nanoparticles. Tests showed that the silver nanoparticles formed in this manner were able to kill larvae of malaria-causing mosquitoes. If this finding can be scaled for use in large water bodies it will obviate the need to use toxic chemicals as larvicides. Silver nanoparticles

synthesized by employing an aqueous extract of *Alternanthera sessilis* under sonication conditions (Sathishkumar et al. 2016; Solgi and Taghizadeh 2012; Gnanajobitha et al. 2012), have been assessed for their efficacy in treating breast cancer. They were found to superior to cisplatin for the same purpose.

11.1.7 Gold Nanoparticles

Gold nanoparticles have special importance because of their biocompatibility in general and their tolerance by the human body in particular. They thus have many applications associated with the health of humans. For instance, gold-capped teeth have been in vogue from time immemorial. The applications of gold nanoparticles are, inter alia, drug delivery, bio-sensing, bio-imaging, tumour imaging, anti-microbial activity, gene delivery and bio-assaying (Chattoraj et al. 2016; Patil and Kim 2017). Of all the methods for synthesising gold nanoparticles, the ones using parts of non-toxic plants and fruits are not only inexpensive but they are also eco-friendly. Examples of this are uses of: fruit *Piper longum* (Kumar et al. 2012; Nakkala et al. 2016); photo synthesis of gold nanoparticles from $HAuCl_4$ by reduction with extract of leaves of *Mappia foetida* (Kora and Arunachala 2012; Mata et al. 2016). The Au nanoparticles were conjugated with activated folic acid. Together with doxorubicin complex, the combination was seen to destroy cancerous cells. They role of the activated Au nanoparticles was to act as a carrier of the doxorubicin to cancer cells (White et al. 2012). This is a prime example of drug delivery listed above as one of the many applications of gold nanoparticles in amelioration of human illnesses.

11.1.8 Platinum Nanoparticles

Platinum metal in the form of thin plates or sheets and as fine wires have been used and continue to be used as catalysts for many reactions. A very simple reaction such as the oxidation of CO to CO_2 proceeds faster when catalysed by Pt metal in its bulk form. However, the nano-sized forms of the metal are expected to have enhanced catalytic activity on the grounds of increased surface area of the nanoparticles. This has been found to be the case for nanoparticles synthesised from platinum compounds using plant material as sources of reductants (Tahir et al. 2017). When *Fumariae herba* was used (White et al. 2012) as reductant, nanoparticles of about 30 nm were obtained. These nanoparticles were shown to catalyse the degradation of two dyes (methylene blue and crystal violet). In the case of cresol red it was found that addition of the plant extract in water caused a significant reduction in the amount of dye. Addition of nanoparticles was found to accelerate the process. This suggests that the herb is capped on to the nanoparticles and enhanced reducing power is due to the larger surface area afforded by the nanoparticles. Another study (Amin et al. 2012) using the plant, *Taraxacum laevigatum* (reputed to have high

medicinal properties) claims that the nanoparticles were capped by a plant-moeity capped and that these nanoparticles act strongly against both gram positive (*Bacillus subtilis*) and gram negative bacteria (*Pseudomonas aeruginosa*) .

11.1.9 Palladium Nanoparticles

Palladium in its bulk form has long been used as a catalayst for many organic reactions (Hemalatha and Madhumitha 2015; Hemalatha et al. 2013; Roopan et al. 2014). Purportedly, the first report (Prashanth et al. 2011; Sheny et al. 2012; Zhan et al. 2011) of the use of a biomaterial for the synthesis of palladium nanoparticles involves an extract of the bark of *Cinnamon zeylancium.* The reduction of palladium II chloride to palladium metal has been attributed to terpenoids present in the cinnamon bark. Another green synthesis of palladium nanoparticles was done (Valodkar et al. 2011) by employing the extract of leaves from *Anacardium occidentale* to reduce Pd II to palladium nanoparticles with sizes below 5 nm. The reducing species in the extract has been identified as polyols whereas the capping moieties have been deduced to be carboxylate and proteins.

The plant, *Cacumen Platycladi,* has been used (Savithramma et al. 2011) to synthesise nanoparticles comprising Pd and Au by reducing a mixture Pd (II) and Au (III) with an aqueous extract of the plant. It appears that plant moieties were responsible for both reducing and stabilizing functions in process of generating bimetallic Au-Pd nanoparticles. No comments on the possible synergistic effects from the linking of two different metals were given in the report.

11.1.10 ZnO nanoparticles as Photo Catalyst

The element zinc is one of many metals needed in trace amounts for the proper functioning of the human body. Zinc is needed, inter alia, to aid in blood clotting, and healing of wounds. Zinc is present in many foods consumed daily. Common source of Zn are red meat, nuts, beans and oatmeal. To ensure that we get sufficient Zn in our food intake some processed foods contain trace amounts of Zn added as crystalline ZnO. It is worth noting that the addition of ZnO to foods has the approval of the United States of America Food and Drug Administration department. In terms of scientific needs, the prime aspect, for which ZnO is well-known, is its behaviour as an n-type semiconductor (Karpovich et al. 2015a, Karpovich et al. 2015b). The secondary aspects, namely, optical and electrical properties have led to many current uses (Ahmed et al. 2014; Omri et al. 2016; Roopan and Khan 2010) of ZnO and hold the potential for other applications in the future. These properties are expected to be accentuated with decrease in size of the particles to nano dimensions. As mentioned above crystalline ZnO is added to processed food as health benefit, the nano particles of ZnO have been recommended (Yu et al. 2016; Hong et al. 2009; Madhumitha et al. 2016) as an additive in food packaging material to serve as

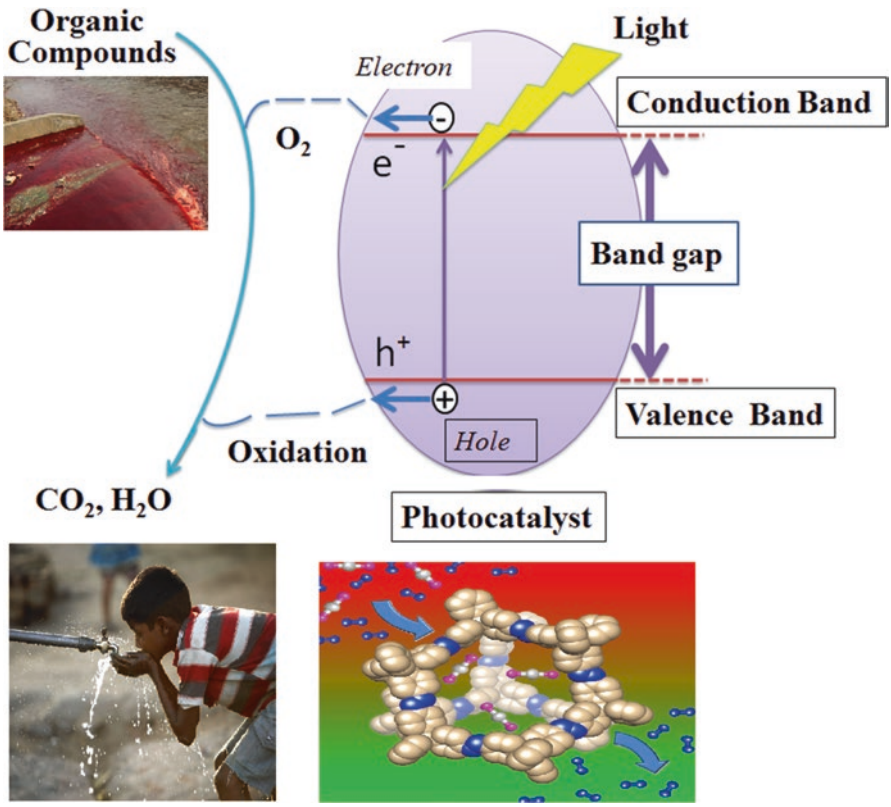

Fig. 11.2 Proposed mechanism for photo-catalysis by phyto synthesised ZnO

an anti-bacterial agent. A particular application (Xin et al. 2014; Roopan and Khan 2010; Espitia et al. 2012; Fowsiya et al. 2016) of ZnO nanoparticles, which is of great relevance to this chapter, is in the field of photo-catalysis. In this regard, the semiconductor properties ae exploited. Further to the points made in Sect. 11.3, it needs to be said that the band gap and its variations with changes need to be considered in assessing the efficiency of photo-catalysts. It appears that this is affected by the method of synthesis and conditions used. The illustration (Fig. 11.2) indicates that the above observations are not too far-fetched.

11.1.11 TiO_2 nanoparticles as Photocatalysts

TiO_2 has been an important resource for the paint industry ever since it was accepted as the whitener of choice in paint manufacture. Titanium dioxide exists in three crystalline forms: rutile, anastase and brookite. Anatase and brookite and mixtures of anatase and brookite have been used to produce nanorods which were found (Ramakrishna et al. 2016) to be highly-active photo-catalysts.

An application where photo-catalysts are extremely useful is in the degradation (Devi and Ahmaruzzaman 2016) of dyes in waste-water. Some of the dyes, for example azo dyes, are known to be carcinogenic. Since degradation produces by products, there is a need to analyze the by-products. If one of the by-products is an amine, which is a carcinogen then the degradation is counter-productive. Of the three known forms of Titanium dioxide, the anatase form is used more frequently for photo-catalyst preparation because is band gap varies with the conditions under which is generated. A further improvement in band gap was achieved (Kanchanamayoon 2015; Elango et al. 2015) by doping the anatase with tungsten isopropoxide to yield nanoparticles with composition TiO_2 / WO_3. Since WO_3 is a semiconductor in its own right, the combination enables the photo-catalyst to be activated by light in the visible region.

11.1.12 Conclusion

This chapter described and discussed the syntheses and applications of nanoparticles of selected metals and metal oxides. All the syntheses described herein were phyto-mediated, that is, the sources of reductants were from plants and their products. The over-riding principle was that all syntheses were achieved by using untainted green chemistry. The advantages of this system are:

- Simplicity
- Relatively low cost
- Clean separation of product from reactants

In some cases a further advantage is that the plant material 'adsorbed' onto the metal or metal oxide to give a 'capped' product. The latter is credited with catalytic activity or enhanced catalytic activity of the 'capped species. Furthermore, some metal capped nanoparticles behave as antifungal, antimicrobial, antibacterial and larvicidal.

The use of metal oxides with semi-conductor properties in generating nanoparticles leads to products which display photo-catalysis. The efficiency of the photo-catalysis can be improved by:

- changing factors which reduce the band gap
- by doping with other metals or metal oxides
- using light wavelength which absorbed more than others

What are the benefits of green synthesis for the food sector? There are many gains for producing healthy foods free of toxic chemicals. The most important one of all, is that green methods of syntheses minimize the amount of pollution in the environment generally and in air, water and soi,l in particular. If pollutants enter any one of these parts of the environment, they will eventually enter the human body via the 'food chain'. The most frightening aspect is that pollutant concentrations increase along the food chain. Also there is the cycle for some chemicals which are used as pesticides in agriculture. These chemicals are meant to kill pests

which destroy crops. It is very difficult to control the amounts of pesticides used. The residual pesticides may enter water bodies such as farm dams through rainwater. The use of the water from these dams for growing crops will allow the residual pesticides to enter plants and thus continue the cycle. In the light of these considerations, the use of 'green pesticides' to control organisms which threaten food crops will be a great contribution to 'food security'.

Although catalysis using nanoparticles have shown tremendous promise in meeting ravages of diseases caused toxic chemicals, there are challenges to be met and overcome. They are inter alia:

- the scaling up the syntheses from laboratory scale to pilot plant scale
- from pilot plant scale to industrial scale / agricultural scale
- finding ways to increase the turnover number for the phyto-synthesized catalysts.

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Chapter 12
Toxicological Studies and Regulatory Aspects of Nanobased Foods

Asaithambi Kalaiselvi, Ravichandran Rathna, and Ekambaram Nakkeeran

Abstract Nanotechnology is a major breakthrough technology that expanded its wings in several dimensions of life. Nanoscale materials found to have a wide range of applications in food sectors by enhancing the palatability, flavor, taste, micronutrient protection and shelf life of the food products. The market of nano-based food products are increasing at an immense rate but uncertainty on safety and risk is also emerging. The current regulatory framework for nano-based food products developed by Europe, United States, and Asia are eager to capture nanotechnology food products. In this chapter, toxicity studies of nanomaterials and knowledge gap between nanoscience and nanotechnology in the food sector are discussed. An overview of nanostructures, potential risk and future perspective of nanomaterials in food sciences is also discussed.

Keywords Nanomaterials · Risk assessment · Toxicity · Food stores Nanoparticles

12.1 Introduction

One of the major breakthroughs in applied biosciences is nanotechnology, opened up new arrays of prospects and opportunities that serve as the cradle for the industrial sector (Singh et al. 2016). In recent decades, nanosciences and nanotechnology have progressed to the next generation phase by elaborating its wings in several dimensions of life, from nanomaterials to smart nanotechnology such as RFID - Radio-frequency identification barcodes (Chaudhry and Castle 2011). Nanotechnology is already in reality in various fields such as electronics, medicine (Aslan et al. 2005), textile (Yetisen et al. 2016), communication (Dressler and Kargl 2012), energy production (Guo 2011), defense (Glenn 2006) and food industries

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© Springer International Publishing AG, part of Springer Nature 2018

S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_12

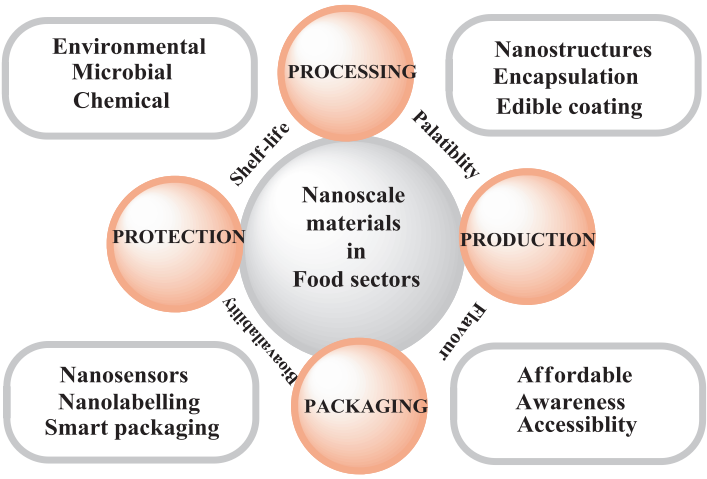

Fig. 12.1 Applications of nanoscale materials in food sector

(He and Hwang 2016). The application of nanotechnology in food sectors is regarded as a new frontier technology that has its mere impact in future (Pradhan et al. 2015; Ravichandran 2010). According to Plunkett Research 2016, the global food and agricultural industry was about an $8.0 trillion market which is almost 10% of the world's GDP. It becomes obvious to generate food sector revenue, the agriculture and food industries continue to progress rapidly for exploring novel products by determining consumers requirements (Ravichandran 2010). Nano-related foods are gaining momentum in developing food science research and offer a wide range of benefits to the industries and consumers (Ravichandran 2010). Nanoscale materials are used in the food sector to enhance several applications in food processing, production, packaging, and protection which is illustrated in Fig. 12.1. Thereby, consumer's procurement and consumption of nano-based food were augmented to intensify the texture, palatability, bioavailability and shelf life (Sekhon 2010).

Nanomaterial incorporated consumer products have been raised much interest in global market compared to last few years (Chaudhry and Castle 2011). Nano-based food and health fitness products have formed the largest category of goods procurement followed by electronics and home appliances. This application based process is initiated from particulate synthesis process from past decade through extensive research. In 1997, about $432 million was supported by the research and development of nanotechnology and the contribution was increased in nine folds in 2005 which is around $4.1 billion (Roco 2007). In 2006, The Institute of Food Science and Technology from the United Kingdom conducted a worldwide survey, estimated and identified that more than 200 companies majorly involved in various applications of nanotechnology (Buzby 2010). Countries like United States, Japan, European Union and China are mainly contributing their research and development in food applications. In 2008, Cientifica reported that about 400 companies involved

and initiated their use nano applications in food processing industries (Chaudhry et al. 2008). The nanotechnology research group estimated in 1996 reported that nano-based food products would reach the international market more than $1 trillion by 2015 (Buzby 2010). A study revealed that the global market on food and beverage packaging products sector would alone raise almost six-fold in the period of 2 years from $150 to $860 million in the year 2002 to 2004 (Buzby 2010). In 2016, 20 participating Federal departments, independent agencies, and commissions requested about $1.5 billion to brief the development of nanoscale science, engineering, and technology (nano) research and development (R&D) (Bhushan 2015). According to Persistence market research 2014 estimates a compound annual growth rate of 12.7% would reach about $15 billion in 2020 (Bumbudsanpharoke and Ko 2015).

Researchers initially focused on developing nanovesicle to enhance the bioavailability of bioactive compound at the targeted site in a low dosage form (Watkins et al. 2015). Taking this into account, researchers developed vital nutrient fortification to overcome individual's daily nutritional needs by considering the permissible limit. Primarily food endures bio-mitigation during its processing that affects its chemical and physicochemical nature (Ravichandran 2010). In order to prevent this, nanomaterials with unique structural properties were used to influence the product from initial stability to final biotransformation in the human body when ingested (Özer et al. 2014). The unique physical, chemical and biological properties of the nanostructures which are significantly different from its original bulk form, and make it ideal for its potential application in the food sector (Armentano et al. 2014). Nanostructured materials like nanocomposite, nanoemulsions, and nanoencapsulation help in improving the shelf life, color, taste, flavor, safety level and nutritional values of the food products (He and Hwang 2016). These nanomaterials are extensively used in food packing due to its barrier properties, mechanical properties (flexibility, durability), heat and moisture resistant properties and biodegradability (Yang 2007). Nanomaterials are also used to enhance antimicrobial effects, prevent and detect food spoilage via nanosensors and labeling (He and Hwang 2016; Ravichandran 2010).

The rapid advancement in nanotechnology in food sector has led to the development of innovative novel process and products for human society but considerably suffers from health, safety, and regulatory issues (Ravichandran 2010). Thereby, the major challenge is to formulate and produce the nano-based product that is economically feasible and safe for human consumption. There are regulatory bodies in the world to formulate the rules and regulations for nano-based materials that have consequences for use in food items (Chaudhry and Castle 2011). Moreover, toxicological studies, pharmacokinetics profile and potential risk of the nanomaterials used in the food sector is in its infancy stage (Chaudhry and Castle 2011; Sekhon 2010) and standardized validation test/procedure for detection and characterization of nanomaterials in food on living cells are currently unavailable (Chaudhry and Castle 2011; Ray et al. 2009). Therefore, there exists a knowledge gap between nanoscience and nanotechnology in food that needed further research.

12.2 Agency and its Regulations in Use of Nanotechnology in Food Sectors

The use of novel materials and methodology in various fields of food sector as food additives and food contact materials, potential risk assessment should be followed to quantify, identify and to overcome human health complications and to prevent the flora and fauna based environment from discarded nanomaterials (Viswanath and Kim 2016). The novel applications that are incorporated with nanotechnology in food sector must be thoroughly assessed, assured and regulated for safe commercialization and consumer use (Sekhon 2010). Till date, there are no proper standard international regulations framed on nanotechnology/ nano-based products. Only few government agencies/ organizations from various developed countries have come forward to define the usage of nanotechnology by establishing regulated standards. The regulations that are established by representatives of several countries are represented in Table 12.1.

In Food and Drug Administration (FDA), Special regulations were not framed initially on the use of nano additives, nanocontact materials during the entry phase of nanotechnology in the food sector. In 2004, FDA regulated nano-based food by its nano range of the particulate source material but failed to focus on their methodology of preparation and its applied technology (Weiss et al. 2006). Nevertheless, there are several other government agencies with various goals and mission set to assess the risk of nanotechnology to solve environmental related problems and to treat diseases with improved technology (Boverhof et al. 2015).

In 2005, a suggestion was passed by the Institute of Food Science and Technology (IFST) stating that if nano-based particle or material used in any form as food additives or food contact formulations, the concerned food product should be labeled with the conventional E-numbering system with subscript “n” before it is into commercial use (Weiss et al. 2006). Later in 2006, the British government accepted the suggestions made by IFST that any nano ingredients added in or in contact with the food material must be subjected to a complete safety assessment prior to use in food products (Chau et al. 2007).

In 1963, Codex Alimentarius has created to monitor the food regulations with a set of regulatory standards for characteristics, practices, handling, recommendations and marketing of the food product. This agency initially updated its standard protocols to the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (UN-FAO) that was followed to maintain nanofood production and use of nanotechnology in promoting food and agriculture sectors (Bumbudsanpharoke and Ko 2015). Later in 2008, WHO and UN-FAO initiated to hold their own committee with expert consultations in the field of food sector to maintain and identify in-depth applications of nanotechnology, which can minimize the health risk at present and future with potential measures taken on food safety sector. Further, they can pave way for exploring future research (Rashidi and Darani 2011).

Table 12.1 List of the regulatory agencies around the World

Country	Regulating agency	Year of establishment	Head quarters
Australia	Food Standards Australia and New Zealand (FSANZ)	1991	Wellington
	Friends of earth (FoE)	1975	Melbourne
	CSIRO Manufacturing and Materials technology (CMMT)	1945	Canberra
Canada	Canadian Food Inspection Agency (CFIA)	1997	Ottawa
	Public Health Agency of Canada (PHAC)	1993	Ottawa
	National Institute for Nanotechnology (NINT)	2001	Alberta
China	Chinese Academy of Sciences	1949	Beijing
	National Center for Nanoscience and Technology (NCNST)	2003	Tianjin
European Union	European Food Safety Authority (EFSA)	2002	Parma
	Federal Agency for the Safety of the Food Chain (FASFC)	2000	Brussels
	Community Research & Development Information Service (CORDIS)	1990	Luxembourg
	European Nanotechnology Gateway	2003	Greece
	European Nanobusiness Association (ENA)	2002	Belgium
France	French Research Network in Micro and Nano Technologies (RMNT)	1998	Cedex
	ANSES - French Agency for Food, Environmental and Occupational Health & Safety	2010	Maisons-Alfort
	Centre National de la Recherche Scientifique (National Center for Scientific Research) (CNRS)	1939	Paris
Germany	Federal Ministry of Education and Research (BMBF)	1955	Heinemannstraße
	German Federal Institute for Risk Assessment (BFR)	2002	Berlin
India	Food Safety Standard Authority of India (FSSAI)	2011	New Delhi
	Department of Science and Technology (DST)	1971	New Delhi
	Department of Biotechnology (DBT)	1986	New Delhi
Iran	Nanotechnology Committee of Food and Drug Organisation	2006	Tehran
	Iran Nanotechnology Initiative Council (INIC)	2003	Tehran
Ireland	Food Safety Authority of Ireland	1999	Dublin

(continued)

Table 12.1 (continued)

Country	Regulating agency	Year of establishment	Head quarters
Italy	Joint FAO/WHO Expert Committee on Food Additives (JECFA)	1956	Rome
Japan	Ministry of Health, Labour, and Welfare	2001	Tokyo
	Nanotechnology Researchers Network Center (NANONET)	2012	Tokyo
	Rikagaku Kenkyusho (RIKEN)	1917	Tokyo
	Ministry of Education, Culture, Sports, Science and Technology (MEXT)	2001	Tokyo
	National Institute of Health Sciences (NIHS)	1874	Tokyo
	National Institute for Environmental Studies (NIES)	2001	Onogawa
	National Institute of Advanced Industrial Science and Technology (AIST)	2001	Tokyo
	Japan Society for the Promotion of Science (JSPS)	1932	Tokyo
Korea	Korean food and Drug Administration (KFDA)	1998	Chungcheongbuk-do
	Korean Agency for Technology and Standards (KATS)	1883	Chungcheongbuk-do
	National NanoFab Center (NNFC)	2002	Chungcheongbuk-do
	National Center for Nanomaterials Technology (NCNT)	2003	Gyeongsangbuk-do
	Center for Nanostructured Materials and Technology (CNMT)	2009	Seoul
Russia	Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor)	2004	Moscow
Switzerland	Swiss Federal Office of Public Health (FOPH)	2006	Bern
	Federal Office for the Environment (FOEN)	1971	Bern
Taiwan	NanoTechnology Research Center (NTRC)	2002	Hsinchu
	National Science and Technology Program for Nanoscience and Nanotechnology	2003	Taipei
USA	Government Accountability Office	1921	Washington, D.C.
	Food and Drug Administration (FDA)	1906	Maryland
	Institute of Food Technologists (IFT)	1939	Chicago
	Environmental Protection Agency (EPA)	1970	Washington, D.C.
UK	Institute of Nanotechnology (IoN)	1994	Ottilia Saxl
	Department for Environment, Food and Rural Affairs (DEFRA)	2001	London

Source: Chau et al. 2007; Bhattacharya et al. 2012

The Directorate-General of Health and Consumer Protection in the European Union structured a Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) in 2010 (Grobe et al. 2008). Emerging environmental and health related risks are assessed regarding the consumer safety and public health by comprehensive risk assessment exclusively on nano-based technologies that fit into the food sector profile.

The Swiss Center for Technology Assessment (TA-Swiss) recently found that nano food additives were in commercial use for many years in Switzerland such as micelles, carotenoids, silicon dioxide, etc., when a study was conducted by TA-Swiss, no indications was found that the nanoparticles used in food products in Switzerland were not dangerous to human health. In major cases, to understand the risk of nanoparticles consumption no specific tests are available in food and health sector (Vishwakarma et al. 2010). Therefore, a regulatory system was introduced as "positive principle" to identify the registered positive nano food additives using E-numbering system such as silicon dioxide (E 551), silver (E 174), gold (E 175), Iron oxide (E 172), titanium oxide (E 171) and aluminium (E173) (Ravichandran 2010).

In Japan, the government agencies along with Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Economic, Trade, and Industry's (METI), Ministry of Health, Labor and Welfare (MHLW) and Ministry of Environment (MOE). MEXT promotes research and development along with academic and industrial sector and creates a platform for nanotechnology, material science and extensively supports the development of nanotechnology in various fields of applications. The standardization protocols of testing methods and nanoparticles safety are evaluated by METI (Thomas et al. 2006). The health impacts of nanomaterials and its route causative agents are assessed and evaluated by MHLW. Therefore, regulation of science academic are worked by METI, MHLW, MOE and the sole responsible for the researcher's performance to public acceptability was evaluated and maintained by MEXT. Further, during the development of nanomaterial using nanotechnology information support was given by National Institute for Materials Science (NIMS) which was established by the Nanotechnology Researchers Network Center (Nanonet).

In 2009, Australian Government launched The National Enabling Technologies Strategy (NETS) in its four-year plan of Federal Budget to explore advanced technologies such as nanotechnology and biotechnology. In this budget, NETS was funded $38.2 million over 4 years. Food Standards Australia New Zealand (FSANZ) is a statutory authority that develops comprehensive safety assessment for nano-related products in Australia and New Zealand.

In 2003, Chinese Academy of Sciences (CAS) and Ministry of Education founded the National Center for Nanoscience and Technology (NCNST) in China. It has several divisions of laboratories which have established a platform to the public about the basics, technology and applied research in the field of nanosciences. In 2005, NCNST established the Commission on Nanotechnology Standardization along with its affiliation. It has the responsibility of developing a technology which should fulfill safety requirements including termination protocol of any processing, materials, bio-mediated products, medicine that are produced

with nanotechnology. Any protocol generated should be based on the china national standards. The commission provides the necessary guidance, governs assessment risk and handles accreditation of nano products which promotes the industries to enhance quality, sustain safety by reducing health risks and to fasten the development of the products.

Singapore has set up Agency for Science, Technology, and Research (A*STAR) in 2006 with the goal to promote nanotechnology research and development and commercialization. In 2010, the Singapore Institute of Manufacturing Technology (SIMTech) organized the first nanotechnology Manufacturing Round Table Discussion (MRTD) to accelerate the adoption of nanotechnology.

Indian government endeavored systematically to promote research in the frontier of nanotechnology since 2001 (Beumer and Bhattacharya 2013). National Institute of Pharmaceutical Education and Research (NIPER) has entered into licensing agreement with Windlas Biotech limited for development and commercialisation of nanocrystals for drug delivery. NIPER is also working on regulatory approval guidelines and standards for toxicological study in nano-based drug delivery systems. In the Twelfth Five Year Plan (2012–2017), a total cost of Rs. 650 crore is approved for the Mission on Nano Science and Technology (Nano Mission). In India, government mainly focuses on the development of infrastructure, skill development and strong institutional base for achieving success in the field of nanoscience and nanotechnology (Beumer and Bhattacharya 2013). Though Indian government does not have specific regulation for nanotechnology but there are checks and balances at places (Beumer and Bhattacharya 2013).

12.3 Nanomaterials in Food

Nanomaterials are structures that fall under nanometer scale with properties different from its bulk materials (Maurice and Hochella 2008). Generally, nanomaterials are categorized into 4 forms based on its structural dimensions as shown in Fig. 12.2.

These nanostructural materials are found naturally in milk proteins and casein, incidentally formed in the byproducts of welding and intentionally produced as nanofibres (Tarafdar et al. 2013). Nanostructures exist in different sizes and shapes as illustrated in Fig. 12.3. The most notable nanostructured materials used in food systems are nanocomposite, nanoemulsions, nanoencapsulations and nanoparticles (NPs) represented in Fig. 12.4.

12.3.1 Nanocomposites

Nanocomposites are defined as a multiphase component acquired from a combination of two or more constituents to form the unique properties than the bulk composite with a nano-sized dimension less than 100 nm in size (Roy et al. 1986).

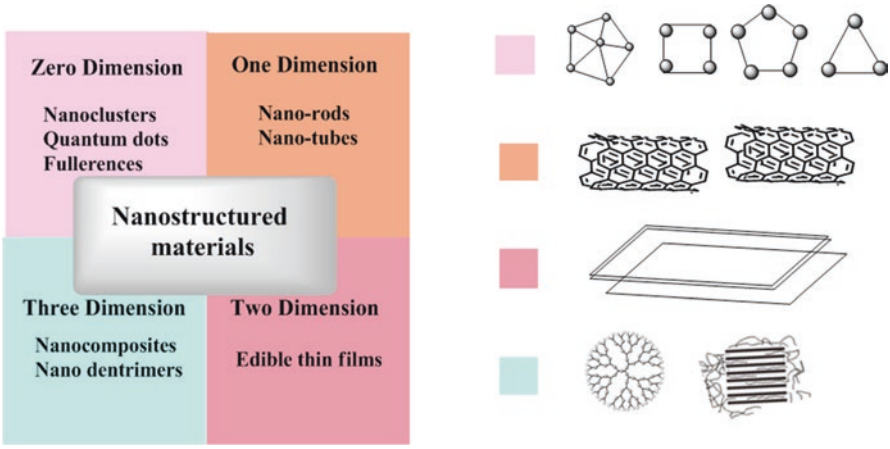

Fig. 12.2 Forms of nanostructured materials

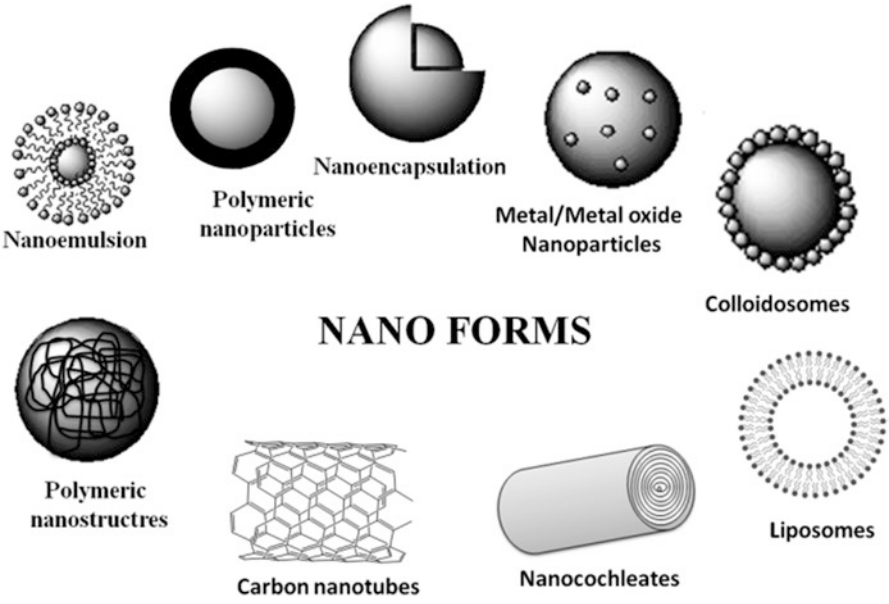

Fig. 12.3 Various nano forms

It is broadly classified into polymeric nanostructures and nanoclays based on the materials used. These nanocomposites are mainly used in food packing as alternative conventional packaging materials due to its advanced functional properties and economic feasibility (Pathakoti et al. 2017).

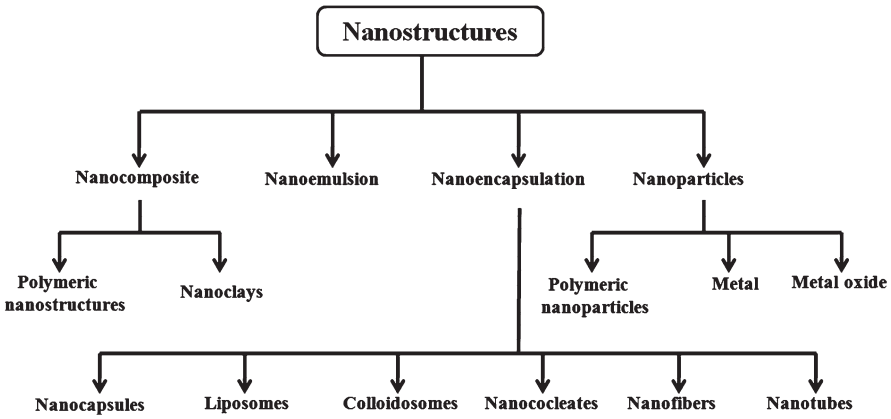

Fig. 12.4 Categories nanostructures

12.3.1.1 Polymeric Nanostructures

Polymeric nanostructures/nanocomposites are materials consisting of two or more phase separated materials, the polymer as its major phase in one or more dispersed phase in nanoscale size. This polymer nanocomposite can be used as a nanocoating material to act as a specific surface gas barrier (Cui et al. 2016). When the polymeric nanocomposites are layered with minerals like silicates, it enhances the physical and mechanical properties in terms of tensile strength (Jumahat et al. 2012), permeability to gas (Beyer et al. 2002), resistance to thermal stress and moisture (Paul and Robeson 2008), etc. The polymeric nanostructure packaging system helps in improving the stability of color, flavor, and palatability and avoids food spoilage (Weiss et al. 2006). The polymer used for preparing nanocomposites can be derived from plant (eg. starch, cellulose), animals (eg. proteins) or microbial (e.g. polyhydroxybutyrate, bacterial cellulose) source.

12.3.1.2 Nanoclays

Nanoclays are crystal lattice structure of layered inorganic mineral which occurs in nanoscale size. Based on the chemical composition, nanoclays are categorized into several classes like montmorillonite, bentonite, kaolinite, hectorite, and halloysite (Nazir et al. 2016) as shown in Fig. 12.5. Nanoclays are extensively implemented in food contact surfaces and food packing application because of their enhanced barrier and mechanical properties over the synthetic packaging materials (Majeed et al. 2013). Food and beverages industries use multilayered nanoclay for the bottling of beer and carbonated drinks (Huang et al. 2015; Othman 2014). These nanoclay composites are reported to be used in pharmaceutical products as excipients and active agents (Aguzzi et al. 2007). Bentonite, considered as the most commonly

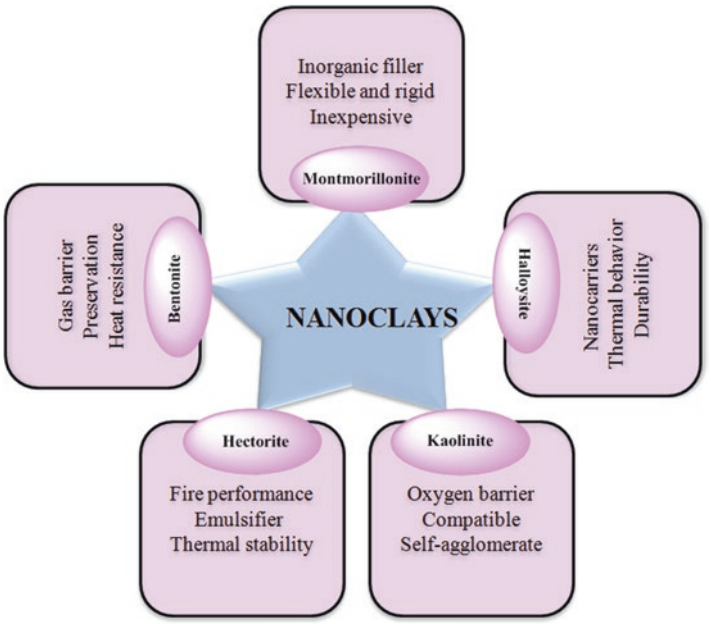

Fig. 12.5 Classifications of nanoclays and its physico-chemical properties

used nanoclay composite with high gas barrier properties which is relativity low cost and availability (Liu et al. 2014). The performance of the nanoclay depends on the polymer used for the preparation of nanoclay which determines its use in food and pharmaceutical packaging applications.

12.3.2 Nanoemulsions

Nanoemulsions are a colloidal dispersion of lipid in the aqueous phase to produce droplets ranging in nanoscale. Nanoemulsions act as a potential carrier of lipophilic (soluble in lipids or oils) compounds which are extensively used in pharmaceutical industries as drug delivery system (Jaiswal et al. 2015). Hence, this concept was recently explored in the food industry to improve the bioavailability of functional compounds like antioxidant (α-Tocopherol, Curcumin, β-carotene, lycopene, lutein, coenzyme Q10), essential fatty acids (omega-3), vitamins (A, D3 and E) and phytosterols in the fortification of food. Nanoemulsions of phytosterols act as an excellent food additive (Garti et al. 2005). They are extensively used to shield the flavor during the processing and increase the shelf life by protecting the food materials from an environmental condition such as oxidative stress and enzymatic hydrolysis (Silva et al. 2012). Commercially available

nanoemulsion-based food products are flavored oils (Rao and McClements 2011), bottled beverages (Mirhosseini et al. 2009) and drinking water (Gu et al. 2005), fortified milk (Joung et al. 2016), sweeteners (Coupland and Hayes 2014), ice-creams (Kumar et al. 2016), food colourants (Yin et al. 2009) and other processed food items (Silva et al. 2012).

12.3.3 Nanoencapsulations

Nanoencapsulation is a technique to protect the active compound in nanoscale range and augment its functionality and stability with controlled release of the active compound. This technique is used in pharmaceutical as particulate carrier system (Reis et al. 2006). They are employed as a tool to improve the pharmacokinetics, bioavailability and to facilitate controlled drug release at targeted site (Diab et al. 2012). This technique is widely used to deliver culinary balance in processed food products and to enhance the flavor and color release and retention in food sample (He and Hwang 2016; Nakagawa 2014). Functional ingredients and additives like vitamins, probiotics, preservatives, antioxidants, peptides, lipids, carbohydrates, etc., are incorporated into the nanovesicles as nano encapsulated bioactive material (Nakagawa 2014). Based on its structure nanoencapsulation is categorized as Nanocapsules, Liposomes, Colloidosomes, Nanocochleates, Nanofibres and Nanotubes.

12.3.3.1 Nanocapsules

Nanocapsules are a nanoscale-sized shell made up of the external polymer layer with internal polymeric matrix capable of holding bioactive compounds. This nanosystem is extensively used for delivering functional compounds by protecting against catalyze oxidation and hydrolytic degradation in food, beverage and nutraceutical industries. Nanocapsules are formed by polymerization of monomers or crosslinking of polyelectrolytes or biomaterials like chitosan, zein, etc. (Chauhan et al. 2017; Patel and Velikov 2014). They have the special property to get expanded and bind with specific chemical receptors of particular cells and the bioactive compounds are released in a controlled manner (Pradhan et al. 2015). Nanocapsules are exclusively used in self-degrading packaging and encapsulate lipid compounds in food products (Sekhon 2010). Nanocapsules has huge potential in the packaging of food and beverage sector but there is a need for further research to reduce the cost and potential risk of the consumer to open up the market for nanoproducts (Sekhon 2010).

12.3.3.2 Liposomes

Liposomes are spherical bilayer vesicles formed with phospholipids. Food industries initiated usage of encapsulated liposomes to increase the bioavailability of functional ingredients (Mozafari et al. 2008). More recently antimicrobial properties of liposomes are explored; it has an ability to integrate food microbes and increases the protection and shelf life of the food products (Mozafari et al. 2008). Its unique properties such as nano size range and interfacial surface area make it ideal for the controlled delivery of nutraceuticals at the specific target site.

12.3.3.3 Colloidosomes

Colloidosomes are self-assembled colloids oil-in-oil emulsion to form microcapsules. This encapsulated topology was found in accordance with liposomes (Thompson et al. 2010). It has gained importance in various felids of science, food, medicine and cosmetics due to their solid hollow structure, computability and physicochemical structure. It is found to be ideal carrier for lipophilic compounds, vitamins, antioxidants and coloring agents with controlled functionality (Lopes et al. 2013).

12.3.3.4 Nanocochleates

Nanocochleates are nano coils the particles by wrapping the micronutrients to stabilize and secure the extended range of micro or macro nutrients by enhancing the bioavailability and nutritional value of the processed food (Lopes et al. 2013). These nanomaterials also have an ability to microencapsulate water soluble cationic drugs/peptides within its lipid bilayer space by interacting with lipids that are negatively charged. Either peptides or drugs, they act as inter-bilayer bridges with multi cations instead of metal ions (Pawar et al. 2015). These nanocochelates are incorporated into bakeries products such as cookies, cakes, and muffins as a carrier for micronutrients, phytosterols etc., without varying the taste and odor of the particular food product (Lopes et al. 2013). This nano cochleate's paves way for the concept of super foodstuffs found to improve mood, energy, immunity, cognitive functions and alleviates depression

12.3.4 Nanofibers

Nanofibers are nanoscaled fibers fabricated using electrospinning process with the very large surface area and high porosity (Vasita and Katti 2006). Honey/Chitosan nanofibers found to be an attractive matrix for wound care with bacericidal effect

(Sarhan et al. 2016). Due to its structural organization it is widely used in food industries for clarication (beer and wine) and food contact materials (Ravichandran 2010). It is also used for enzyme immobilization (Jia 2011), scaffold geometry of bioreactor (Hardick et al. 2015), delivery of bioactive compound (Hrib et al. 2015), the concentration of fruit juice (Bélafi-Bakó and Koroknai 2006) and scaffold to remove bacteria in milk (Fahim et al. 2016). Edible biopolymers are used in the preparation of nanofibers that has its potential application in encapsulating the bioactive compound for its use in food and nutraceutical sectors (Azeredo et al. 2012). Food and beverage industries use nanofiber membranes/composites as an alternative membrane system for purification and concentration of the desired compounds with higher flux, rejection rate and anti-fouling characteristics.

12.3.5 Nanotubes

Nanotubes are cylindrical fullerenes representing buckytubes structure used in sports, medicine and food industries for its novel mechanical properties. Carbon nanotubes are used in food sector to improve the shelf life of the food produced from microbial deterioration (Honarvar et al. 2016). Further, self-assembled alpha-lactalbumin nanotubes from partial enzyme hydrolysis of the milk protein were used as thickening and gelling agent in food sector (McClements et al. 2009). It is also used to encapsulate matrix to protect and promote the stability of the food ingredients. Improved mechanical strength and resistance to environment stress of nanotubes paves the way in processing and packaging technologies in food industries (Honarvar et al. 2016).

12.3.6 Nanoparticles

Proteins and polysaccharides produce food grade biopolymeric nanoparticles in the nanoscale range (He and Hwang 2016). Polylactic acid is used as one of the major component due to its biodegradable properties. These biopolymeric polylactic NPs are used regularly in the delivery of bioactive micro and macro nutrients to the targeted site through encapsulation (Pathakoti et al. 2017). Polysaccharides based starch like NPs prevents oxidation of lipids and improves the stability and prevents the food degradation (eg. α- tocopherol and sodium caseinate stabilized lipid-based nanostructures) (Pathakoti et al. 2017).

To overcome the adverse effect of chemically synthesized metal nanoparticles, various secondary derivatives were used as a reducing agent to produce biologically mediated nano particles. Example silver nanoparticles from *Annona squamosa* (Kumar et al. 2012) and *Cocos nucifera* (Elango et al. 2016), etc. Silver nanoparticles have increased utility in food industries to retained aroma and sensory characters. Several nano-based color additives are extensively studied and manufactured in

food industries. Customer's personal and psychological characters are highly influenced by the color to select the particular food products. TiO_2 is a major metal oxide used in food additives and SiO_2 and Al_2O_3 are traces used. SiO_2 nanomaterials are used as vesicle for flavors, fragrance and as an anti-caking agent in food products (Martirosyan and Schneider 2014). The US FDA approved the use of TiO_2 not exceeding its permissible limits more than 1% w/w and for SiO_2 and Al_2O_3 not exceeding 2% of the total (Kuznesof and Rao 2006). The European Union indicated the least containing of SiO_2 in food additive products are widely certified and registered as E551 within the permissible limits.

12.3.7 Nanolaminates

Apart from nanodispersions and capsules, the most important technique used commercially in the food sector is nanolaminates (Ravichandran 2010). This nanomaterial consists of two or more layers in nano dimensions. The size of laminates ranges about 1–100 nm/layer thin films that are extremely food grade. These edible thin film nanolaminates have several advantages in the preparation of various fruits, vegetables, meat, chocolate, candies, french fries and bakery products and protect deterioration by acting as a barrier to moisture, lipids, and gasses (Weiss et al. 2006; McClements et al. 2009). It serves as nanocarriers by enhancing the color, flavor, nutrient availability, textural property, antioxidant and antimicrobial properties and increases the shelf life of the food materials (Ravichandran 2010). Presently, edible lipid-based nanolaminates are commercially used due to its moisture resistant property but have a certain resistance to limited gasses compared to polysaccharide and protein based edible nanolaminates (Ravichandran 2010; Pradhan et al. 2015).

12.4 Categories of Nanotechnology Used in Food Sectors

There are two categories of nanotechnology in the food sector, one involves in the production of nano-based technologies for food processing. Nano products such as nano-sieves to filter bacteria and food packaging materials incorporated with nanosensors to detect food deterioration caused by microorganisms (Bouwmeester et al. 2007). Two is to introducing nanostructured material into the food items with the idea of maintaining and to increase the shelf life of food (He and Hwang 2016). In this category, whole diversity of inert nanoparticles and nanocapsules are used for various purposes in the food chain production such as soil cleaning and water purification process based on nanotechnology, in storage of food and to increase its period of duration, nanoscale quantity of lanthanum particles and iron powder, intellectual food packaging systems are carried out frequently with silver, magnesium, zinc oxide, silica nanoparticles (García et al. 2010). Hence, consumers

remain riskless that inert nanoparticles remain bound within the packaging material than the particles are directly exposed or migrated inside food substances (House of Lords 2010). However, the nano-based drug delivery system such as nanocapsules promotes a way to deliver desired active compound to its target in its desired way in the human biological system by reducing the size and dosage of the desired bioactive compound (Singh and Lillard 2009). These nanocapsules are used as active compounds in the production of nutraceuticals and medicines to increase the absorption and bioavailability of the lead bioactive compound (Sekhon 2010; Nair et al. 2010). Table 12.2 represents the commercial nano-based products available in the market.

12.5 Strategies of Engineered NPs in Food

An extensive research and special attention are needed in a forthcoming generation since the majority of food industries on the globe initiated to advance their food products, production, and protection with novel ideas using various applications of exposed and unexposed fields of nanotechnology. Therefore, detection of these engineered nanoparticles in food matrices is found to be difficult at present due to lack of methodologies to determine the actual amount of nanoparticles present in the food in a consumable form (De Jong and Borm 2008). It is advisable to consider and evaluate the nutritional implications of nanoparticles when ingested along with the food. Bioactive compound when ingested along with the food, such as nanocapsules, which has the capability to increase the bioavailability even to contaminants that are normally present in the food matrix (Viswanath and Kim 2016). Further, these nano-based particles with an active charge on their surface can easily absorb biomolecules when they pass through the gastrointestinal (GI) tract. This effect is also called as "Trojan Horses" effect due to the transportation of toxins in the intestinal mucosa, which leads to intestinal cellular line exposure and damages the cells (Bouwmeester et al. 2007). It is possible and feasible that the nanoparticles are measured and assessed according to its permissible limits before it enters into the food matrix at pilot scale production of the particular food chain process. However, protocols are currently available only to detect and assess conventional chemicals but not for the nanoparticles present in the food matrix. This area should be pivoted; more importance should be given because functionalities of nanoparticles get modified from one biological matrix to the other depending on thermodynamic conditions that occur in each matrix. Relying on producer's information can be an alternative approach to understanding exposure of NPs as an initial assessment to predict health effects. A scrutinized primary data that is lacking behind should be assessed and maintained by novel governance.

Table 12.2 Nanotechnology based commercial FoodProducts

Product name	Nanomaterial used	Uses	Company name	Country
Canola Active Oil	Nanoencapsulation	Fortified phytosterol	Shemen	Israel
Nanotea	Selenium nanoparticle	Micronutrient	Shenzhen Become Industry Trading Co.	China
Fortified Fruit juice	Nanoencapsulation	Nutritional supplements	High Vive.com	USA
Nanocecuticals slim shake	Nanoencapsulation of cocoa	Assorted flavour	RBC Life Sciences	USA
NanoSlim beverage	Nano diffuse technology	Diet supplements	Nanoslim	Canada
Oat Nutritional Drink	Iron nanoparticles	Assorted flavour	Toddler Health	USA
Daily vitamin boost	Nanoencapsulation	Nutritional supplements	Jamba juice	USA
Nanocapsule – Tuna fish oil	Nanocapsules	Omega fatty acid protection	Tip-Top Up bread	Australia
Low-Fat Cottage Cheese	Titanium dioxide	Pigment properties	Daisy	USA
Coffee Creamer	Titanium dioxide	Pigment and anticaking agent	Albertsons	USA
Greek Plain Yogurt	Titanium dioxide	Pigment	Dannon	France
Eclipse Spearmint Gum	Titanium dioxide	Anticaking agent	Eclipse	Canada
Whipped Cream Frosting	Titanium dioxide	Anticaking agent and pigment	Betty Crocker	USA
Cereal	Titanium dioxide	Anticaking agent	Fiber One	USA
Chocolate Syrup	Titanium dioxide	Pigment	The Hershey Company	USA
Breathsavers Mints	Titanium dioxide	Anticaking agent and pigment	The Hershey Company	USA
Kool-Aid Lemonade	Titanium dioxide	Anticaking agent	Kool-Aid	Mexico
Silk soy milk	Titanium dioxide	Anticaking agent	Silk Vanilla Soy drink	USA
Roasted Garlic	Titanium dioxide	Anticaking agent and pigment	Betty Crocker Mashed Potatoes	USA
Oreos chocolate biscuit	Titanium dioxide	Anticaking agent	Oreos	USA

(continued)

Table 12.2 (continued)

Product name	Nanomaterial used	Uses	Company name	Country
Antibacterial Pet products	Silver nanoparticles	Antibacterial agent	Nano Care Technology Ltd.	China
ASAP health max 30	Silver nanoparticles	Nutrient supplements	American Biotech Labs	USA
BlueMoonGoods™ fresh box silver nanoparticle food storage containers	Silver nanoparticles	Packaging	Blue Moon Goods, LLC	USA
Utopia silver supplements®	Advanced colloidal silver	Healing	Utopia	USA
Lypo- Spheric Vitamin C	Liposome	Nutrient supplement	LivOn Labs	USA
Colour emulsion	Nanoemulsion	Coloring agent	Wild Flavors	USA
Bioral Omega 3	Nanocochelates	Food additives	Bioral	USA

Sources: Pradhan et al. 2015; Rao and McClements 2011; Sekhon 2010; Silva et al. 2012

12.6 Consumer Consumption and Exposure Assessment

From various standardized food baskets utilized to obtain the consumption data of nano-based food using various sources from pre-marketing to households. The individual dietary survey was assessed with post-marketing studies (Bouwmeester and Marvin 2010). It is found that no additional information was given regarding the usage of nano additives or nano-based substances. Hence, usage of NPs in food which is generally lacking should be reframed along with consumption databases to maintain prominent assessment on evaluating food supplements those are frequently incorporated into nanoparticles.

Evaluating a number of nanoparticles and its conventional chemicals that are integrated into the consumption of food is the final step performed for exposure assessment (Contado 2015). To integrate the exposure data one among the three approaches are followed such as point estimation, simple distribution, and probabilistic analyses (Arisseto and Toledo 2008). Using this analysis, consumer exposure to particular nano-based food is compared with a toxicological reference value, such as recommended daily allowances, tolerable permissible value, a minimal referral doses, and the upper safe level of intake. Currently, these type reference values regarding NPs are lagging which should be established to provide a healthier lifestyle for humans.

12.7 Potential Risks Assessments

Using nanotechnology, the nano range materials brings several benefits and prospects in midst of consumers in the global market (Beumer and Bhattacharya 2013). In spite, due to some biopersistent (insoluble or hard NPs) used in food

and beverages for human consumption (Laux et al. 2017). It is more concerned when NPs enter inside the human body, they have large reactive surfaces and crosses biological barriers and enters another biological system of the body. This large particulate material initiates its unknown reaction in the new biological matrix, where NPs entry is restricted. Therefore, the knowledge gaps should be assessed in understanding thermodynamic properties and behavioral effects of biopersistent NPs used in food application to prevent the raise of any special health concerns (Laux et al. 2017). Case by case assessment is needed to avoid risk on consumer consumption. Natural foods with nanostructures are considered as soft nanoparticles are known well to be digested and degraded in the GI tract (Estelrich et al. 2014). Detailed evaluations for soft NPs are not required compared to hard NPs.

It is minimally considered about the food products that contain natural food structures that are not biopersistent. They are easily digested and absorbed in GI tract. Some areas are more concerned though food nanocarriers are not produced with biopersistent material. This nano encapsulated food carriers when crosses the GI tract, the materials present in nanocarriers may be different from the conventional bulk equivalents (Chaudhry and Castle 2011). Moreover, due to enhanced bioavailability, the vitamins and minerals than recommended permissible limit may not benefit consumers health. Major concerns are given on potentially biopersistent, insoluble, indigestible food products (Chaudhry and Castle 2011). Nano-additives / nano-functionalized materials produced from hard materials with poor ADME (adsorption, distribution, metabolism and elimination) profile and several toxicological properties that are not completely explored at present may cause risk when food and agriculture products exposed to consumption (Singh et al. 2016).

Nanotechnology derived packaging material can raise some potential health risk depending on migrating behavior from the intact pack (Honarvar et al. 2016). On the basis of the packaging system, few modeling and experimental studies reported that likelihood of migration behavior of NPs is very low or nil (Wyser et al. 2016). Based on the model, it is predictable that any NPs that is migrated from the polymer matrix will be minimal because only nano range quantity are incorporated with low dynamic viscosity but further research should be proceeded to determine the behavior of migration patterns of polymer composites as well derived biopolymers (Noonan et al. 2014).

It is noted that in relation to risk assessment of nanotechnology applications in the food sector, it is unlikely that knowingly acute biopersistent toxic materials are used in food products. The usage of NPs should mainly concern of consumer safety. Several transformations occur in nano-based food, due to aggregation, agglomeration, adhesion with other components of food, its binding reactions with enzymes, acids and many other biotransformations in the human GI tract system may lead to losing actual characteristics of the nanomaterials (Martirosyan and Schneider 2014). Currently, there is some understanding on the safety of nano food products and its biotransformation nature/ impact.

12.8 Entry of Nanoparticles into Human Body

Nanoparticles in food when consumed, they can be easily translocated from one to the other organ due to its particles size (nano range) can cause its own reaction and risk (Oberdörster et al. 2005). Only limited data information is available on handling nanomaterials and its risks. Therefore, a stringent control is essential and it should be strictly implemented until adequate knowledge is available on handling nanomaterials. Inhalation, ingestion and dermal exposure are the three possible routes for NPs to enter the human system as shown in Fig. 12.6.

12.8.1 NPs through Dermal Exposure

The entry of NPs depends on their ability to penetrate the skin from dermal hair, outer protective layers of the epidermis to the dermis (Chau et al. 2007). In the case of healthy intact skin, epidermis provides excellent protection from nanostructured particles (Filon et al. 2015). The keratinized dead cells that are composed and glued with lipids known as Stratum corneum, acts as a rate limiting to chemicals, soluble molecule, water and ionic compounds (10 mm) from entering in the cutaneous layer (Riviere and Monteiro-Riviere 2005). There are few NPs such as fine fluorescent microspheres or dextran beads (±1 mm) can reach epidermis by penetrating stratum corneum (Filon et al. 2015). The NPs very rarely get translocated in lymph to regional lymph nodes by penetrating dermis layer (Oberdörster et al. 2005).

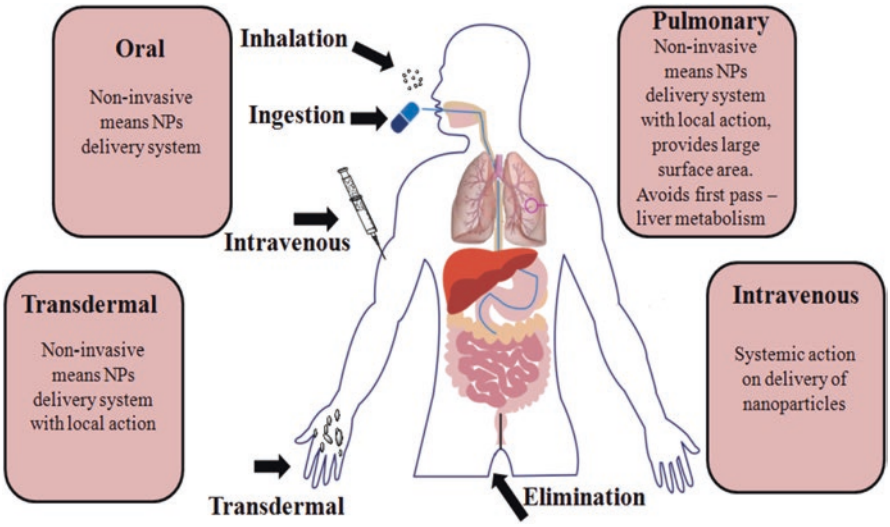

Fig. 12.6 Ways of entry for nanoparticles into human body

Titanium dioxide (20 nm) can interact with the immune system if particles penetrate into the skin and they possibly involve photogeneration of hydroxyl radicals and oxidative damage occurs (Bhattacharya et al. 2009; Wakefield et al. 2004). Only few information is available on hazards of NPs exposure to skin. Therefore, NPs mechanisms of interaction and possible health consequences are still speculative.

12.8.2 NPs through Inhalation

The aerodynamic ambient diameter of 10 μm has a chance of 50% probability to penetrate into the alveolar region through nasal cavity and lungs (Brown et al. 2013). As the size ranges in nano meters, NPs can travel deeper into the lungs (Politis et al. 2008). The pulmonary toxicity and its adverse pathogenic effects of inhaled NPs are determined from the shape (Stoehr et al. 2011), size (Taylor et al. 2012), surface coating (Suresh et al. 2012), chemical composition (Limbach et al. 2007), and surface charge (Schlinkert et al. 2015). The low-solubility ultrafine particles indicate more toxic than large particles. Titanium dioxide, carbon tube gets accumulated in the lungs, induces chronic diseases such as pulmonary inflammation, pneumonia, pulmonary granuloma, and oxidative stress (Forbe et al. 2011). If the nanoparticles are efficient to cross blood brain barrier system, they can evade and translocate out easily even from specific defense mechanisms through different pathways (De Jong and Borm 2008). Based on the size of NPs alone the potential toxicity cannot be determined to reach the possible generic conclusions.

12.8.3 NPs through Ingestion

Based on toxicological perspective, material characteristics of particle size and surface area are considered to be more important. The nano-based material entering the human system particularly through oral ingestion is given more importance because NPs can prolong their retention period dramatically in GI tract by interrupting the intestinal clearance mechanisms (Posocco et al. 2015). This promotes surface availability to increase the interaction by penetrating deeply through fine capillaries into the tissues and efficiently delivers the compound to the targeted sites in the human system. The NPs either directly ingested or inhaled through various forms are cleared via mucociliary escalator and ends up in GI tract (Oberdörster et al. 2005). A study was experimentally proved that intestinal mucus barrier acts as a barrier system, the particles were unable to pass through if the size was larger than 1 mm (Hoet et al. 2004). The particle translocation study was evidentially performed with female Sprague-Dawley rats to study the uptake of polystyrene spheres nanoparticles in GI tract (Jani et al. 1990). The rats were fed with polystyrene spheres (50 nm- 3 mm) by gavage for 10 days, the results revealed that about 26 to 34% of NPs (50 to 100 nm) was absorbed and NPs that are larger than 300 nm

was not present in blood, lung and heart tissues (Jani et al. 1990; Chau et al. 2007). Another observation study was conducted using gel penetration action by using hydrophobic latex nanospheres (14 and 415 nm) which penetrated the mucus gel layer which is of 30–50 μm in thickness in 2 and 30 mins (Chau et al. 2007). Therefore, it was concluded that the smaller particles would be able to penetrate faster across the mucus barrier systems.

12.9 Kinetics of Toxicology Studies

From the available information on experimental data, it indicates that the physicochemical characteristics of NPs such as size, charge on the surface and its functionalizations are involved in influencing the properties of Absorption, metabolism, distribution and excretion (ADME) of the nano-based food matrix (Shin et al. 2015). The various exposure routes along with kinetics of NPs reveal that the oral exposure of NPs from the food matrices that directly affects the characteristics of ADME and also an emphasis on special NPs based agro-food.

12.10 Behavior and Fate of nanomaterials Used in Food

The nano-based food that contains NPs is ingested by the consumers in the form of food and beverages. The food consumed along with nano incorporated material further undergoes various physiological changes. Some of the NPs directly absorbed by the biological system or along with the food components. These NPs predispose themselves across the biological barrier of GI tract depending on their size, structure, and shape. They maintain and reside in GI certain period either bounded or unbounded form inside the GI tract. At this period, NPs are either beneficially or adversely interact with biomolecules (Kumar et al. 2015). Depending on the interaction of biomolecules and its physicochemical features, NPs are eliminated from the body by using different modes (Kumar et al. 2015). Some of the engineered nanomaterials that are specifically designed for an important purpose raise problem during their elimination process from the body relying on the type of material and fabrication methodology used.

The elimination of nanofabricated quantum dots (QDs) was investigated with in vivo studies, which resulted that the behavior of quantum dots is based on surface chemistry and size of the particles (Choi et al. 2007). In particular, the QDs of 5.5 nm diameter size and QDs with cysteine were eliminated from kidneys (Choi et al. 2007). However, QDs with various dimensions with altered surface chemistry need to be extensively investigated. Opsonization plays a vital role in eliminating the foreign materials (Owens and Peppas 2006); NPs based materials and pathogens depending on size and surface charge (Donaldson et al. 2005).

12.11 Toxicokinetics Involved in Clearance of NPs

The nano-based materials that are administered orally through food and supplements are absorbed, crosses GI tract and get distributed in respective targeted parts and organs of the body. NPs are maximum get eliminated from the body along feces or urine (Kumar et al. 2015; Hemalatha and Madhumitha 2015). The entry and clearance of NPs from the human system are illustrated in Fig. 12.7.

Nanomaterials with high concentrations are eliminated through the hepatobiliary pathway and excreted through the kidney (Zhang et al. 2016). The exposure of carbon nanotubes to neural and neuronal cell lines, cells were well grown and differentiated better (Jan and Kotov 2007). In the alveolar zone, the nanomaterials are cleared by macrophages using phagocytosis mode of engulfing action by enhancing the chemotactic attraction (Gustafson et al. 2015). Clearance of nanomaterials gets initiated when it reaches the circulatory system or targeted organs in the body involving the live macrophages and phagocytic process (Gustafson et al. 2015).

In food and pharmaceuticals industries, nanomaterials such as polysorbate 80 are coated with poly(n-butylcyano-acrylate) and pegylated polylactic acid (PEG-PLA) immune nanoparticles (Kumar et al. 2015). These NPs are intravenously administered which moves through the blood-brain barrier and accumulates in the brain tissues. Due to their respective physiological features, brain tissues results in neurotoxicity. Zinc oxide (ZnO) NPs when administered in the chorioallantoic fluid of chicken egg (50 µg/g wet of egg), the embryonic hepatic tissue was reached by ZnO

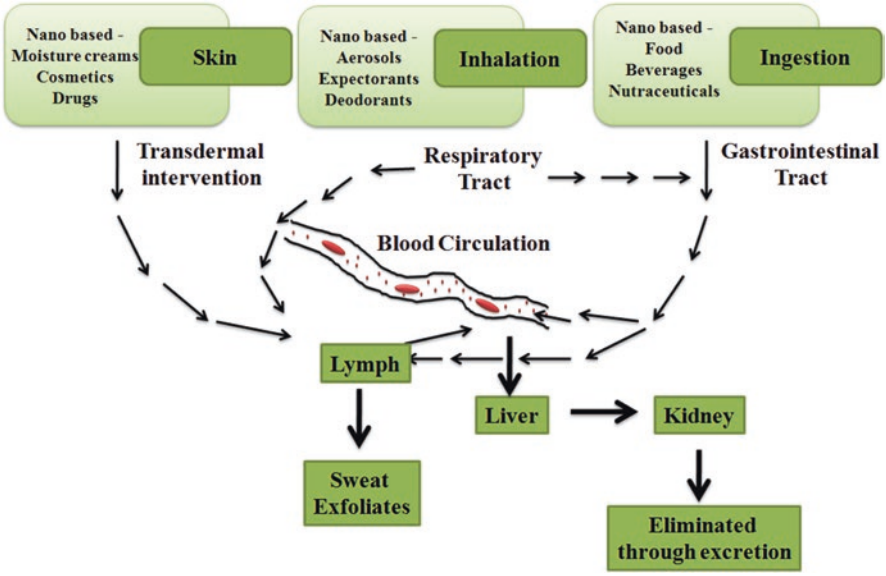

Fig. 12.7 Entry and metabolic routes involved in clearance of NPs in humans

NPs within 24 to 48 h (Pardeshi et al. 2014). On the 18/19 incubation day, the human RBCs exhibited viability and hemolytic response against ZnO NPs (20, 30, 40 μg/mL) (Clift et al. 2011).

Oral administration of ZnO NPs ranging size of 20, 70 nm was fed to male and female rats in dose-dependent pattern, within 24 h of the concentration of ZnO NPs was found increased in the blood, plasma, lungs, liver and kidneys (Baek et al. 2012; Elango et al. 2015; Madhumitha et al. 2016). Elimination degree of renal was very less than fecal elimination comparatively. The study exhibited that ZnO NPs are absorbed unevenly from the GI tract. Sprague-Dawley rats were studied to evaluate the excretion of TiO_2 and ZnO NPs with 1041.5 mg/Kg for 13 days (Cho et al. 2013). The concentrations were estimated considering various biological samples, such as blood, liver, spleen, brain, feces and urine. TiO_2 in tissues was absorbed very less compared to ZnO NPs but the concentration was found low in brain and spleen compared to TiO_2 NPs. Renal excretion was found to be low in TiO_2 NPs but the amount of ZnO NPs excretion was greater in urine and feces than TiO_2 NPs (Cho et al. 2013).

In the human biological system, the intestinal goblet cell secretion pathway is one of the important pathway models to eliminate NPs from the body (Zhao et al. 2014). This particular pathway was investigated using activated carbon NPs by injecting 30–200 nm sized NPs in Zebrafish yolk and resulted that NPs injected was excreted in the lumen as hepatobiliary pathway mode was not preferred (Zhao et al. 2014).

Nanomaterials that are present in circulation stream in our biological system are cleared by the action of reticuloendothelial cells and NPs that degrade in slow phase will have a low degree of renal clearance, further NPs that are not eliminated get accumulated in liver and spleen (Lee et al. 2010). The elimination of NPs primarily depends on the size of the NPs: example 5 nm in blood circulation have increased the degree of renal clearance and NPs 10–20 nm are cleared by the liver cells, 200 nm NPs are picked by sinusoidal spleen and Kupffer cells. The exempted nanomaterials by the above cells and organs are taken care of by macrophages, opsonins by phagocytosis mechanism (Yu and Zheng 2015; Longmire et al. 2008). Therefore, the nanomaterials in all three forms when entering the biosystem of the human body specific pathway are designed to eliminate the NPS irrespective of the nature and features of nanomaterials immediately after completion of its specific intended purpose.

12.12 Future Perspective

“The Convergence of Information and Communication Technology (ICT), nanotechnology and biological sciences are on the horizon. India is even better placed to exploit this revolution than any other nation”, says the Missile man of India, India’s Former President Dr. APJ Abdul Kalam. In his vision for 2020, agriculture, stem cell research and nanotechnology hold the future India. Prof. CNR Rao, chairman

of the Scientific Advisory Committee says to the Prime Minister, "We missed the semiconductor revolution in the early 1950s. We had just gained independence. But with nanoscience and technology, we can certainly be on an equal footing with the rest of the world".

Nanotechnology can promise myriad opportunities for innovations in the field of food sector from its processing to packaging. The future prospects of nanotechnology in the food sector are far from certain reasons because it can meet the needs of current and future generations through its scientific principles and foreseeable applications (Roopan et al. 2014; Elango and Roopan 2016). Even in twenty-first century, it is difficult to have a breakthrough technology without any craze, hype, and controversy because similar things happened to biotechnology and information technology in the past. Consumer acquires the scientific information primarily via television, social networks, newspaper, magazines and online sites (Duncan 2011). If these media, amplifies the consumer's risk perception of new and existing technologies without a level-headed debate, then there exist a distrust which could foster consumers opposition to it. In UK and Europe, acceptance of GMO (genetically modified organism) foods was partly influenced by mass media (Duncan 2011). Nanotechnology food products also suffer from a similar problem because negative aspects are mainly focussed. As a result, consumers acceptance for nanotechnology-based food products is reducing in Australia, America, Europe, etc. and creates a great challenge for government and industries (Duncan 2011). For an effective future flight, nano-based food products should mainly focus on the regulatory gap, promotion of good laboratory practice (GLP) in the industries and safety/ethical issues for consumers acceptance/confidence.

Nanotechnology can support distinctive edge for products developed by food processing sector in innumerable ways. Nano-based food and packing are current interest by the major food corporations globally. Over past 8 years, European government has funded £1.7 billion for nanotechnology in food research. Kraft, a food company is working on developing 'programmable food' by considering the consumer's vision for their desired food. They are currently developing food items that are mainly disliked by children by appetizing flavor – e.g. chocolate taste cabbage, milk taste like cola beverage. The main idea is to develop colorless, flavorless drink which could be customized according to the satifisfaction of the customers. This could be achieved by nanocapsules, which is activated by programmed microwave transmitter. Further breakthroughs in the future food world is to design and produce food products by manipulating the shape and structure of the food matrixes in its molecular/atomic level with precision by strictly considering the permissible limits of nanomaterials involved (Ravichandran 2010). Nano-modification helps to remove excess fats and sugar content from processed food. Food nanotechnology mainly emphasized on improving the solubility nature, stability, bioavailability effect, facilitates sustained release and fortifies micronutrients in food. In future, nutritional assert can be brought in processed food as per customer interest through nano food fortification. Smart foods developed using nanotechnology would detect the compounds present in the food that causes an allergic reaction and could to be occluded. Specific dietary needs of the consumer could be detected and released into the food

using nanotechnology. Nanotechnology would also help to determine the chemical contaminants and harmful microorganism in food products that could augment food safety level.

Based on nanotechnology literatures, India ranks third next to China and USA. The main goal of the Indian government is foster, assist and develops nanoscience and nanotechnology in all facets for the betterment of the country. In India, the National Nanoscience and Nanotechnology Initiative (NSTI) was launched under the Department of Science and Technology of the Ministry of Science and Technology to develop nanofood products. Nano Mission primarily focused on developing infrastructure, skilled manpower and academia-Industry partnerships for nanotechnology projects. Indian food processing sector needs nanotechnology that bestows flavor, taste, mouth sensation, appetite, color, and nutrients to keep ahead in the market. Therefore, nanotechnology would revolutionize future food products and food industries. However, there is a need for comprehensive potential risk assessment system to manage the menace associated with nano-based food before commercialization.

12.13 Conclusion

The perspective of nanotechnology has inexhaustible potential applications that would change and improve the food sector in the economy. Nanotechnology has its application in all facets of food industries from raw materials production to processing to storage to packaging. It is typically implemented to benefit and enhance the quality of food produced from nano-related methodologies and instrumentations with standard and acceptability. Yet, its application in food industries still clawed back due to its safety issues. Consumers perceive that nano-based food products constitute enormous environmental and health related risks which have to be eliminated carefully with new technologies. There is currently no definite data or evidence indicating that food incorporated with nanomaterials will become a serious threat or irreversible damage. Scientific committees have extensively reviewed the applications of nanomaterials in food products and deduced that proactive approach is required while customers are more likely to benefit from this technology. Public acceptance to nano food packing is more on board than nano-based foods. Lack of scientific certainty on the safety evaluation of nanomaterials shall not be a reason for the postponement. We are at the beginning stage of development of nanotechnology in food sector; we have the chance to get utmost benefit from nano foods with negligible risk to human health.

The most important characteristic of nano foods is to enhance the food products quality, desirability, and acceptability as per consumer's demands. Though issues of using nanomaterials in food products may foster distress in customer, it is highly necessary to apprise them about the benefits and risks associated with the product. In the current scenario, nano-based foods are still on the drawing board due insufficient scientific exploration, knowledge gap and awareness about the technology. Many scientific types of research state that nanomaterials are toxic in nature but

none explained the cause for toxicity. Therefore, the nature of the interaction of nanomaterials with its surrounding system is still unknown. More researches are required to completely determine the potential cause of human health on exposure to nanoscale materials available in the food products.

The novel functional properties of nanomaterials make them attractive could potentially lead to health complications. The literatures sttes that nanomaterials ingested into humans gets accumulated in several organs like lungs, brain, liver, bones and spleen. The toxicological studies published on nanomaterials have focused on in-vitro cell culture which is different from animal studies (Ray et al. 2009). Hence, analytical methods are required to study the interactions of nanomaterial with biological components available in the human body to understand the basic relationship of physicochemical properties and mechanistic information. Biomedical field is currently involved in studying the nanomaterials ingested/injected into the living system through in vivo imaging which shortens the gap on how living system respond to these nanomaterials. Advances in information technology leads to the development of computational models that predicts the potential toxicity of nanomaterials through quantitative structure-activity relationships.

The fundamental for toxicity profile assessment of nanomaterials depends on the morphology, chemical constituents, size, mass, concentration, surface modification, agglomeration nature and biotransformation when exposed to the biological matrix (Oberdörster et al. 2005). For the effective application of nanomaterials in food products, basic mechanisms of interaction and reactivity of nanomaterials with biomolecules have to be studied. Therefore, for the realistic implications standardized protocols are needed to study the toxicity of the nanomaterials.

In the present scenario, nanotechnology has the ability to produce novel food products and processes that have the ability to stand high in this competitive market. Future food industries would involve in customizing the products and produce food items by modifying its atomic structures by enhancing its quality and safety level. The existences of strict and rigid regulatory systems in countries that consider nanotechnology as a big push in the future provides reassurances that only safe products will be available in the market. However, there is a need for standardized procedures and novel approaches to test the toxicology/safety profile of nanomaterials used in food products. With no doubt, in mere future smart foods and programmable foods with the aim to customize the product as the individual's concern. The first step in progress would be the development of advanced regulations, toxicological studies and potential risk assessment concerning the impact of nanomaterials used in food products on human health and environment to assure food safety.

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Chapter 13
Halochromic Sensors for Monitoring Quality of Aqua Food

Kesavan Devarayan

Abstract The spoilage of food is often observed by its odor rather than a change of its appearance. However, in the case of packed food, especially aqua foods, detection of such odor is impossible. The degree of spoilage is directly proportional to the quantities of chemicals released during the process. Based on this principle, researchers developed both invasive and non-invasive techniques for monitoring quality of aqua food. Naturally, humans prefer any information in visual format. Indeed, many of the inventions starting from telescopes to microscopes to infrared cameras are simple extensions of our visual senses. It is always preferable to transduce any complex data invisible than any other formats. In this view, recent progress in the development of halochromic sensors for evaluation of freshness/spoilage of aqua food is discussed.

Keywords Halochromic sensors · Aqua food · Time-temperature indicator · Nanomaterials

13.1 Introduction

Aqua foods such as fishery products are an important economic source of protein. Freshness is the most important quality for fishery products. However, aqua foods are easily perishable. Spoilage of fishery products involve in three stages (i) rigor mortis, (ii) autolysis, and (iii) bacterial invasion and putrefaction. Different stages of spoilage are due to enzymatic action, mechanical damage, bacterial action and chemical decomposition (oxidation).

Several instrumental techniques such as spectrophotometers, texture meters, image analyzers, colorimeters, devices to test surface electrical properties and electronic noses are available to measure physical, chemical and biological param-

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_13

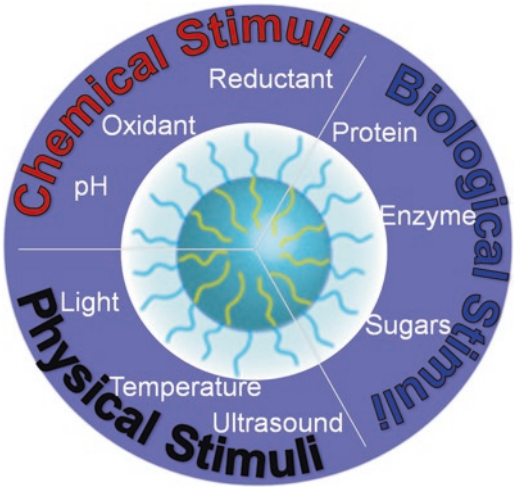

Fig. 13.1 Different stimuli available in nature

eters of packed fish. There are several preceding reviews on the freshness of aqua foods as well as spoilage of fishery products are available. As early as in 1985. (Daniels et al. 1985) reviewed the role of carbon dioxide on food quality. (Haard 1993) reviewed the technologies available for processing and preservation of seafood. Influence of contaminant bacterial proteases was reviewed by (Venugopal 1990). (Olafsdottir et al. 1997; Cheng et al. 2015) reviewed different methods available for evaluation of fish freshness and multisensors (Hyldig and Nielsen 2007) reviewed the techniques developed for evaluation of texture of fish muscle. (Abbas et al. 2008) reviewed the relationship between pH and fish freshness and its impact during cold storage. Besides the conventional strategies for freshness and spoilage evaluation, techniques such as machine-vision and NIR spectroscopy (Liu et al. 2013) were also reviewed. More recently (Kiani et al. 2016) reviewed the artificial senses such as electronic noses, tongues, and machine vision for food quality assessment.

Determination of overall freshness/spoilage was shown to be viable for a complete quality evaluation. The most important chemicals involved in fresh fish are long-chain alcohols and carbonyls, bromophenols and amine-based compounds. On the other side, microbial spoilage produces short-chain alcohols and carbonyls, amines, sulphur compounds, aromatic, and acid compounds. Concentrations of these chemicals are directly correlated to the degree of spoilage. Among these compounds, non-volatile amine such as histamine and volatile amines such as ammonia, dimethylamine, and trimethyl amine are considered as the typical markers for freshness/spoilage detection.

In general, a stimulus is a detectable change expressed by a substance due to internal or external environment. The ability of the substance to respond to the external stimuli is known as sensitivity. There are many stimuli such as chemical, physical, and biological stimuli are available in nature (Fig. 13.1).

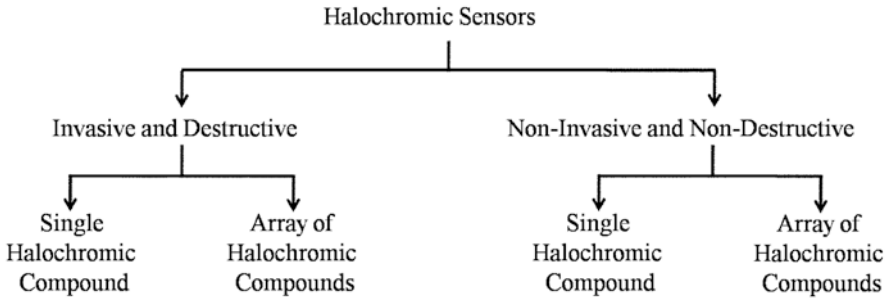

Fig. 13.2 Classification of halochromic sensors for evaluation of freshness of aqua foods

Naturally humans prefer any information in visual format. Many of the inventions starting from telescopes to microscopes are the results of our preference towards visual sense. Colors play important role in sensors. Especially, materials that can reversibly change their colors depending upon the external stimulus such as light and pH are interesting in the field of sensors. Materials that reversibly change their color depending upon the external stimuli are known as chromic materials. The chromic materials are preferred since they can respond with less stimuli. Halochromic or pH sensitive materials can change color due to change in pH, which can be used for applications such as freshness evaluation of fishery products. The following section briefly describes the recent progress in development halochromic sensors for monitoring quality of aqua foods.

13.2 Halochromic Sensors for Evaluation of Freshness of Aqua Foods

It should be noted that the primary aim of any research on aqua food quality is to find suitable methods and techniques to accurately and quantitatively measure the spoilage throughout the course. Depending on the freshness evaluation method, halochromic sensors can be broadly classified into two, namely (i) invasive and destructive and (ii) non-invasive and non-desctructive sensors (Fig. 13.2). Further these sensors are classified into two based on whether the halochromic component is a single compound or an array of compounds. The halochromic sensors can also be grouped into two based on the natural or synthetic origin.

13.3 Invasive Halochromic Sensors and Detection of Histamine

Histamine is a biogenic amine produced during microbial action in fishery products. During spoilage of fishes, for instance tuna and mackerel, histidine is converted into histamine by an enzyme produced by certain bacteria. Though trace amounts of histamine is required for proper functioning of the human immune system, large quantities of histamine lead to allergic reactions known as scombroid poisoning. It should be noted that presence of larger quantities of histamine is an indicator of fish spoilage even if the decomposition is not recognized by naked eye.

Unlike other amines evolve from microbial degradation of fish flesh; histamine is non-volatile at ambient conditions and non-destroyable by cooking. Hence, histamine could be a useful marker especially considering the temperature gradient. The preceding researches on colorimetric arrays involve in multi-step extraction and purification of histamine by chromatographic techniques. (Patange et al. 2005) reported a multi-step determination of histamine present in tuna. It involved in extraction of histamine from tuna and treatment of the extract with several reagents and finally treated with p-phenyldiazonium sulfonate to develop colors between pink and red. However, the change of colors was very narrow ranged and non-distinguishable with naked eye.

In an attempt, (Oguri et al. 2006) accidently found that 2,3-naphthalenedicarboxaldehyde (NDA) as a suitable halochromic material for sensing of histamine. The authors extracted histamine from sample using trichloroacetic acid and neutralized using dilute sodium hydroxide solution. The extracted histamine was passed through a column packed with silica gel (HA catridge). Then the least concentrated NDA solution was loaded in the column. After 3 mins of the loading color of the column changes from white to indigo-blue. It should be noted that this HA catridge sensor coupled with NDA could detect histamine raging from 25 to 1000 mg/kg of the sample.

13.4 Aggregation-Induced Response-Based Halochromic Sensor

(Nakamura et al. 2011) developed a sensor that not only detect but also identify biogenic amines. The sensor developed in this study is based on the principle that the interaction between amines and carboxylic acid moieties occur through hydrogen bonding and/or electrostatic interactions. The authors synthesized analogs of tetraphenylethenes (TPE) with carboxylic acid. TPEs integrated with carboxylic acid moieties exhibit fluorescence emission when they recognize amines and then form aggregates. 1,2-ethylenediamine, 1,3-propanediamine, 1,5-pentanediamine, 1,6-hexanediamine, spermidine, spermine, histamine, tryptamine, and phenethylamine were examined in this study. The multivalent interaction between carboxylic

acid and amine that lead aggregation was used to distinguish one amine from another since the fluorescence response pattern and intensity are unique for each amine. Further, the sensor was demonstrated to work as a freshness sensor for tuna fish based on the histamine concentration present on the matrix.

13.5 Multistate Response-Based Halochromic Sensor

One of the major drawbacks of the halochromic sensors is that they show color changes irrespective of the chemical structure of the amines. In other words, the colorimetric sensors developed so far cannot provide specific information about the amines or the compound that cause spoilage. It would be beneficial if the sensor could respond depending upon interaction with different amines. In an attempt to address this issue, (Maynor et al. 2007) evaluated a single cross-reactive conjugated poly(thiophene) as a sensor to detect amines that are closely relevant to biogenic amines. In this study, response of poly(thiophene) was examined against 22 amines using the principle of analyte induced aggregation of the polymer. Depending on the amine that interacts with the sensor, the interchain conformational changes were produced along with specific optical finger prints. The absorbance curve observed was the collective response of all the characteristic interactions with different amines. The variations in the optical response can be monitored for distinction of different amines.

13.6 Non-Invasive Electronic Noses as Halochromic Sensors

Though histamine is a good indicator for aqua food spoilage, detection of histamine requires tedious extraction procedures, invasive and destructive techniques. Volatile amines are general by-products of fish spoilage. Further humans can sense these volatile amines 10^4 times than other compounds such as alkanes, alcohols, and ketones. Thus, volatile amines evolve from the spoilage of aqua food can be used for developing non-invasive and non-destructive sensors.

Generally, the application of halochromic sensors for freshness evaluation is limited since they cannot detect the total volatile amines at low concentration. However, the fish at an initial stage of spoilage releases lower levels of volatile amines. Therefore, it is important to develop sensors that can detect low concentration of amines at incipient stages of spoilage. In this view, Kenneth S. Suslick et al. developed a simple colorimetric sensor array for identification of volatile amines by four different chemically responsive dyes. Molecular recognition was done based on four different chemical properties of the volatile amines namely (i) behavior of analytes towards metal coordination, molecular size and shape, acidity and basicity, and polarity. Thus the following four dyes were employed, (i) metalated tetraphenylporphyrins were used to sense the Lewis acid/base interactions of the amine;

(ii) bis-pocketed Zn porphyrins were used to distinguish between amines based on their size and shape; (iii) common pH indicators such as methyl red and Nile red to sense the amines on the basis of Bronsted basicity, and (iv) highly solvatochromic dyes such as Reichardt's ET_{30} betaine dye to sense the polarity of the amines. In order to avoid influence of humidity on the response of colorimetric array, hydrophobic dyes and substrates were selected. Amines such as n-butylamine, n-hexylamine, n-octylamine, cyclohexylamine, pyrrolidine, piperidine, homopiperidine, pyridine, diethylamine, dipropylamine, diisopropylamine, and trimethylamine were analytes in this study. The results showed that the sensitivities of the colorimetric sensing array were well below 1 ppmv with distinction between isomeric amines.

In an attempt, (Huang et al. 2011) designed a colorimetric sensor array based on chemosensitive dye having strong interaction center coupled with active intense chromophores. The dyes such as bromocresol green, bromocresol purple, and cresol red were used as halochromic components. Porphyrins and their corresponding metal complexes were employed for intense chromophores. The authors developed an artificial olfaction system that comprises of a sampling chamber, reaction chamber with sensor array, and a scanner connected with a computer. The halochromic sensor array reacts with the compounds emitted by the fish sample and the color changes were monitored by a scanner and recorded at 24 h interval in the computer combined with analyzing software. The authors also employed principal component analysis and neural network for determining the degree of spoilage.

Similarly, in an attempt (Zhonglin et al. 2010) developed a novel halochromic sensor array based on set of six halochromic dyes. Zinc and cobalt complexes of phorphyrin compounds were considered as chemically sensitive dyes. The sensor array consisted of sampling system with a flow controller, sensor array combined with digital camera that is connected to a computer. The halochromic sensor array demonstrated to detect six-health related trimethyl amines.

Morsy et al. developed a colorimetric sensor array based on sixteen chemosensitive compounds such as alizarin, bromocresol green, bromocresol purple, bromomethymol blue sodium salt, bromophenol blue, Carminic acid, chlorophenol red, cresol red, crystal violet lectone, Curcumin, Methyl Red, Phenol Red, Reichardts dye, 2,6-dichloro-4-(2,4,6-triphenyl-1-pyridinio)phenolate, Rosolic acid, and xylenol blue. The sensor was prepared by dropping these dyes separately on silica gel Kieselgel $60F_{254}$ plates using microsized poly(methyl methacrylate) as a mask. Then this sensor array was fixed inner side of the lit of a jar. As a control the sensor arrays were placed inside the jar and exposed the spoilage compounds such as trimethyl amine, dimethy amine, and cadaverine each 200 ppm for 1 h at room temperature and the color changes were noted. Besides, freshness markers such as octen-3ol and hexanal each 10 ppb solution were also kept inside the bottle. The fillets of fresh atlantic salmon was placed in the jars and the spoilage was monitored at room temperature and 4 °C up to 9 days. The color changes exhibited by the colorimetric sensor well correlated with the pH and volatile amines content (Morsy et al. 2016).

A versatile and highly selective colorimetric sensor was developed using Meldrum's activated furan (MAF) for detection of sub ppm level amines in solution as well as in vapor state. In this study, MAF is synthesized via a one step reaction from economic materials. MAFs are sensitive towards both primary and secondary amines and respond by exhibiting different colors. The authors evaluated the usefulness of this MAF coated nylon filters for sensing of spoilage of cold and tilapia. The freshly thawed fish samples were placed in a glass jars containing the sensor and the color changes were monitored for 48 h. The sensor exhibited very distinct color changes on exposure to volatile amines evolved from the fishes. The sensor exhibited detection limit lesser than 1 ppm of volatile amines (Diaz et al. 2017).

A TiO_2 based nanoporous colorimetric sensor array was developed by Xiao-wei et al. for detection of trimethylamine. The following eight chemoresponsive dyes were used for preparing the mixture: gential violet, leucomalachite green, tymol, methyl yellow, bromophenol blue, congo red, methyl orange and screened methyl orange. The dye mixture was printed on a nanoporous film prepared from TiO_2 and tested for its sensing abilities. The colorific changes were observed in the sensor upon exposure to TMA. Using a computational program the RGB values were evaluated to understand the limits of the sensor (Xiao-wei et al. 2016)

In an interesting study, a colorimetric array sensor was developed for freshness evaluation of sea bream. In this study, five chromogenic dyes such as bromocresol purple, resorufin, bromophenol blue, phenol red and dinuclear complex of rhodium were used. Each dye was coated on inorganic supports such as aluminium oxide and silica gel via simple absorption process. Finally the colorimetric array was prepared by placing dye-coated inorganic supports into a microplate. In order to correlate the spoilage and the sensor activity in a better sense the authors performed physic-chemical and microbiological analysis of the sea bream samples. CIELAB values were calculated using photoshop software and statistical analysis such as principal component analysis also performed using the physic-chemical and microbiological analyses data. The results of optoelectronic nose and analytical data correlated well with each other which indicated the ease of using the developed sensor for monitoring fish spoilage (Zaragozá et al. 2013)

Alexis Pacquit et al (2006) developed a volatile amine sensor for detection of fish spoilage. In this study, optically clear PET was used as a substrate and sensor solution containing bromocresol green, cellulose acetate binder, an ammonium salt such as octadecyl trimethyl ammonium bromide and its analogs, and a plasticizer such as DBS or NPOE were used to fabricate the sensor. The sensor solution was spin-coated onto the substrate and dried appropriately. Then the sensor was covered with gas permeable PTFE. The membrane serves as a protective layer from condensation of water vapor where as the PET minimizes the reflectance loss during reflectance measurement. The color change of the sensor was monitored using an in-house developed reflectance colorimeter comprising of light emitting diodes and a photodetector. The developed sensor exhibited color changes from yellowish green to dark green depending upon the concentration of the volatile amines. In addition, the authors performed fish spoilage trial using cod fish. At first the sensor did not show

any color change until 18 h. Thereafter, the sensor developed colors from yellow to blue between 20 and 38 h. After 38 h the sensor did not exhibit any significant color changes which were observed to be the saturation point of the sensor. It is interesting to note that the thicker sensors with spin coating speed 1000 rpm exhibited more intense color to the naked eye than 2000 or 3000 ppm speeds.

13.7 Time-Temperature Indicators (TTI)

During post-processing phase the aquatic foods are handled at different temperatures. Indeed temperature plays vital role in spoilage of fish. Therefore, it is important to monitor, record, and control the time-temperature during the post-processing phase. In an attempt by Chahattuche et al. Bromothymol blue and methyl red were used to prepare dye mixture solution. Then the dye mixture was mixed at four different concentrations with agar homogeneously. As a control measurement lactic acid at different concentrations were tested on this TTI at different time scale. The results indicated that the developed TTI could exhibit different colors based on the concentration of lactic acid and the time-temperature (Wanihsuksombat et al. 2010).

In an attempt, Valdir Aniceto Pereira Junior et al. has prepared a TTI based on polyvinyl alcohol (PVA)/chitosan composite film incorporated with anthocynains extracted from red cabbage. The authors used CIELab scale for measurement of color changes exhibited by the sensor due to change in the pH. Though the sensor was found to be sensitive against pH changes, experiments on sensing of volatile amines were not performed (Pereira Jr et al. 2015).

Shukla et al. developed a colorimetric indicator using bromophenol blue/filter paper strip for sensing of total volatile amines released from red meat. The sensor was fabricated by coating the dye onto the filter paper via centrifugation. Then the indicator sensor was covered with porous low-density polyethylene. This sealed indicator sensor was placed inside a red meat pack which is completed closed. The sensor exhibited different colors from yellow to green to blue depending on the storage days. The colors were highly visible and clearly distinguishable to the naked eye (Shukla et al. 2015).

13.8 Natural Dyes-Based Halochromic Sensors

Most of the synthetic dyes exhibit halochromism. Therefore, many of the preceding reports on halochromic sensors involve in synthetic dyes. Meanwhile, use of synthetic dyes is associated with detrimental effects on the environment and human health. Alternatively, bio-based dyes or pigments extracted from plant sources can be used. However, use of natural dyes is challenging due to lesser stability towards light, oxidation, temperature, and pH.

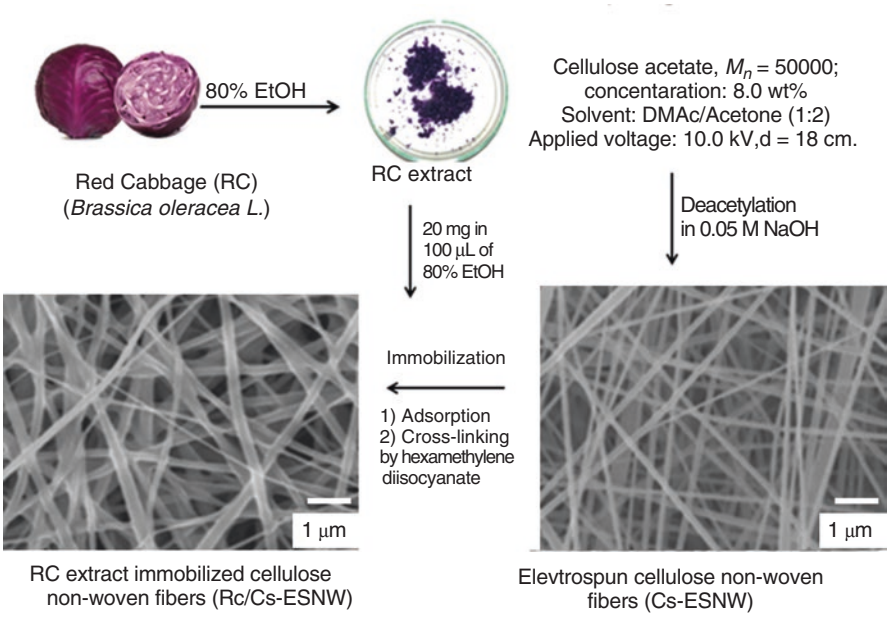

Fig. 13.3 Schematic representation of preparation of red cabbage extract/cellulose nanofiber non-woven (RC/Cs-ESNW) mat based halochromic sensor

Anthocynanins are the most abundant natural pigment. It is significantly available in black raspberry, blueberry, red cabbage and others. Studies on natural food colorants revealed that acylated anthocyanins are more stable against light and temperature than other forms (Anna 2005). Anthocyanins present in red cabbage (RC) (*Brassica oleracea L.*) were found to contain acyl moieties. In addition anthocyanin extracted from red cabbage possesses good water solubility and sensitivity towards extended range of pH. Cellulose is the most abundant natural polysaccharide which is biocompatible and ecofriendly. The hydroxyl groups present in cellulose opens up opportunity for chemical modification for immobilization or conjugation of biomolecules (Devarayan et al. 2013a; Devarayan et al. 2013b; Devarayan et al. 2013c, d; Ohkawa et al. 2013; Devarayan and Kim 2015; Viswanathamurthi et al. 2012).

Electrospinning is convenient and economical technique used for preparation of nanofibers from natural polysaccharides. Nanofibers possess unique properties such as high surface area and high porosity which are preferable for sensors. In view of unique properties of nanofibers combined with natural origin of cellulose, the author of this chapter developed a reversible and universal halochromic sensor based on RC extract and cellulose (RC/Cs ESNW) nanofiber mat .

Figure 13.3 shows the preparation of the RC extract/cellulose nanofiber mat. In brief, the bulbs of the fresh red cabbage were smashed and soaked in 80% and 100% ethanol separately for 24 h. Then the solvent was removed under *vacuo* at 40 °C followed by storage at 4 °C to obtain crystalline crude extract of RC. On the other

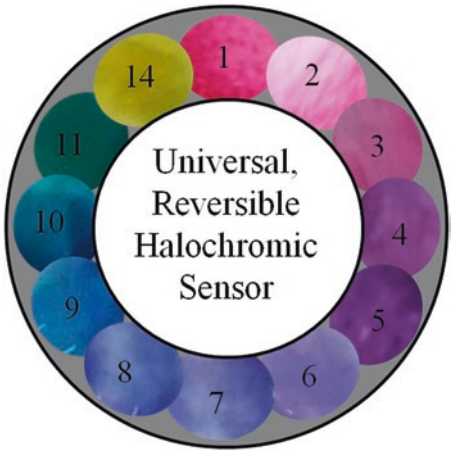

Fig. 13.4 Halochromic response of RC/Cs-ESNW nanofiber mat sensor

hand, cellulose acetate solution prepared in Dimethylacetamide and acetone (1:2) was electrospun and deacetylated in 0.05 M NaOH to obtain cellulose nanofiber mats (Cs-ESNW).

At first the authors tried to incorporate the RC extract by simple adsorption process. The response of the halochromic sensor was recorded in aqueous medium at different pH. However, leaching of large quantities of natural dye was observed during test of halochromism of the sensor. Therefore, after adsorption process a bifunctional cross-linker, hexamethylene diisocyanate was employed to immobilize the natural dye on the cellulose nanofiber mat. Thus introduction of cross-linker reduced leach out of natural dye by 65%.

The RC/Cs ESNW nanofiber sensor developed different colors in 5–10 s with respect to different pH as shown in Fig. 13.4. Unlike the curcumin based halochromic sensor, the RC based sensor exhibits unique colors for each pH. For pH 12 to 14 the sensor shows more or less similar yellow color response. The developed bio based nanofiber sensor was tested at two extreme temperatures such as −50 and 100 °C. The results indicated that the sensor retains its halochromic behavior even after treatments at different temperatures. Further, RC/Cs ESNW nanofiber sensor exhibited excellent color reversibility.

The potential application of this sensor could be for freshness evaluation of fishery products. For instance, the developed halochromic sensor can be used for 'on-package' monitoring. In this case, the volatile amines evolve out of the fishery product interacts with the RC/Cs ESNW nanosensor and can develop different colors depending on the concentration of the amines. It should be noted that the RC/Cs ESNW nanofiber mat function as an 'on-package' sensor in the absence of any liquid. Therefore, it is expected that the sensor do not show any leach out of the halochromic component. Further, the RC extract is a natural dye which is expected to be biocompatible.

In an attempt, Zhai et al. (2017) developed a new colorimetric sensor based on starch/PVA films incorporated with anthocynains extracted from flowers of roselle (*Hibiseus sabdariffa* L.). At first the authors extracted anthocyanins from dry flowers of roselle. Then the natural pigments were immobilized onto the starch/PVA by casting/solvent evaporation method. It was observed that the colors of the developed films were stable at refrigeration and at room temperature up to 14 days. As an example, the authors subjected this sensor for freshness evaluation of silver carp (*Hypophthalmichthys molitrix*) at refrigeration. The colorimetric sensor exhibited color changes over the time due to changes in the pH which is attributed to the evolution of total volatile amines from spoilage of the fish. This colorimetric/thin film sensor can be used as a smart packaging sensor.

Kuswandi et al. (2012) developed a curcumin-based sensor for detection of volatile amines. The authors extracted the major yellow pigment from turmeric, a commonly used spice and immobilized on bacterial cellulose membrane via absorption method. The curcumin/bacterial cellulose nanocomposite exhibited color changes from yellow to orange to reddish orange depending on the pH developed by the volatile amines evolved from shrimp spoilage. The colors were clearly visible to naked eye. The quantitative measurement of the total volatile amines was performed by measuring colors via photoshop software. The results indicated that the color changes were directly proportional to the bacterial growth patterns in the shrimp samples. This bionanocomposite was employed as an on-package sticker sensor for real-monitoring of shrimp spoilage.

13.9 Conclusion

Freshness is an important quality for fishery products. The research on development of bio and nanocomposite based halochromic sensor is at incipient stage. Very few reports are available for bio and nano-based halochromic sensor for monitoring the quality of aqua food. The recent progress in halochromic sensors for freshness evaluation of aqua foods covers a variety of methods including multi-step determination of histamine, halochromic array sensor coupled with chemoresponsive dye and chromophore, multi-state response from analyte induced aggregation, fluorometric sensor with aggregation induced emission, and bionanocomposite based sensor developed using halochromic dye extracted from curcumin and an universal sensor developed using red cabbage extract and cellulose nanofiber mats. Almost all of the methods employ techniques for detection of total volatile amines such as ammonia, dimethylamine and trimethylamine.

Natural dyes are potential alternatives for synthetic dyes for preparation of halochromic sensors. However, much more research on development of bio based nanosensors is required in order to address issues such as biocompatibility, stability of the natural dyes, and leach out of halochromic component at extraordinary situations.

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Chapter 14
Mechanism and Application of Nano Assisted Carrier Systems in Food

Ekambaram Nakkeeran, Asaithambi Kalaiselvi, Ravichandran Rathna, and Gnanaleela Aswin Jeno Jose

Abstract Nanotechnology is the most interesting area pivoted on several disciplinary of sciences and engineering. Nano based materials are designed to exhibit unique tunable attributes tailored with distinct physicochemical properties for its desired application in various fields. Even bacteria would need a microscope to understand and study the size range of nano materials. More than tens of million dollars are invested and spent globally in companies to promote nano based applications in food sectors from production to packaging. Nano assisted carrier systems (NACs) are promising delivery system in food sector that has the capability to augment the stability and bioavailability of encapsulated bioactive compounds, flavours and colours. However, the importance of NACs led to the consideration of attributes, mode of action on living system and biological fate. This chapter outlines the current status of nanofoods, nano formulations, effects of NACs features, interactions and fate of the edible NACs exploited in the food industries.

Keywords Nanocarrier system · Nano foods · Delivery systems · Nanocarrier attributes · Biological fate

14.1 Introduction

Implementation of "science of small" across the field of science and technology has tremendous prospective to significantly improve the economy and social conditions globally. During the era of Greek, Roman, and Egyptian empire, nano based materials used in arts, crafts and cosmetics before the exploration of nanotechnology unintentionally. Many researchers and technologists consider nanotechnology as the milestone for mankind in exploring the advancements in science and technology.

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© Springer International Publishing AG, part of Springer Nature 2018

S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_14

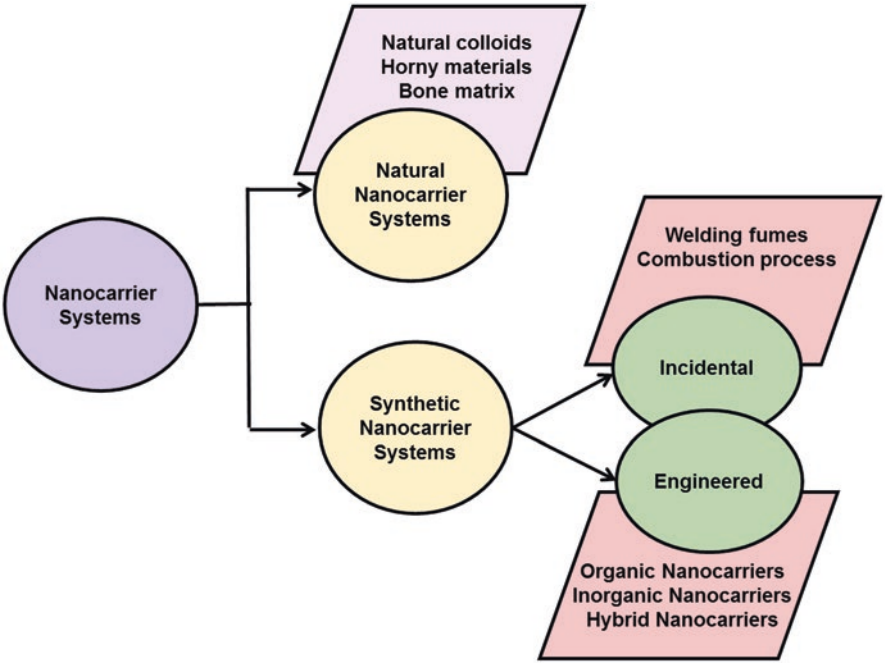

Fig. 14.1 Classification of nano assisted carrier systems

Dimensions of a material are highly responsible for its physicochemical nature. The nature and physicochemical properties of nano-sized materials are diverged from its bulk form that allows its unique use in biomedicine, remediation, cosmetics, robotics, ceramics, etc (Elango et al. 2015; Madhumitha et al. 2016; Roopan et al. 2014). From the current state-of-art, nano assisted food technology is still in its commencement, however, nano assisted carrier systems (NACs) are used to impart better quality of food product in food sector. Emergence of pasteurization technique by Louis Pasteur in the nineteenth century is regarded as a prodigious entry of nanotechnology into food technology. In general, NACs are grouped into two types namely natural and synthetic NACs as depicted in Fig. 14.1.

The structural components such as polysaccharides, proteins, starch granules, etc., in food are nanomaterials which is accountable for the organoleptic aspects. NACs are predominantly used in tissue engineering and pharmaceutical application as delivery scaffolds and delivery system, respectively. In recent years, NACs are used as supplements, fortified and nutraceuticals in food sectors. There are three types of NACs, namely, organic, inorganic and hybrid NACs. Organic NACs are generally known as smart particles fabricated using high-density organic constituents like lipid, protein, polymers etc., to obtain unique functionality that helps in improving the palatability nature of food products. Examples of organic NACs are liposomes, polymersomes, ferritin, dendrimers, micelles, nanospheres, nanoemulsion, nanogels, etc. Inorganic NACs are the nano-sized carrier system that

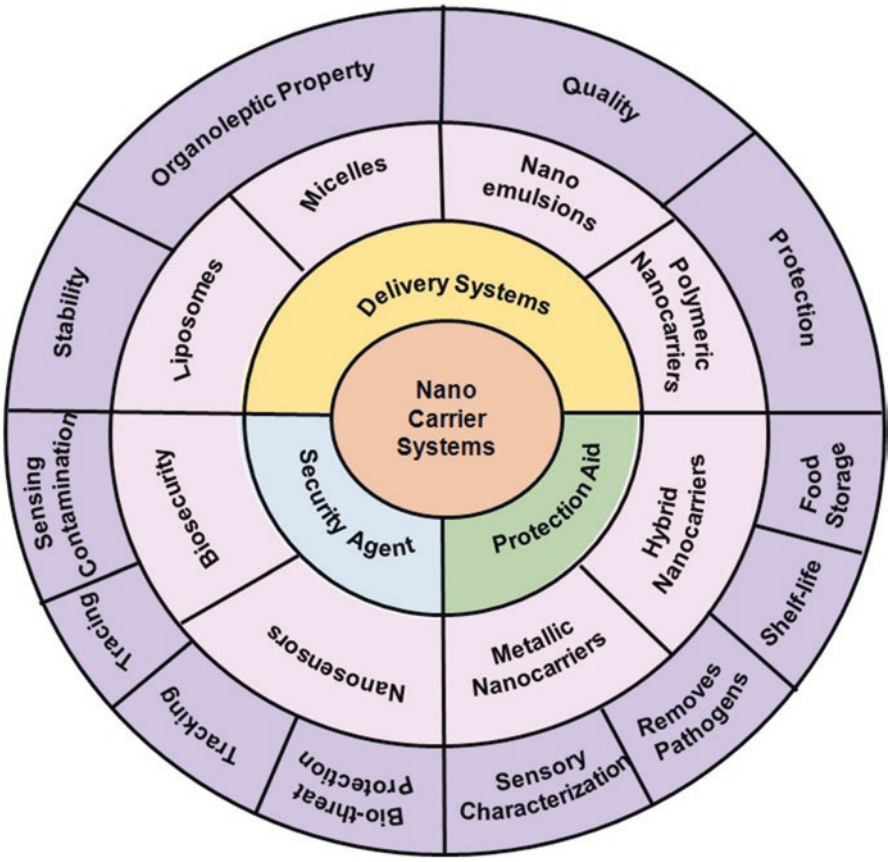

Fig. 14.2 Applications of nano assisted carrier systems in food sector

possesses the characteristics of the inorganic matrix such as metal, metal oxide or semiconducting matters used for its synthesis (Elango and Roopan 2016). Examples of inorganic NACs are nanoclays, quantum dots, metal nanocarriers, metal-oxide nanocarriers, magnetic nanocarriers, etc. Notably, inorganic NACs are used in food industry as packaging materials, antimicrobial agent, and sensors. Hybrid NACs are amalgamation of organic and inorganic matrix functionalities for the synthesis. Hybrid NACs are mainly used in food protection and applications in beverages and nutraceuticals. The distinct functionality of these NACs helps in enhancing the texture, sensorial, flavor, antimicrobial, self-life, absorption, and nutritional properties of the food products.

Nanotechnology uses NACs as next generation system in food processing and packing. Traditionally, nanocarriers are implemented into three distinguished categories in food sector, namely, delivery system, protection aid and security agent. Fig. 14.2 illustrates the categories of NACs and its application in food based sectors. In 2005, Woodrow Wilson International Center facilitated commercialization and

easy access of nano based products to the consumers globally through Nanotechnology Consumer Products Inventory (CPI) (Vance et al. 2015). Nanotechnology has proven to solve one of the leading food shortage problems in the world by tailor-made precision farming and food production by augmenting its quantity, quality and safety (Abbott and Maynard 2010). Bio-nanotechnology is contemplated to be one of the highly interdisciplinary fields that combine both life sciences and engineering (Hemalatha and Madhumitha 2015; Hemalatha et al. 2013). Thus, bridging the gap between biosciences and nanotechnology by means of biosensors and lab-on-a-chip systems (Kampers 2008) (Fig. 14.2).

For the past few decades, nano based researches, innovations, patents and products are rapidly increasing for its world-wide applications. Minimal usage of nano-salt gives the exact salty taste as that of the commercial salt. GuardIN Fresh uses silver-coated nanoparticles to enhance the shelf life of perishable food products by avoiding microbial interventions through the conversion of ethylene gas to ethylene oxide (Anuar et al. 2013). Silver nanoparticles are known for its antimicrobial activity and used as a coating agent to preserve stored foods for longer duration, therefore, silver nanoparticles impregnated bacteriocins effectively inhibits the broad-spectrum of microbial food contaminants with enhanced shelf life (Sharma et al. 2012). Recently, Bionanotechnology center (BioNT) encourages new startups and nano based sectors to effectively deploy the application of nanotechnology in food and its allied fields to improve nutritional quality of food products (Sekhon 2010). Several Nano-structured materials are currently under progress in research and development. The nano-laminated coatings along with encapsulated lipids, bioactive lipophilic compounds could be easily incorporated into foods or beverages, which may increase its stability, palatability, desirability and bioactivity (McClements 2010).

This chapter emphasis on the mechanisms and applications of NACs reported in the literatures for food sector. It starts by the different formulations of NACs used in food items to enhance the quality and stability. The next part is devoted to the effect, fate and mechanism of NACs inside a living system.

14.2 Nano Foods

The term “Nanofood” implies the use of nanotechnology proficiency in the course of cultivation to product commercialization. Nanofoods are termed as “The small food revolution” which was scientifically possible to design fantasy food stuffs using nanotechnology (Davies 2010). Presently, nanofoods have secured more focus globally as smart foods by altering the nutritional, dietary, shelf life and organoleptic profiles of the classical food products. Nano mediated formulations helps in enriching the taste, texture and masks odours. Nano- designed foods evidentially proved its beneficiary effects by facilitating low calorie intake of high fat and oil rich foods such as bread spreads, ice creams, hollandaise sauce and mayonnaise. Emulsion based nanofoods helps in transforming fats into tiny oil in

water droplets through whipping process and stability is maintained by protein layers. These nanoemulsions are strengthened by protein coating which assists in bypassing the gastric digestion and leads lipids to get exposed in the ileum region by burst release to attain satiety. Probiotic based foods with nano delivery formulations are potentially delivered into living system that enhances the benefits of bacterial cells in the gut of human system (Lee 2014). Global malnutrition can be tackled by using nano based food supplements. Recently, silica nanoparticles coated coco ingredients are used in chocolate industries to enhance the flavor, texture, palatability and giving a pleasure hit to the taste gustatory cells when consumed. In fortified food products, NACs are used to encapsulate essential oils, vitamins, minerals and lipophilic nutrients by masking its nature without altering the organoleptic profiles. NACs based food products such as Nanotea, meal replacement Silm shakes, nano assisted cooking oil, nano-mediated chocolate diet shake, nanosalt, nanosurgars, nano assisted probiotics, nano mediated milk beverage, etc., are few examples of commercially available nanofoods. Therefore, nanotechnology would eventually provide several applications in food and beverages industries.

14.3 Formulations in Food Technology

The properties and applications of various nano assisted carrier systems used in food are given in Table 14.1.

14.3.1 Self-assembled Natural Nanostructures

Self-assembled naturally produced nanostructures such as starches, protein and fats are consumed as an important raw material in day-to-day life (Morris and Parker 2008). During food processing, the naturally assembled nano ranged structures undergo several structural modifications through various physicochemical reactions. Further, components reassemble into large aggregated structures and assemble as gel networks (yogurt). Nano tubes (α-lactalbumin) obtained from hydrolyzed milk protein behaves as a potential carrier system which enhances encapsulation of micro- and macro- nutritional supplements (Bugusu et al. 2009). Sensitive hydrophobic nutraceuticals are fortified with other edible food merchandise and delivered through nano vehicles for protection and entrapment of active compound, casein micelles (Livney and Dalgleish 2007). Nano assembled structures present in food ingredients are developed to increase and improve taste, texture, colour, consistency and palatability of food products. For example, various blends of starches are contained in green peas (Greenshaft) variety, mayonnaise and spreads with low-fat content due to nano structured emulsions. Using nano structured carrier systems, ice creams are creamier due to altered full-fat content and healthier option is given to the consumers (Meetoo 2011).

Table 14.1 Properties and applications of nanocarrier systems in food technology

Nanocarrier systems	Properties	Applications
Self assembles natural nano structures	Highly sensitive to changes around	Nano tubes (α-lactalbumin) used in encapsulation
	Highly stable	Production of low starch green peas (Greenshaft)
		Lactoferrin, protein conjugated nanocarriers in dairy industry
Engineered nano materials	Exhibits anti-bacterial property	Nano-selenium added green tea
	Highly stable and site targeted delivery	Nano-calcium and magnesium salts
		Nano-enriched chewing gum
Polymer based nanocarriers and edible coatings	Exhibits controlled release of active compounds	Used as edible coatings in food industry
	Highly targeted delivery	Cellulose nano-fibres are used in improving taste of foods
Nano liquid formulations	Highly specific sized structure	Iron or zinc-containing nano structures in pharmaceutical industries
	High stability, non-antigenic, non-toxic and increased biodegradability	
Nano-encapsulated carrier systems	Highly specific to the site of action	Octenyl succinic anhydride-ε-polylysine, a bifunctional molecule that can be used an antimicrobial agent
	Exhibit controlled release kinetics	Hydrophobically modified starch formed with curcumin
Liposomes	Have a very good stability over its size	Used in the synthesis of anti-inflammatory agents, anti-cancer, anti-infection
	Can contain one or more lipids within their structure	Used in the synthesis of hydrophilic drugs such as anticancer agent doxorubicin or acyclovir
	Can exhibit controlled release of the bioactive compounds	
	Non-toxic, flexible, bio-degradable, biocompatible	
Archaesomes	Highly thermostable	Used in the synthesis of intravenous medications
	Resistant to low pH and high salt concentration	Anti-cancer formulations
	Excellent carrier for bioactive compounds and cell delivery	Targeted gene delivery and delivery of natural antioxidant compounds
Colloidosomes	Can exhibit controlled release mechanism	Used in food and beverages

(continued)

Table 14.1 (continued)

Nanocarrier systems	Properties	Applications
	Extremely small in size	Zein-sheets (protectant sheet synthesized from Zein)
	Exhibits easy dispersion mechanism	
	Highly stable	
Nanocochleates	They are more stable than liposomes	Nanocochleates can deliver Omega-3 fatty acids to cakes, muffins, pasta, soups, and cookies without altering the products taste or odour
	They maintain structure even after lyophilisation	Delivery of amphotericin B, a potential antifungal agent, orally and parentally.
	Exhibit efficient incorporation of biological molecules	Apo-A1 formulation of the treatment of atherosclerosis
	Highly protected against degradation	

The most frequently addressed natural nano device is cow's udder because it has the ability to produce and dispense nano ranged protein micelles and phospholipid globule structures in milk (Rai et al. 2015). In general, naturally available nanostructured food products are fat globules, micellar caseins, yoghurt (gel networks), cheese (plastic solids), ice cream and whipped cream (foams) and whey proteins build a myriad of proteins as butter (emulsions) (Aguilera and Stanley 1999). Microtechnology as well nanotechnology is existed in natural foods for long. These nanostructures are focused by the researchers in recent years mainly to control the functional behaviour of food such as colour, flavour, quality control, processing time and production cost. Also, researchers focus on modification of food matrices with a different function behaviour from its originality.

From field to fork, nano sciences and their applications are found in all phases of the food cycle. Therefore, nano structured materials are utilized as building blocks to create and introduce novel functions into food matrices such as emulsions, carriers, liposomes and fibres. Various nano products are produced using natural nano-vehicles derived from protein-polysaccharide conjugate, core-shell nanocarriers, lactoferrin nanocarriers, ferritin nanoparticles, β-casein nanocarriers etc., in delivering hydrophobic or lipophilic active compounds with effective in-vivo delivery across the blood-brain barrier (Livney 2010).

14.3.2 Engineered Nanomaterials

In food sector, engineered nanomaterials (ENs) are regarded as one of the pillars of next generation food products. ENs are considered as a tool to develop advancements in food sectors by augmenting the production of crop material, food processing and

intelligent systems to systematically monitor the merchandised products (Martirosyan and Schneider 2014). The most commonly used ENs are polymeric nanoparticles (PLGA (poly(lactic-co-glycolic) acid) -nanoparticle, chitosan nanoparticles), phospholipid nanoparticles (liposomes), carbon nanotubes, metallic (gold, silver) and metal oxide (zinc oxide, titanium oxide) nanoparticles. These ENs have enormous function from processing to packing of the food materials. Postmenopausal osteoporosis can be treated with nanocalcium fortified milk (Park et al. 2008). The deformation and flow of xanthan gum can be modified using sodium magnesium silicate nanoparticles (Attia and Musa 2015). Iron oxide nanomaterials act as an excellent adsorbent and photocatalysts that makes it a promising EN to treat water by breaking down the organic pollutants and destroying microbial pathogens (Xu et al. 2012).

In early days, metal oxides like titanium dioxide nanoparticles were used as colourants for confectionery and beverages (Shi et al. 2013). Wageningen University, Holland has launched two nanofood products such as cola taste nanomilk and low fat nanomayonnaise (Grumezescu 2016). Nanotea developed by Chinese is presumed to contain nanoselenium (Grumezescu 2016) and beta-carotene protected nanoparticle in juice fortification (Pourreza and Naghdi 2015). Surface functionalized ENs (SF-ENs) has certain functions such as microbicidal activity, preservative action by absorbing oxygen. SF-ENs protects the food matrixes against oxidation, volatile compounds and moisture (Robson 2010). Nanocomposites of montmorillonite are considered as magnificent food packaging material for its enhanced gas-barrier properties (Nazir et al. 2016). Nanoclays are utilized as food supplements (vitamins, flavonoids, essential fatty acids) and additives (ascorbic acid, citric acid) in various food products (Putheti 2015). Nano charcoal from bamboo is a promising adsorbent and helps in decolouration and purification (Augustin and Hemar 2009).

14.3.3 Polymeric Nanocarriers and Nano Coatings

Polymeric nanocarriers are prepared using surfactants and polymers such as alginic acid, polylactic-co-glycolic acid, chitosan etc. It is mainly involved in the site/target directed delivery of functional compounds with a controlled release that serves as nanocarriers for anti-microbial components. The physicochemical properties such as stability, cohesiveness, solubility, and reactivity of polymeric nanocarriers can be altered than conventional materials. Nano metallic oxide compounds (zinc and magnesium) exhibits more potency towards microbes and employed as an affordable material in various nano food packaging systems as coatings (Honarvar et al. 2016).

Nano coating efficiently retains carbon-dioxide and prevents oxygen entry into the package (oxygen scavengers) and about 1 to 2-micron coating is deposited with amorphous carbon inside polyethylene terephthalate bottle prevents entry of gases

(De Azeredo 2009). Similar to conventional packaging systems, nano edible coatings improve the shell life of the edible product by protecting the food matrix from exposure to gas, moisture and also act as a delivery system of anti-browning agents, enzymes, antioxidants. Edible films effectively improve the taste and texture of mango puree due to reinforcement of nano-structured cellulose (cellulose nanofibers) (Azeredo et al. 2009).

14.3.4 Nano Emulsion Systems

Nanoemulsion is a typical nano ranged colloidal micellar structure generally removing harmful substances from the packed food matrixes. These NACs have gained a lot of importance in the food processing sector for its decontamination and high lucidity of product quality and organoleptic properties. For example, nanoemulsion is used for fortification of beverages with vitamins, antioxidants and minerals. Growth of harmful bacteria's like *Salmonella* sp. can be eliminated using nanoemusion systems (Shah 2014). Nanoemulsion system could be stabilized and used for delivery of functionally active compound by polymeric components (alginate, chitosan) to the system (Pathakoti et al. 2017). Submicron-sized lipid emulsions formed with solid lipid through controlled crystallization is promulgated for the consignment of bioactive compounds like tetraterpenoids (Weiss et al. 2008). Nanoemulsion assist in augmenting the stability and bioavailability of the protected functional compound, example, epigallocatechin gallate and curcumin nanoemusion system (Wang et al. 2009). The stability of nanoemulsions could be improved by sodium caseinate (de Oca-Ávalos et al. 2017) or protein concentration (Yerramilli and Ghosh 2017).

14.3.5 Nano-encapsulated Carrier Systems

Nano-mediated encapsulation helps in protecting active functional core compounds till it reaches particular surface area according to its functionality. Nano-encapsulated active components like carbohydrates, proteins, vitamins, antioxidants, lipids etc., are used to produce functional foods to improve and enhance taste, texture and stability. After extensive research on nano-encapsulation, researchers have found that using nanotechnology, the bioavailability of poorly absorbed ingredients is efficiently utilized with controlled target release onto its specific sites thereby reduces the dosage of active ingredients. For example, octenyl succinic anhydride-ε-polylysine is a bifunctional molecule can be used as an antimicrobial agent and curcumin encapsulated with hydrophobically modified starch micelle (Yu et al. 2009).

Table 14.2 Liposomal types, properties and applications in food sector

Type of liposome	Size Range (nm)	Property	Applications
Multi lamellar vesicles (MLV)	500–5000	Has more than one bi-layer which looks like onion skin like arrangement	Helps in entrapment of lipid-soluble molecules
		Has very high lipid content	
Large Unilamellar vesicles (LUV)	200–800	Has the property to be scavenged more easily by the immune system	Can be used as a tool to study cell interactions, recognition processes and mode of action of certain substances in human cell
			They can be coupled with antitumor drugs with reduced toxicities and enhanced efficacy
Small Unilamellar vesicles (SUV)	20–150	Has long circulation half-life	Hydrophobic drugs can be carried as solutions with the help of SUVs
		Has better cellular accumulation compared to particles of larger size	

14.3.6 Liposomes

Liposomes are intensively investigated and developed by the food and pharmaceutical industries as micro/nanocarrier systems for the delivery and protection of active compounds. Recent scientific studies showed that naturally-occurring liposomes are present in breast milk (Mozafari et al. 2008). Liposomes are the most biocompatible NACs made up of one or more phospholipid bilayer with or without other molecules like polymer and protein. The active compounds get loaded either into the internal aqueous medium (hydrophilic compounds) or within the lipid bilayer (lipophilic/hydrophobic compounds). Based on nature and number of bilayer liposomes are categorized into three groups, namely, Multi-Lamellar Vesicles (MLV), Large Unilamellar Vesicles (LUV) and Small Unilamellar Vesicles (SUV). The application and properties of liposomes group is given in Table 14.2.

Liposomes can aggregate and form micrometric particles with increased size upon storage, the nanoliposomes also have an adequate stability to retain its original size as ‘bilayer lipid’ and maintain its nano size range upon storage (Bozzuto and Molinari 2015). In Dairy industries, they are used in entrapment and protection of proteinaceous cheese enzymes into whey during cheese production with enhanced organoleptic characteristics (Bhat 2017). The surface properties, size distribution and charge can be manipulated for its distinct application in food products. Using

liposomes, maximum efficacy of bioactive compounds can be attained with minimal quantity of bioactive compounds. The concept of bifunctional liposomes assists in incorporation and release of one or more bioactive compounds of different solubility simultaneously. Similar study was carried out by loading two antioxidant agents (α-tocopherol and glutathione) into the bifunctional liposomes for ameliorating paraquat-induced lung injury in male Sprague-Dawley rats (Suntres and Shek 1996). Liposomes were also extensive used as artificial membrane systems to compare and investigate the antioxidant properties of several agents (Sengupta et al. 2004). Liposomal artificial membrane systems can be regulated using different process condition (lipid composition) for its distinct application. For instance, the neuronal membranes are rich in sphingomyelin, while the liver mitochondrial membranes contain phosphatidylcholine, lysophosphatidylcholine, diacylglycerol and phosphatidylethanolamine (Gimenez et al. 2011). Nanoencapsulated carrier systems such as liposomes provide various opportunities for food technologists to improve the performance, bioavailablity, shelf-life and release of active food ingredients in a living system at controlled manner (Mozafari et al. 2008; Shah 2014).

14.3.7 Archaeosomes

Archaesomes are liposomes with ester phospholipids bilayer that are considerably more thermostable, stable at acidic and slight alkaline (bile salts) conditions and can withstand chemical, enzymatic and oxidative reactions (Luykx et al. 2008). Archaeosomes prepared from the archaea polar lipid extract to form the lipid lamellar vesicles with a great potential to deliver active agents via oral delivery system with high encapsulation efficiency (Mozafari et al. 2006). As liposomes, archaeosomes can also be prepared by incorporating ligands (polymers, proteins) which promotes stability and enhance residence time in systematic circulation. Oral and intravenous administration of archaeosomes by incorporating polyethene glycol and Coenzyme Q10 in mice increases the bioavailability and tissue distribution (Omri et al. 1999).

14.4 Effect of Nanocarriers Attributes

The physicochemical properties of NACs greatly determined by the surrounding environment and the materials used for the synthesis. Primarily, composition and structural embodiment highly regulate the behaviour of nanocarrier in food merchandise. The important physical and chemical properties of nanocarrier systems are illustrated in Fig. 14.3.

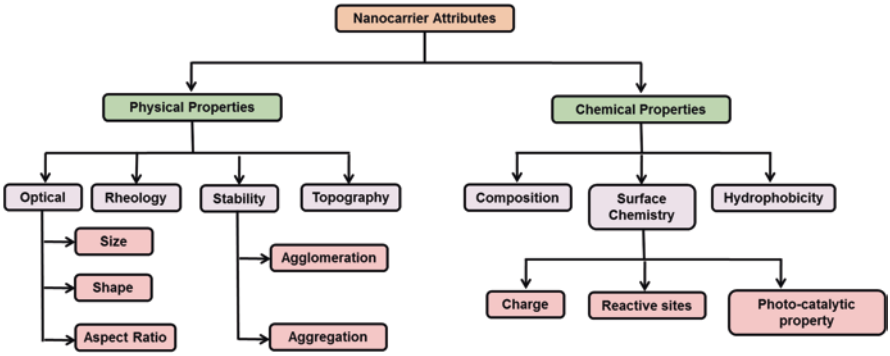

Fig. 14.3 Physicochemical properties of nano assisted carrier systems

14.4.1 Optical Properties

NACs are used in medicine, food and other related approaches due to its superior optical properties. In physics, light absorption produces colour whereas scattering of light helps to visualize the solid particles. The characteristic of turbidity is simultaneous absorption and scattering. The optical properties of NACs are described by its size, shape, concentration, scattering behaviour, and particle size distribution (Huang and El-Sayed 2010; McClements and Rao 2011). Phospholipid based nanocarriers are not optically homogenous and turbidity or light scattering highly depends on the size of particle and incident wavelength (Matsuzaki et al. 2000). For nanoemulsion, the turbidity found to increase with increase in refractive index and particle concentration (McClements and Rao 2011). In case of metallic and semiconductor nanocarriers, the absorption does not rely on the intensity and possess nonlinear optical properties (Kumbhakar et al. 2014). In general, Mie theory for spherical nanocarriers is used to calculate the scattering intensity using refractive index and absorption of that particle (Fu and Sun 2001). The colour and turbidity are inversely proportional in nanoemulsions system (McClements and Rao 2011). In case of metal nanocarriers, the turbidity of the solution depends on various operating parameters like temperature, pH, etc., while colours are due to particle concentration. In phospholipid based nanocarriers, significant increase in particle size and aggregation of nanocarrier systems leads to increase in turbidity (Thompson 2005).

14.4.2 Topology

Topology is the important characteristic in food merchandise for enhancing the organoleptic properties, bioactivity, absorption and nutrition compared to the bulk equivalent. The surface topology is liable for the interaction with other components present in foods. The long-term stability and the absorption by ingestion are greatly influenced by the topology of the nanocarrier systems. Surface topology of

the NACs is one of the main parameters that influence the toxicological effect in the living system. Greater the surface area of the NACs greater will be the biological activity (Anandharamakrishnan 2014). This renders several vistas in food application. For instance, NACs are used to protect the bioactive compounds present in the functional food products. Surface topology and morphology of the nanocarrier systems lead to aggregative and segregative interactions with the food matrix (Piperigkou et al. 2016). The low resistance conductivity and catalytic action in carbon nanotubes are due to its topology.

14.4.3 Stability

In general, stability of the nano-sized system is relatively discrete from the bulk materials. The stability of NACs is subdivided into chemical and physical stability after formulation and administration into various routes in a biological system. The solidity of metallic nanocarrier depends on synthesis method and surrounding including the solvent polarity and polymeric matrix (Egorova et al. 2016). Nanocrystals and phospholipid nanocarrier system stability is similar to colloidal particles. In case of nanocrystals, stability is influences by ionic medium and presence of ligand shells (Rao et al. 2007). The phospholipid nanocarrier system tends to sediment and aggregate due to its size and surface charge, respectively (Grit and Crommelin 1993). Notably, phospholipid nanocarrier system contains unsaturated acyl chains which are susceptible to oxidation (lipid oxidation) and the phospholipid tends to hydrolysis to form free fatty acids (Grit and Crommelin 1993). Lipid oxidation and hydrolysis can be prevented by selecting the suitable source of phospholipid and optimizing other operating conditions such as pH, temperature, etc. Nanoemulsions are metastable than the typical emulsion system and the important physicochemical parameters that affect the stability are the difference in density with surrounding liquid (sedimentation and creaming), droplet size (aggregation, oxidation or hydrolysis) and concentration of solubilized oil (Ostwald ripening) (McClements and Rao 2011).

14.4.4 Rheology

While designing a food, rheology is one of the most prime characteristics because beverages should possess relatively low viscosity, desserts like items should be in a gel like consistency and ice creams has to be viscous and elastic in nature. Emulsion based food delivery system exhibits different rheological characteristics (deformation and flow of matter) based on its composition and microstructure (McClements 2014). The important factors that determine the rheological modulations of phospholipid based nanocarrier are the composition, membrane rigidity and phospholipid concentration; however, it is not based on the size (Mourtas et al. 2008). In case of organic NACs, the rheological attributes depend on the hydrogen ion concentration, ionic strength, size distribution of particle and volume of particle dispersed (Taheri et al. 2016).

14.5 Mechanistic Action of Nano Carriers in Living System

The potential of NACs is to incorporate, protect and release the functionally active components like vitamins, nutraceuticals, flavours, antimicrobial agents and other active compounds with higher bioavailability. The utilization of NACs in foods, beverages and nutraceuticals is a great concern due to its reduction in dimension from bulk to nanoscale. When a food material is ingested into the human body, it undergoes absorption, distribution, metabolism, excretion and toxicology processes (Bouwmeester et al. 2009). The distinct biological effects of different nanocarrier systems are due to its composition, surface charge, particle size, concentration, interfacial characteristics and interaction with biological molecules in the living system. The pharmacokinetics of organic and inorganic NACs is largely different in terms of absorption and toxicity. According to European Food Safety Authority (EFSA), 2011, novel foods with engineered nanomaterials shall be focused for its in vitro digestion and toxicokinetic as in the EFSA Scientific Committee Guidance on the risk assessment for a nano system administration in food and feed chain. Only few literatures are available related to nanocarrier's bioavailability and its effect on the biological system because nanocarriers, larger than 1 nm in food matrix seems to have no concern (Šimon et al. 2008).

The higher surface to mass ratio of NACs assists in enhancing the interaction with the biological fluids in the living system like saliva, mucus and so forth. Biomolecules such as proteins, carbohydrates, etc. in the living system found to change the identity of nanocarrier system. For example, protein corona formed around the nanocarrier plays a vital role in biocompatibility of the nanocarrier system (Lundqvist et al. 2017). Blood serum and few proteins interact inevitably with nanocarrier system unintentionally and reduce the absorption rate (Aggarwal et al. 2009). These interactions and corona associated mechanism are high in organic nanocarrier systems than inorganic nanocarrier systems. Semiconductor nanocarriers with size below 6 nm filtered by the renal excretion and interaction with protein molecules is absent in zwitter ionic nanocarrier system (Zrazhevskiy et al. 2010). In general, smaller nanocarrier systems found to interact more with proteins and absorption is more specific and selective (Lynch and Dawson 2008; Aggarwal et al. 2009). However, interaction of organic and inorganic absorption mechanism with protein is almost same.

Researchers reported that higher concentration of protein molecules lead to minimal nanocarrier agglomeration by sealing the surface (Wells et al. 2012; Müller et al. 2014). However, it is also reported that organic acids and serum proteins enhance the agglomeration of NACs (Díaz et al. 2008). This may be due to the intrinsic and non-homogeneity property of the nanocarrier system. Inorganic nanocarrier is subjected to cytotoxicity test, toxicity of nanocarrier system is due to inorganic material rather than particle effect. Literatures presume that inorganic nanocarrier system produces reactive oxygen species in cells that destroy the various molecules and cause cell death (Frohlich 2013). Notably, production of free radicals is purely based on dosage and time. Traditionally available assays like oxidative stress and substrate oxidation tend to produce false positive results (Landsiedel et al. 2010).

Therefore, NACs with proper size, morphology, chemical constituent and composition is relatively safe, however, its interaction with the biological compound in living system is not the same for organic and inorganic nanocarrier system.

14.6 Destination of NACs

Knowledge about the fate of NACs is highly important to ensure the safety profile of formulation. As discussed earlier, the nano sized dimension may have the tendency to alter the biological fate inside a living system and it largely depends on the physical and chemical nature. There are limited literatures and knowledge are available on the behaviour of ingested NACs. It is obvious that advanced research is required in this area to have a clear understanding on the release and potential toxicity.

Food formulated with NACs after ingestion gets dissoluted immediately due to change in ionic strength and action of enzymes present in saliva (McClements and Rao 2011). However, NACs do not dissolve or dissociate immediately upon oral administration but it slowly interacts with the biological tissues and experience inundation into the GI tract (Lu et al. 2017). This process may alter the interfacial characteristic and physical attributes of nanocarrier systems.

The bolus is passed via the gullet and reaches the gut region containing gastric acid with pH 1.5 to 3.5 where the dissolution process is further accelerated and reduction in bulk area results in solubilized phase. The dissolution rate is proportional to the solubility of the active compound and the surface area of the NACs (Lu et al. 2017). The proteins and lipids present in the formulation are digested using the gastric enzymes. Thereby, enhancing the cellular uptake of the digested material and gets transported to the systemic circulation.

The mechanical propulsion, grinding and retropulsion mixing in the stomach results in flocculation and coalescence and promote aggregation of nanocarrier system and nano sized dimension is disturbed. Later in the small intestine, partially hydrolyzed compounds are acted with alkaline digestive juice with pH close to neutral. The surface-active agents present in the small bowel compete with the endogenous, exogenous and other internally generated compounds generated in the nanocarrier system. The biomolecules like protein, lipids and others are converted into its simplest forms and transported via mucous layer to the intestinal absorptive cells (McClements and Rao 2011). At this stage, there is a change in interfacial characteristics due the digestive process. In case of silica-based nanocarrier system, the nanoparticulate silica is found to disappear at the initial intestinal pH (Bergin and Witzmann 2013). The absorption of metallic NACs in the GI tract is still under study, it is not clear whether the NACs is dissolved or absorbed during the process.

The absorption occurs in epithelium cells (lining of GI tract) and micro fold cells or M cells (gut-associated lymphoid tissue of the Peyer's patches) of the intestine. It is surmised that M cells are efficient in absorbing nanocarriers while epithelium cells are poor at absorbing nanocarriers. Nanocarrier system gets absorbed via paracellular absorption mechanism (transported via the gaps between

the cells), transcellular absorption mechanism (transported via active or passive absorption), or endocytosis (transported via engulfment) (McClements and Rao 2011). The absorption of NACs is found associated with the surface hydrophilicity. After absorption process, NACs is digested by the cellular enzymes and transported into the systemic circulation or lymphatic circulation. Some nanocarrier system may accumulate at the specific site in the cell. The absorption mechanism purely influences by the nanocarrier attributes such as size, surface area, charge and hydrophilicity.

14.7 Concluding Remarks and Perspectives

A quick revolutionary nanocarrier system has been regard as a boon to food industries in transforming natural food matrixes. NACs have the potential to develop next generation food products with better physical stability, organoleptic properties and bioavailability. However, the utilization of this technology is in elementary level with a number of challenges aimed to overcome and produce high value-added products for its wide applications. The progress of nano based food is a great challenge for the food related industries and government. Hence, both the government and food industries must ascertain the consumer's faith and acceptance of this technology in food products. Research is under progress to develop nanocarrier system in food with negligible impact on living and environmental system. The problems associated with stability and aggregation of nanocarrier is influenced by its size, shape, morphology and composition. Insufficient scientific exploration on biological impacts, biosphere impacts and benefits contributed by nanocarrier systems in food materials hindered the development of nanotechnology in practical applications. It is important to study and recognize the surface chemistry and purity profiling of the nanocarrier system. Moreover, knowledge about of the NAC formation, mechanism of action in the living system and fate has to be improved to enhance the economic and rational development. Thus, nanocarrier incorporated food products have to be subjected to food safety testing before commercialization. Government agencies have to develop new methodology and systematic protocols to investigate the bias in nanocarrier incorporated food products on the biological systems. Thus, exposure of nanocarrier and its hazards effects on human has to be evaluated for its successful implementation in food merchandise in future.

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Chapter 15
Controlling of Food Borne Pathogens by Nanoparticles

S. Rajeshkumar and L. V. Bharath

Abstract Food borne diseases remain a major cause of lots of diseases and death in the universal population, particularly in susceptible groups. These diseases originate from either the toxin of the microbes which cause disease. There are hundreds of bacteria, viruses, toxins, parasites, prions and metals are together with food borne diseases in human beings, which are mainly patented as gastroenteritis (acute). The different types of nanoparticles such as zinc oxide, gold, silver etc. are used for the controlling of food borne disease causing pathogens. In this book chapter we have discussed about nanoparticles and its characterization and mechanism of action on food borne disease causing microorganisms.

Keywords Food · Nanoparticles · Food borne pathogens · Mechanism

15.1 Introduction

Magical spell has the capability to turn each thing touched into gold, in real time situation one such spell is "Nanotechnology" which has the astonishing power to transform every field touched by it. Nanotechnology is now entering the food processing industry and creating prodigious potential. Food nanotechnology has its antiquity from Pasteurization method introduced by Louis Pasteur to kill the pathogenic bacteria, made the initial step of transformation in food processing technology (Smith 2012). Contamination of food with pathogens such as bacteria, fungi, virus, protozoa and algae is a threat to human health and has the possibility to produce terminal illness (Fig. 15.1) (Loharikar et al. 2012). There are several microorganisms accountable for the occurrence of food-borne diseases and the three significant ones are *Escherichia coli 0157:H7* (Kaper et al. 2004), *Listeria monocytogenes* (Farber and Peterkin 1991), *Vibrio parahaemolyticus* (Letchumanan et al. 2014).

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6_15

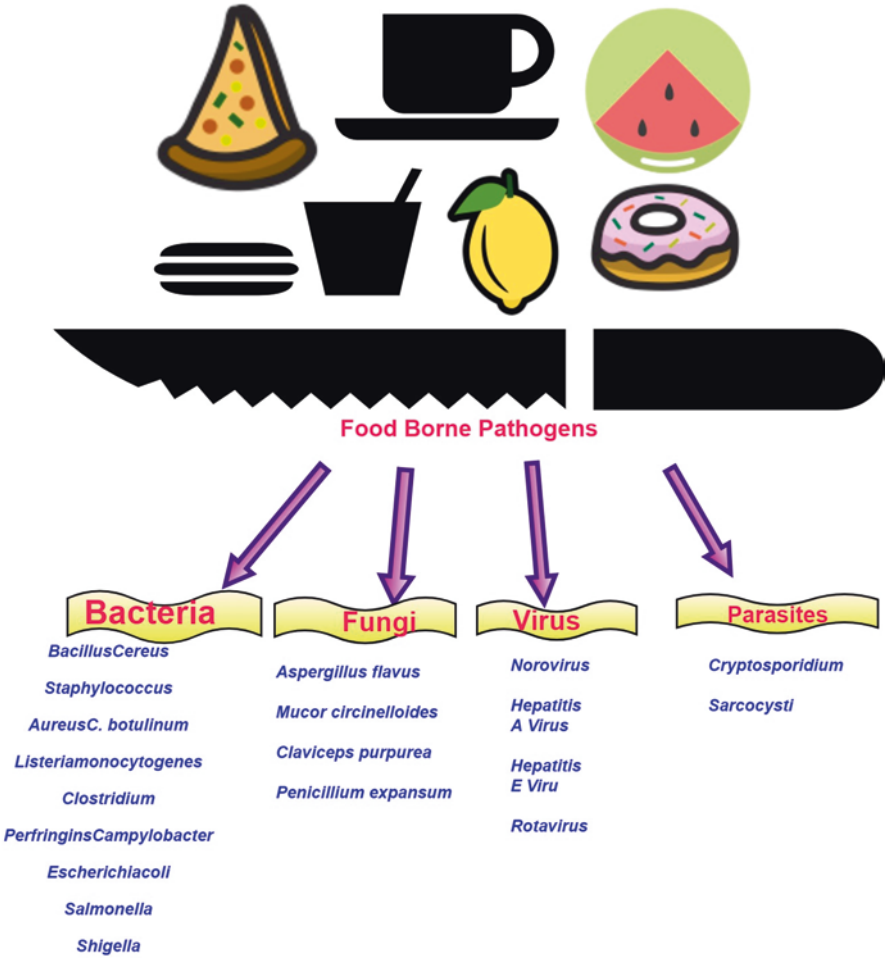

Fig. 15.1 Food borne pathogens

Listeriosis is a serious disease typically caused by eating contaminated food with the Listeria monocytogenes. This disease is most likely to sicken people with weakened immune systems, pregnant women, new-borns and adults aged 65 or older. Listeria monocytogenes found in dairy products, raw and improperly cooked meat, seafood, soil and in contaminated water (Wing and Gregory 2002). Vibrio parahaemolyticus has been related with the consumption of raw or undercooked seafood or exposing a wound to seawater. Nausea, headache, vomiting, fever, abdominal cramps and diarrhoea may be associated with infections caused by this pathogen (Letchumanan et al. 2014). E. coli 0157:H7 is a bacterium that can release potent toxins. It is usually found in raw milk, and improperly cooked meat or raw hamburger. People typically get sick when they consume contaminated food or water with microscopic amounts of cow faecal matter. Some symptoms of the disease are

pain abdominal cramps and diarrhoea, and in severe cases, can cause kidney failure, temporary anaemia, and even death (Kaper et al. 2004).

Various types of antimicrobials agents have been developed over the decades to control disease causing pathogens. However, rapid emergence of the antibiotic resistance bacteria has become a serious health problem and therefore, several studies have been described to improve the existing antimicrobial therapies. It is identified that over 70% of bacterial diseases are resistant to one or more of the antibiotic agents that are commonly used to eradicate the disease (Williams and Sefton 1999). Food-borne viral pathogens such as norovirus, rotavirus, hepatitis A virus, hepatitis E virus are the most common agents for the stomach flu (gastroenteritis) and cause severe symptoms including diarrhoea, nausea, vomiting in immunocompromised patients (Newell et al. 2010; Lee et al. 2014). Filamentous fungi and moulds produce a vast range of secondary metabolites, including mycotoxins and antibiotics. The term mycotoxin denotes to those secondary metabolites which, at a low concentration, are capable of causing disease and death in animals and humans. The foodborne mycotoxins such as alfatoxins, fumonisins, and trichothecenes (Wagacha and Muthomi 2008; Fowsiya and Madhumitha 2017) contaminate various food items, including meat, milk products, cereals, maize and ground nuts (Streit et al. 2012). The most common toxigenic fungi are Penicillium, Fusarium and *Aspergillus* (Logrieco et al. 2003). In addition, parasites such as *Cryptosporidium, Sarcocysti* and *Trypanosoma cruzi* can cause food-borne diseases, and currently, nearly 70 protozoan species and 300 parasitic worms are known to infect animals and humans (Newell et al. 2010). Food borne pathogens that cause serious illness, their common sources, incubation period, common symptoms and references are mentioned in Table 15.1.

Various antimicrobial agents have been used in the food processing industry to preserve food, decontamination of food, and destroy the disease-causing organisms. However, some of these antimicrobial agents may responsible for surviving pathogens to become more resistant to other antimicrobial agents. Henceforth, strategies need to be formulating to prevent any form of cross-protection that may arise because of the usage of a combination of these antimicrobial agents. Development of new antimicrobial agents appears to be of major importance. The antimicrobial activity of metals such as copper, gold, silver, titanium, zinc, each having various potencies, properties has been acknowledged and used for centuries (Dizaj et al. 2014; Madhumitha et al. 2012; Madhumitha et al. 2016; Roopan and Khan 2010). In recent years, nanotechnology has been presented numerous opportunities in several fields of science and technology. Various types of metal NPs and their derivatives have been established massive attention in medical technology due to their potential antimicrobial activity against several pathogens (Fig. 15.2). Metal NPs such as copper oxide (CuO) (Thahirakhatoon et al. 2013), gold(Au) (Lima et al. 2013), magnesium oxide (Mgo) (He et al. 2016), silicon oxide (SiO_2) (Kretusheva et al. 2014), titanium oxide (TiO_2) (Mogal et al. 2014), silver(Ag) (Iravani et al. 2014b), zinc oxide(ZnO) (Aleaghil et al. 2016) and iron oxide(FeO_3) (Teja and Koh 2009) were recognized to display antimicrobial activity. The resultant antimicrobial activity depends upon the several parameters such as kind of material

Table 15.1 Food borne pathogens that cause serious illness, their common sources, incubation period, common symptoms and references

S.NO	Food Borne Pathogens	Common Sources	Incubation Period	Common Symptoms	References
Bacteria					
1.	*Botulism (C. Botulinum)*	Improperly canned home and commercial foods such as sausage, meats, fish, potatoes, and water.	12 to 72 h	Nausea, fatigue, headache, vomiting, diarrhoea, double vision, respiratory failure and muscle paralysis.	(O'Mahony et al. 1990; Thippareddi et al. 2009)
2.	*Bacillus cereus*	Soil organism typically found in raw dry and processed foods such as rice.	1–6 h (vomiting) 6–24 h (diarrhoea)	Nausea and diarrhoea.	(Andersson et al. 1995)
3.	*Staphylococcus Aureus*	Cream fillings, custards potato-type salads and sliced meats.	30 min to 8 h	Nausea, vomiting, diarrhoea and abdominal cramps.	(Springer et al. 2009)
4.	*Listeria monocytogenes*	Unpasteurized or inadequately pasteurized milk, Fresh soft cheeses and hot dogs.	9–48 h (gastrointestinal symptoms) 2 to 6 weeks (for invasive disease)	Fever, muscle aches, nausea, diarrhoea, flu-like symptoms	(Jemmi and Stephan 2006)
5.	*Clostridium Perfringins*	Poultry and other meats.	8 to 22 h	Diarrhoea, vomiting and abdominal cramps.	(García and Heredia 2011)
6.	*Campylobacter*	Raw milk and eggs, raw or undercooked beef, poultry and shellfish, and water.	2 to 7 days	Nausea, headaches diarrhoea and abdominal Cramps.	(Altekruse et al. 1999)
7.	*Escherichia coli O157:H7*	Ground beef, raw milk, raw produce and Vegetables.	24 h to 10 days	Diarrhoea (bloody), abdominal cramps and vomiting	(Lim et al. 2010)
8.	*Salmonella*	Poultry, eggs, meats, sprouts	6 to 72 h	Diarrhoea, abdominal cramps, nausea	(Jay 2000)
9.	*Shigella*	Contaminated foods, raw vegetables, egg salads and water.	24 to 72 h	Diarrhoea, fever, nausea, vomiting and abdominal cramps.	(Jay 2000)

Fungal					
10.	*Aspergillus flavus*	Grains, milk, peanuts.	Varies with dose	Abdominal pain, vomiting, liver damage, liver cancer.	(George et al. 2014)
11.	*Mucor circinelloides*	Yogurt	–	Abdominal cramping, nausea and diarrhoea.	(Lee et al. 2014)
12.	*Claviceps purpurea*	Wheat, oats and barley	Varies with dose	Gangrene and dementia	(Tudzynski et al. 1986)
13.	*Penicillium expansum*	Stored apples	–	Neurotoxic, immunotoxic and gastrointestinal effects	(Butinar et al. 2011)
Viruses					
14.	*Norovirus*	Contaminated food and water.	12 to 72 h	Diarrhoea, vomiting, headaches, fever and abdominal cramps.	(La Bella et al. 2017)
14.	*Hepatitis A Virus*	Contaminated food and water.	15 to 50 days	Abdominal discomfort, nausea and anorexia followed within a few days by jaundice.	(Sánchez 2013)
15.	*Hepatitis E Virus*	Contaminated food or water	3 to 8 weeks	Jaundice, nausea and vomiting, skin rash	(Yugo and Meng 2013)
16.	*Rotavirus*	Contaminated food or water	1 to 3 days	Diarrhoeal, fever, headaches, vomiting	(Mukherjee et al. 2012)
Parasites					
17.	*Cryptosporidium*	Contaminated water and food, vegetables, unpasteurized milk	2 to 28 days	Diarrhoea, stomach cramping, vomiting, headaches, fever and abdominal cramps.	(Newell et al. 2010)
18.	*Sarcocysti*	Meat and meat products, fruits and vegetables	–	Mild fever, diarrhoea, chills, vomiting and respiratory	(Fayer 2004)

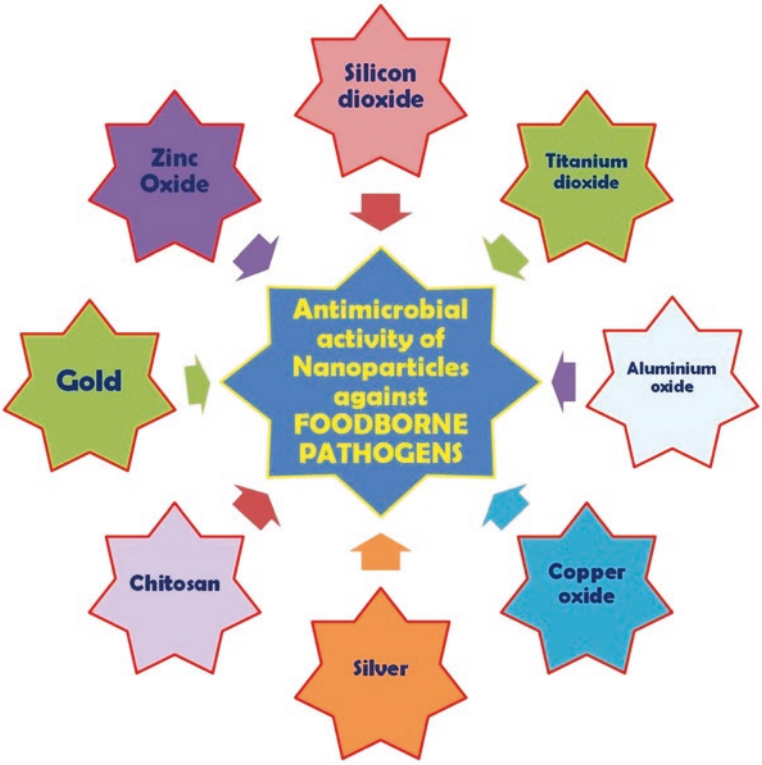

Fig. 15.2 Different types of nanoparticles used against food borne pathogens

used for the synthesis of NPs as well as the particle shape and size (Stoimenov et al. 2002; Hajipour et al. 2012; Dizaj et al. 2014). The precise mechanisms for antimicrobial effect of metal NPs are still being studied, but there are several proposed possibilities in this regard: (a), metal ion toxicity ascending from suspension of the metals from surface of the NPs (Hajipour et al. 2012; Dizaj et al. 2014; Ahmed et al. 2016; Raza et al. 2016) and (b), oxidative stress through the production of reactive oxygen species (ROS) on surfaces of the NPs (Naqvi et al. 2010; Tayel et al. 2011; Hajipour et al. 2012; Dizaj et al. 2014; Radhakrishnan and Gajivaradhan 2014).

The nanoparticles were characterized using different techniques (Fig. 15.3). The characters of nanoparticles were play an important role in the biomedical applications. It has been reported that the small sized NPs have the robust antimicrobial effect (Sun and Xia 2002; He et al. 2004; Xia et al. 2009).The morphology of the NPs also effects their antimicrobial effects (Sun and Xia 2002; He et al. 2004; Li et al. 2005; Kim et al. 2007a; Xia et al. 2009). The positive charge on the surface of the NPs facilitates their binding to the negatively charged membrane surface of the bacteria which may result in an enhancement of the antimicrobial effect (Shrivastava et al. 2010; Lengke et al. 2011; Nguyen

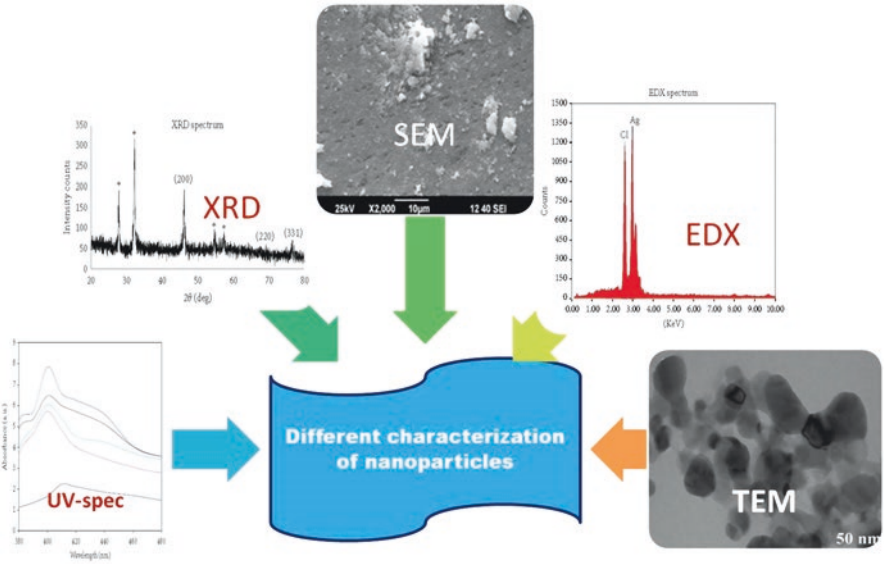

Fig. 15.3 Characterization of nanoparticles

et al. 2013). This book chapter provides a comprehensive review on the available research works considering the various metal nanoparticles antimicrobial activity against food-borne pathogens

15.2 Nanoparticles and their Antimicrobial Activity Against Food Borne Pathogens

15.2.1 Zinc Oxide Nanoparticles

Zinc Oxide NPs have been received an increasing attention as antimicrobial agent in recent years because of their ease of synthesis, stability under various conditions and also, they have been considered as safe metal NPs for humans and animals (Stoimenov et al. 2002) (Tayel et al. 2011). Many experimental studies have been revealed that zinc oxide NPs have selective toxicity to various food borne pathogens such as bacteria, fungi, viruses.(Roberta Brayner et al. 2006; Reddy et al. 2007; Jin et al. 2009). A variety of synthetic methods are employed for the synthesis of Zinc oxide NPs. Physical methods of zinc oxide NPs synthesis include sputter deposition (Damiani and Mansano 2012), ball milling (Salah et al. 2011), physical vapour deposition (Podrezova et al. 2013), electric arc discharge (Ashkarran et al. 2009) and laser ablation (Ismail et al. 2011). These methods can be separated into three types; physical, chemical, biological methods. Chemical synthesis method can be

further separated into gas phase synthesis (Bagamadova and Omaev 2015) and liquid phase synthesis (Mantzaris 2005). Gas phase synthesis includes inert gas condensation (Uhm et al. 2007) and pyrolysis methods (Lee et al. 2010) and liquid phase synthesis includes coprecipitation method sol-gel processing (Khan et al. 2016), hydrothermal synthesis (Li et al. 2015), micro emulsions method (Yıldırım and Durucan 2010), colloidal method (Alvarado et al. 2013), sonochemical (Heshmat et al. 2015) and polyol method (Chieng and Loo 2012). The use of living organisms for the production of zinc oxide NPs facilitating lot of interest due to its ecological, quick, inexpensive procedure. Biological synthesis of zinc oxide NPs enables advancement over chemical and physical methods and easily scaled up for large scale synthesis (Naveed Ul Haq et al. 2017).

Zinc oxide NPs application in food processing industries could be effective at inhibiting various food borne pathogens. These NPs have been showed strong antimicrobial activity against several food borne pathogens such as *salmonella enteritidis* (Jin et al. 2009), *Escherichia coli* (Mirhosseini and Firouzabadi 2013), *Staphylococcus* (Mirhosseini and Firouzabadi 2013) and *Listeria monocytogenes*(Fatemeh.B.F 2011). Padmavathy et al. reported the antibacterial activity of zinc oxide NPs with several particle sizes. Their results have been demonstrated that the antimicrobial efficacy of zinc oxide NPs improved by reducing particle size(Padmavathy and Vijayaraghavan 2008). Azam et al. has been conducted a comparative study of antimicrobial activity of zinc oxide, copper oxide, iron oxide NPs against gram-positive bacteria (*Bacillus subtilis and staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli, pseudomonas aeruginosa*). According to their study, the most antimicrobial activity was established for the zinc oxide NPs while iron oxide NPs displayed the least antimicrobial effect (Azam et al. 2012). Zinc oxide NPs reduces the microbe's viability; however, the detailed mechanism of its antimicrobial activity has not been well understood (Zhang et al. 2008). One described possibility is the accumulation of the NPs on the pathogen surface due to the electrostatic force between the particles and surface of the cell could be the mechanism of the antimicrobial effect of zinc oxide NPs (Dizaj et al. 2014). Production of hydrogen peroxide could be another factor of the antimicrobial activity (Radhakrishnan and Gajivaradhan 2014). Furthermore, disruption of transmembrane electron transport has been reported in the case of the few metal NPs such as zinc and gold (Hajipour et al. 2012). Xie et al. assessed antimicrobial activity of zinc oxide NPs against a food borne pathogenic bacteria *Campylobacter jejuni*. This experimental study has been reported that zinc oxide NPs might be due to the oxidative stress and interruption of the cell wall. Their reported results displayed that zinc oxide NPs caused membrane leakage, morphological changes and rise in oxidative stress in *Campylobacter jejuni.* The antimicrobial activity of zinc oxide NPs depended on the surface area and concentration. Thus, zinc oxide NPs with larger surface area and higher concentrations displayed superior antimicrobial activity (Xie et al. 2011). Hossein–khani et al. studied the antimicrobial properties of zinc oxide NPs against food borne pathogen Shigella dysenteriae. According to their results, a significant decrease in the bacteria number was detected as result of reduction in particle size (Hosseinkhani et al. 2011).

Lili et al. demonstrated antimicrobial activity of zinc oxide NPs against food borne pathogenic fungi such as *Penicillium expansum*. According to their study zinc oxide NPs with sizes of nearly 70 nm has shown significant antifungal activity (He et al. 2011). In another experimental study zinc oxide NPs have been shown significant antifungal activity against *Candida Albicans* yeast and *Aspergillus Fumigatus* fungus. This experimental study revealed that the growth of *Candida Albicans* and *Aspergillus Fumigatus* were inhibited at concentrations of 3 to 12 mM/l zinc oxide NPs (Jasim 2015). George et al. reported a comparative study of the antimicrobial activity of zinc oxide NPs and titanium dioxide NPs against eight fungal cultures; *Fusarium, Aspergillus niger, Fonsecaea, Trichophyton, Aspergillus flavus (food borne pathogen), Cladosporium, Rhizopus oryzae and Ramichloridium schulzeri* isolated from the dandruff flakes and infected skin. Results obtained from this research study have shown that zinc oxide NPs have better antifungal activity than titanium dioxide NPs(George et al. 2014).

15.2.2 Iron Oxide Nanoparticles

Iron oxide NPs have several distinctive properties such as high coercivity, high magnetic susceptibility, superparamagnetic, low Curie temperature, etc. Iron oxide NPs are of prodigious interest for researchers from a wide range of disciplines, including data storage, fluids, catalysis, and applications in biology (Naik et al. 2004; Teja and Koh 2009; Carter 2015). The iron oxide NPs must be pre-coated with a biopolymer such as chitosan that increases their biodegradability, non-toxicity and stability in the physiological medium (Naqvi et al. 2010). Iron oxide NPs synthesis methods have been developed not only for its scientific interest but also for its many advanced technological applications such as resonance imaging(MRI) (Yang et al. 2008), thermos ablation (Espinosa et al. 2016), bio-sensing(Hasanzadeh et al. 2015) and bio-separation (Fatima and Kim 2017). Mostly, bio-applications based on iron oxide NPs have established significant attention because NPs offer exclusive advantages over other metal NPs. For instance, iron oxide NPs are low-cost to synthesise, chemically and physically highly stable and biocompatible (Wu et al. 2015). Until now a variety of synthesis procedures such as sol-gel synthesis (Hasany et al. 2013), ultrasound irradiation (Bolden et al. 2013), microemulsion (Chin and Yaacob 2007), Co-precipitation method (Behera et al. 2012), laser ablation (Ismail et al. 2015a), microwave assisted synthesis(Toulemon et al. 2013), sonolysis (Freitas et al. 2015), hydrothermal and solvothermal synthesis(Ge et al. 2009) (Wu et al. 2015) and biological synthesis (Elfick et al. 2017) have been applied to synthesise iron oxide NPs.

Ismail et al. reported the antimicrobial activity of iron oxide nanoparticles against food borne pathogens such as Escherichia coli, Pseudomonas aeruginosa and staphylococcus aureus. This experimental study has shown a noteworthy inhibition on mentioned pathogens (Ismail et al. 2015b). Shekhar Behera et al. demonstrated antimicrobial activity of iron oxide NPs against various food borne pathogenic bacteria. In this experimental study iron oxide NPs have been synthesised via

co-precipitation method. Synthesised iron oxide NPs have shown significant antimicrobial activity against both gram negative and gram positive bacterial stains (Behera et al. 2012).

15.2.3 Magnesium Oxide Nanoparticles

Various techniques have been established for the synthesis of magnesium oxide NPs such as, hydrothermal method (Paper and Technology 2016), sol-gel method (Wahab et al. 2007), mechanochemical method (Chow et al. 2010), microemulsion method (Chow et al. 2010), vapor phase method (Razouk and Mikhail 1958) etc., have been employed for the synthesis of *Magnesium oxide* NPs. The regulation of processing conditions allows the synthesis of magnesium oxide NPs of various morphologies and with different sizes (Yi Ding et al. 2001).

Magnesium oxide NPs have significant potential as antimicrobial agents in food processing technology due to their stability, surface and structural properties. Several analytical methods have been reported to assess the antimicrobial activity of Magnesium oxide NPs against food borne pathogens. Magnesium oxide NPs showed the antimicrobial activity against both Gram-negative and Gram-positive bacteria [69]. Various mechanisms have been described to explain the antimicrobial activity of magnesium oxide NPs, which include the lipid peroxidation, formation of ROS, alkaline effects, and electrostatic interactions(Dizaj et al. 2014). The electrostatic interaction between magnesium oxide NPs and bacterial cell surface leads to the cell death. The surface of magnesium oxide NPs has a usually high pH due to the formation of a very thin layer of water (Stoimenov et al. 2002). When pathogens get contact magnesium oxide NPs, the high pH (alkaline effect) damages the cell membrane, eventually leading to death (Rudramurthy et al. 2016). However, the exact mechanism of magnesium oxide NPs action on pathogens is complicated and not well understood. It has been described that the antimicrobial activity of magnesium oxide NPs is attributed to the release of reactive oxygen species (ROS) which induce oxidative degradation of lipids in bacteria (He et al. 2016). In contrast, non-ROS mediated antimicrobial toxicity was also established in magnesium oxide NPs, signifying oxidative stress might not be the principal mechanism of cell death (Leung et al. 2014). It has been confirmed that the antimicrobial mechanism of magnesium oxide NPs is fetched about by the production of superoxide on the surface of these NPs, and also an escalation in pH value by the hydration of magnesium oxide NPs with water. According to the various experimental studies, magnesium oxide NPs damage the cell membrane and then cause the intracellular contents leakage which in turn lead to the cell death (He et al. 2016). Sawai et al. reported antibacterial activity of magnesium oxide NPs against Staphylococcus aureus and Escherichia coli. They have suggested that the existence of active oxygen, such as superoxide, on the surfaces of magnesium oxide NPs was one of the primary reason that affects their antimicrobial activity (Dizaj et al. 2014). Leung et al. reported that the antimicrobial activity of magnesium oxide NPs nanoparticles could be investigated in the absence of any ROS production. They

have been declared that the cell membrane damage might be responsible for the mechanism of antimicrobial activity (Leung et al. 2014). Jin et al. also assessed antimicrobial activities of Magnesium oxide NPs alone or in combination with other nanoparticles such as nisin and zinc oxide NPs against Salmonella Stanley and Escherichia coli. Magnesium oxide NPs displayed antimicrobial activity against these pathogens. In their experimental study, the antimicrobial activity of Magnesium oxide NPs was enhanced as the concentrations of Magnesium oxide NPs increased. The researchers proposed that Magnesium oxide NPs alone or in combination with nisin could be used as an effective antimicrobial agent to improve food safety[16] [66].

15.2.4 Titanium Dioxide Nanoparticles

Titanium dioxide is a chemically stable and non-toxic molecule used in cosmetics, food colorants, sunscreens lotions and pharmaceuticals (Nsi 2012). Moreover, they have substantial antimicrobial activity against certain pathogens. Several procedures have been proposed for the synthesis of titanium dioxide NPs including electrochemical (Fray et al. 2000), sol-gel (Ullattil and Periyat 2017) techniques.

Antimicrobial property of titanium dioxide NPs is associated to its shape, size and structure of the crystal (Gupta et al. 2010). It is reported that oxidative stress through the production of ROS may be a predominantly important mechanism for titanium dioxide NPs (Besinis et al. 2014). It has been conveyed that production of ROS responsible for site specific DNA damage (Hirakawa et al. 2004). Roy et al. assessed the effect of titanium dioxide NPs with different antibiotics against Methicillin-resistant Staphylococcus aureus (MRSA). They have been reported that, titanium dioxide NPs enhanced the antimicrobial effect of cephalosporins, beta lactums, glycopeptides, aminoglycosides, macrolids, tetracycline and lincosamides against MRSA (S. Roy et al. 2010). In another experimental study, their outcomes displayed that antimicrobial resistance of MRSA against several antibiotics diminished in the presence of titanium dioxide NPs (Rudramurthy et al. 2016). Haghighi et al. studied antifungal effect of titanium dioxide NPs on the fungal biofilms *Candida albicans*. According to their outcomes, the synthesized titanium dioxide NPs had enhanced antifungal effect on the Candida albicans biofilms. The authors have been proposed that titanium dioxide NPs could inhibit the fungal biofilms particularly those formed on the medical devices surface (Haghighi et al. 2012). Photocatalytic properties of the titanium dioxide NPs support them to efficiently eradicate the pathogens (Mattioli et al. 2014). In fact, titanium dioxide NPs releases ROS under Ultraviolet light. Carré et al. described that the antimicrobial photocatalytic activity was accompanied by oxidative degradation of lipids that causes to increase cell membrane fluidity and interrupt the cell integrity. However, the use of titanium dioxide NPs under Ultraviolet light (10 nm (30 to 400 nm) is controlled because of genetic damage in cells (Carré et al. 2014). It has been demonstrated that, doping of titanium dioxide NPs with metal ions can be a solution to overcome this problem. In addition, antimicrobial and photocatalytic properties of titanium

dioxide NPs are significantly improved by doping them with metal ions [1,47]. By way of explanation, doping with metal ions shifts titanium dioxide NPs light absorption range to visible light (390 to 700 nm) and therefore, there is no requirement to irradiate them with Ultraviolet light (Ahamed et al. 2016). Conjugation of titanium dioxide NPs with non-toxic polymers is alternative method to overcome toxicity complications of titanium dioxide NPs(von Nussbaum et al. 2006).

15.2.5 Alumina Nanoparticles

Alumina NPs have an extensive range of applications in medicine and industry. These are corundum like structure with oxygen atoms embracing hexagonal close encase with alumina ions filling the octahedral sites in the lattice (Sadiq et al. 2009). Aluminium oxide is a white oxide with different phases: alpha, gamma, delta, and theta. Alpha phase alumina NPs are thermodynamically stable particles over a wide range of a temperatures (Mukherjee et al. 2011). Various different methods have been employed for the synthesis of alumina NPs such as hydrothermal processing, sol-gel pyrolysis, laser ablation and sputtering. The laser ablation method is a quick and high-purity process; henceforth, it is most commonly used in the synthesis of alumina NPs. Park and his co-workers were synthesised alumina NPs by the hydrolysis of aluminium oxide alkoxides followed by calcinations in the presence of Dioctyl sulfosuccinate sodium salt (Na(AOT)) which acts as a stabilising agent (Park et al. 2005). Very few studies have been reported antimicrobial properties of alumina NPs against food borne pathogens. Sadiq has been conducted an antimicrobial study of alumina NPs against food borne pathogen such as E. coli has shown a significant growth – inhibitory effect, only at the high concentration, which would be due to surface charge interactions between the cells and nanoparticles. This experimental study has been suggested that alumina NPs may only exhibit mild toxicity towards food borne pathogens (Sadiq et al. 2009).

15.2.6 Copper Oxide Nanoparticles

For centuries, copper has been used as disinfectant agent due to their antimicrobial activity against various pathogens such as bacteria, virus and fungus (Borkow and Gabbay 2004). Copper is relatively inexpensive in comparison to expensive metals like silver and gold and also has high antimicrobial properties (Luechinger et al. 2008). Usually, NPs are synthesised through three kinds of different methods: physical, chemical, biological (Iravani et al. 2014b). Various chemical synthetic methods were described so far for the synthesis of copper NPs. Also, it has been reported that morphology and growth of NPs can be optimised by various factors such as concentration of the precursors and temperature. In case of chemical reduction method Copper (II) salts can be reduced by various reducing agents, for instance: sodium borohydride (Thahirakhatoon et al. 2013), Ascorbic acid (Umer

et al. 2014), Hydrazine (Saikova et al. 2010), hypophosphite (Lai et al. 2012) and polyol (Park et al. 2007). These reducing agents were used to synthesise copper NPs with controlled shape and size. Ostaeva and his co-workers were synthesised copper NPs with a particle size below 10 nm by reducing Cu^{+2} in aqueous solution of pluronic-poly (acrylic -acid) (Ostaeva et al. 2008). In another study copper NPs were synthesised with a diameter of nearly 16 nm using sodium borohydride which acts as a reducing agent (Thahirakhatoon et al. 2013). In case of physical synthesis methods, the laser ablation technique is typically designed to produce copper NPs in a variety of solvents such as water, ethanol and acetone (Kazakevich et al. 2004). The laser ablation procedure takes place in the presence of some inert gases under the vacuum compartment. In this process, factors like the duration of radiation time, the type of laser and the type of solvent can influence the final product properties (Khodashenas and Ghorbani 2014). Many studies have been revealed that the living organisms such as plants, bacteria, fungi have huge potential for metal NPs synthesis. Ramanathan proposed an aqueous phase biological synthesis procedure to synthesise copper NPs using *Morganella morganii* (gram-negative bacteria) (Ramanathan et al. 2013). Varshney and her co-workers were synthesised copper NPs using *Pseudomonas stutzeri* (gram-negative bacteria) which is isolated from the soil (Varshney et al. 2010). Lee synthesised copper NPs using plant material extract as reducing agent. On treatment of aqueous solution of Copper(II) sulfate pentahydrate (CuSO4· 5H2O) with *Magnolia* leaf extract, stable copper NPs were obtained (Laudon et al. 2011). However, the main limitation in the synthesis of copper NPs is their ease of oxidation to Copper oxide (CuO) or copper peroxide (CuO_2) during and after synthesis. This makes it problematic to synthesise copper NPs without providing an inert atmosphere (Thahirakhatoon et al. 2013). Many research studies have been indicated that a good number of copper NPs synthesis were done in protective environment or inert environment (Usman et al. 2012).

The antimicrobial activity of copper oxide NPs appears to be diverse depending on the particularities of pathogens. For examples, their cell membrane appears to impact the antimicrobial effect of copper oxide NPs, Gram character being a crucial aspect (Wang et al. 2017). It has been reported that 100% of food borne pathogenic bacterial cells such as E. coli, which are Gram- negative bacteria, were killed when high concentration of Copper oxide NPs used, while copper oxide NPs have been shown lower killing ability for food borne pathogenic gram-positive bacteria such as Staphylococcus aureus (Ungur and Hrůza 2015). It has been also reported that copper oxide NPs inhibit the growth of food borne pathogenic bacteria such as Pseudomonas aeruginosa, S. aureus and E. coli in a time dependent manner (Das et al. 2013).

15.2.7 Silver Nanoparticles

Among various metal NPs, silver NPs have special attention due to their extraordinary antimicrobial and surface plasmon Resonance (SPR) properties, which render them exclusive properties such as broad-spectrum antimicrobial (Mlalila et al. 2017). Currently, several approaches have been reported for the synthesis of silver

NPs by using physical, chemical, and biological routes. Physical methods usually require very high energy, pressure and temperature conditions to synthesise the NPs (Kim et al. 2007b). Among the existing methods, the chemical methods have been used widely for the production of silver NPs (Wang et al. 2005). In chemical method, the synthesis of silver NPs with colloidal dispersions organic solvents or in water in water or organic solvents is achieved by chemical reduction (Gao and Xu 2007). The reduction of silver ions in solvents yields silver NPs. It well known fact that chemical reduction methods deliver an easy way to synthesise well-defined, shape and size controlled nanoparticles with simple equipment usage (Smetana et al. 2005; Lee et al. 2005; WAKUDA et al. 2008; Zielińska et al. 2009; Abou El-Nour et al. 2010). The use of plant materials for the synthesis of silver NPs facilitating lot of interest due to its simple, ecological, inexpensive and non-pathogenic procedure (Iravani et al. 2014a). Green synthesis of AgNPs enables huge advancement over physical and chemical methods and simply scaled up for large scale synthesis (Parveen et al. 2016). The very first literature on the green synthesis of AgNPs using Alfalfa *(Medicago sativa)* has been reported in 2003 a step toward nanobiotechnology (Ks et al. 2011). In physical method, silver NPs are usually synthesised by evaporation condensation, which could be processed at atmospheric pressure using a tube furnace (Gurav et al. 1994). However, the production of silver NPs using a tube furnace has associated with numerous drawbacks, because a tube furnace consumes large amounts of energy, occupies a very large space and requires lot of time to attain thermal stability (Ghorbani et al. 2011; Zhang et al. 2016). Furthermore, silver NPs have been produced with laser ablation of metallic silver in aqueous solution (Fumitaka Mafuné et al. 2000). Synthesis of metallic silver NPs via chemical method is most common approach because of its convenience and usage of simple equipment. Usually, the chemical synthesis method of AgNPs in aqueous phase solution usually employs the following components: metal precursors, stabilizing and capping agents and reducing agents (Hussain et al. 2011). The formation of silver NPs from the reduction of silver salts associated with two phases: nucleation and growth. It has been revealed that the morphology and size of the silver NPs depend upon these stages (Kim et al. 2006). The nucleation phase and the successive growth phase can be controlled by regulating the reaction constraints such as reaction, pH, temperature, precursors (Silver nitrate), reducing agents (i.e. ethylene glycol, Sodium borohydride, glucose) and stabilizing/ capping agents (i.e. Poly vinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), sodium citrate) (Patil et al. 2012; Dung Dang et al. 2012) (Fig. 15.4).

According to several experimental studies silver NPs are the most popular NPs employed as antimicrobial agents. It has been reported that, silver NPs display a high antimicrobial activity analogous with its ionic form (Rao et al. 2014; Pulit-Prociak and Banach 2016). Several research studies have been reported that antimicrobial action of silver NPs results from the bacterial membrane damage (Rai et al. 2012; Dorobantu et al. 2015). Some researchers were demonstrated that silver NPs can induce pits and gaps in the bacterial cell membrane which in turn cause cell fragmentation (Li et al. 2010). It has also been found that silver NPs interact with sulfhydryl groups of enzymes that lead to interruption of metabolic processes and then responsible for the cell death (Aleaghil et al. 2016). Zarei et al.

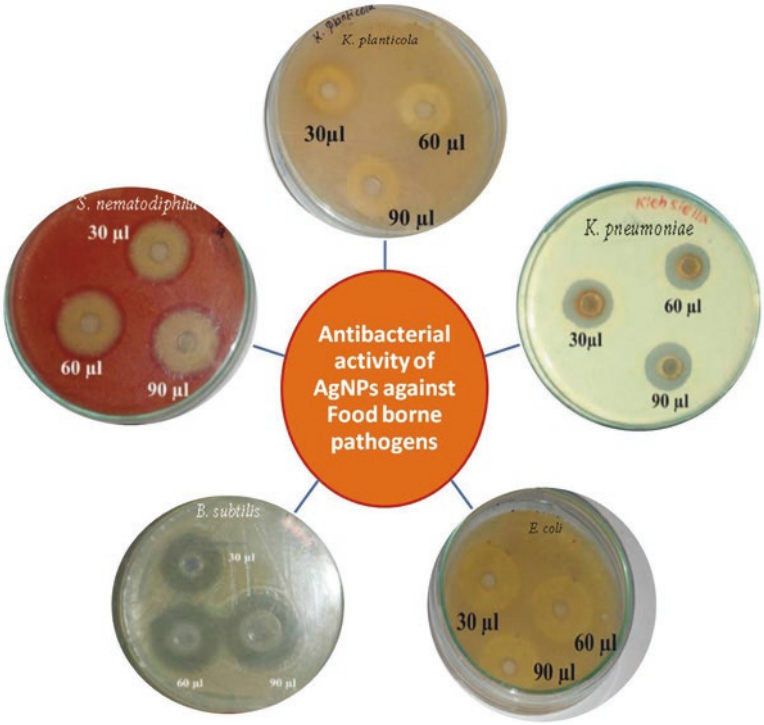

Fig. 15.4 Antibacterial activity of AgNPs against food borne pathogens (Rajeshkumar and malarkodi, 2014)

investigated antimicrobial effect of silver NPs against foodborne pathogens such as Escherichia coli, Vibrio parahaemolyticus, Listeria monocytogenes and Salmonella typhimurium. According to their reported results, silver NPs have shown great antimicrobial effect on the tested pathogens (Zarei et al. 2014). Pamela et al. reported the antimicrobial activity of silver NPs against food borne pathogenic parasite Cryptosporidium parvum. They claimed that, silver NPs exhibited substantial antimicrobial activity for the mentioned parasite.

15.2.8 Gold Nanoparticles

Gold NPs have been extensively used in bionanotechnology based on their exclusive properties and several surface functionalities. Starting from ancient medicine to modern medicine, gold (Au) was used for therapeutic purposes. Intense research studies on gold NPs were undertaken, using advantages of its exclusive properties, but few adverse effects (Alkilany and Murphy 2010) of gold NPs have been reported, which would need further researches. Gold NPs are synthesised using physical, chemical, biological methods (Alaqad and Saleh 2016). However, frequently used

method for synthesis of gold NPs by the chemical reduction method (Arvizo et al. 2010). For shape and size controlled AuNPs synthesis, various chemical reduction methods such as sodium borohydride ($NaBH_4$) mediated reduction method reported by Brust in 1990 (Liz-Marzán 2013) and citrate mediated reduction described by Fren's in 1973 (FRENS and G. 1973) and Turkevich in 1951 (J. Kimling et al. 2006). Schmid et al. demonstrated seed mediated growth which is widely used chemical method to synthesise gold NPs (Schmid 2010; Scharfe et al. 2010). chemical methods are very convenient to take control over the shape and size NPs. However, their application is limited due to the toxicity (Wang et al. 2008). Therefore, biological methods have also been widely employed for synthesis of gold NPs (Patra and Baek 2014). The use of living organisms such as plant material, bacteria and fungi for the synthesis of gold NPs facilitating lot of interest due to its simple, ease, ecological, inexpensive procedure (Lengke et al. 2011). Physical methods such as microwave (Augustine et al. 2014), laser ablation (Wender et al. 2011), electrochemical (Sun et al. 2017), γ- irradiation (Misra et al. 2012), photochemical (Dong et al. 2004) and solvothermal (Choi et al. 2013) methods have been employed in the synthesis of gold NPs. However, γ- irradiation method was reported to be best for the synthesis of gold NPs with controlled shape and size. Physical methods usually require very high-pressure, energy and temperature conditions to synthesise the NPs (Herizchi et al. 2016).

Gold NPs are considered to be so important in the development of antimicrobial agent's due to their polyvalent effects, nontoxicity, photothermal activity and ease of detection (Tiwari et al. 2011; Zhou et al. 2012; Lima et al. 2013; Lokina and Narayanan 2013). Even though production of ROS is the primary cause of cellular death for most antimicrobial agents and antimicrobial NPs; however, antimicrobial activity of gold NPs do not induce ROS-process (Cui et al. 2012). Cui et al. reported that antimicrobial activity of the gold NPs was associated with (1) attachment of these NPs to the bacterial cell membrane followed by membrane potential change and ATP level reduction and (2) inhibition of transfer ribonucleic acid (tRNA) binding to the ribosome (Cui et al. 2012).Tiwari et al. demonstrated the antimicrobial activity of the gold NPs against common food borne pathogens such as *staphylococcus aureus, pseudomonas aeruginosa, Micrococcus luteus, Escherichia coli, Aspergillus niger* and *Aspergillus fumigates.* This experimental study revealed that these NPs showed more antimicrobial activity on Gram-negative bacteria than Gram positive bacteria due to the easier penetration into the bacterial cell membrane (Tiwari et al. 2011). Zhou et al. assessed antimicrobial activities of gold and silver nanoparticles against *Bacillus Calmette-Guerin* (BCG) and *Escherichia coli.* They have been concluded that, gold and silver nanoparticles displayed substantial antibacterial activity against both Gram positive bacteria (BCG) and Gram negative bacteria (*Escherichia coli)* (Wiegand et al. 2008). In another research study, Lima et al. described antimicrobial effect of gold NPs (5 nm) against food borne pathogenic bacteria such as Salmonella typhi and Escherichia coli. According to their results, these NPs reduced nearly 90–95% of Salmonella typhi and Escherichia coli colonies. The authors accentuated that, the key factors that influenced the antimicrobial properties were the dispersion and roughness of the gold NPs on the medium (Lima

et al. 2013). A new procedure of synthesis of a vaccine for hepatitis E virus using in situ development of gold clusters in the vaccine was recently demonstrated (Figs. 15.2 and 15.3) (Tables 15.2 and 15.3).

Table 15.2 Nanoparticles mechanism of antimicrobial action and factors that influence antimicrobial activity

S.NO	NPs	Reported mechanism of antimicrobial action	The main factors that influence antimicrobial activity	References
1.	Gold	Attachment of these NPs to cell membrane which alters the membrane potential and then cause the ATP level reduction; and inhibition of transfer RNA(tRNA) binding to the ribosome.	Particle size and roughness	(Tiwari et al. 2011) (Lima et al. 2013)
2.	Titanium dioxide	Oxidative stress via the production of ROS; lipid peroxidation that cause to increase cell membrane fluidity and disrupt the cell integrity.	Shape and size, crystal structure	(Fray et al. 2000; Kedziora et al. 2012; George et al. 2014; Besinis et al. 2014; Mogal et al. 2014)
3.	Zinc oxide	ROS production on the surface of the NPs; zinc ion release, cell membrane dysfunction; and NPs penetration into cell	Particle size and concentration.	(Fatemeh.B.F 2011; Tayel et al. 2011; Jasim 2015; Koupaei et al. 2016)
4.	Silver	Ion release; formation of pits and gaps in the cell membrane; interact with sulfhydryl or disulfide groups of enzymes that lead to interruption of metabolic processes.	Particles shape and size	(Prabhu and Poulose 2012; Rodríguez-León et al. 2013; Parveen et al. 2016)
5.	Copper oxide	Crossing of NPs from the cell membrane and then damaging the vital enzymes of cell.	Particle size and concentration	(Hajipour et al. 2012; Das et al. 2013; Thahirakhatoon et al. 2013)
6.	Magnesium oxide	Damaging the cell membrane and then causing the intracellular contents leakage lead to the cell death.	Particle size and pH	(von Nussbaum et al. 2006; Wahab et al. 2007; Leung et al. 2014)
7.	Iron	Through ROS-generated oxidative stress.	Particles shape and size	(Bolden et al. 2013)
8.	Alumina	Disrupt cell walls through ROS.	Particles size and concentration	(Park et al. 2005; Sadiq et al. 2009; Mukherjee et al. 2011)

Table 15.3 Antimicrobial activity of different nanoparticles

S.No	Food borne pathogens	NPs	Antimicrobial activity		References
Bacteria					
1.	*Listeria monocytogenes*	Zinc oxide	**Concentration(mM)**	**ZI(mm)**	(Fatemeh.B.F 2011)
			0	*	
			0.5	*	
			2	**gr	
			5	9 ± 0.3	
			10	10 ± 0.1	
		Silver	MIC – 6.25 μg/mL		(Zarei et al. 2014)
2.	*Bacillus cereus*	Zinc oxide	**Concentration(mM)**	**ZI(mm)**	(Fatemeh.B.F 2011)
			0	*	
			0.5	*	
			2	**Gr	
			5	*	
			10	8 ± 0.1	
	Bacillus subtilis	Zinc oxide	MIC – 10 ± 0.1 μg/mL		(Azam et al. 2012)
		Iron oxide	**Concentration(mM)**	**ZI(mm)**	(Behera et al. 2012)
			50 mg/ml	20 ± 1.11	

	Escherichia coli O157:H7	Zinc oxide	**Concentration(mM)**	**ZI(mm)**	(Mirhosseini and Firouzabadi 2013)
			0	*	
			0.5	*	
			2	*	
			5	**Gr	
			10	**Gr	
		Magnesium oxide	MIC – 10 mg/ml		(He et al. 2016)
		Silver	MIC – 3.12 μg/mL		(Zarei et al. 2014)
		Iron oxide	**Concentration(mM)**	**ZI(mm)**	(Behera et al. 2012)
			50 mg/ml	11 ± 0.44	
		Gold	**Dose (μL)**	**ZI(mm)**	(Shamaila et al. 2016)
			5	10	
			15	28	
			30	**31**	
4.	*Staphylococcus aureus*	Zinc Oxide	**Concentration(mM)**	**ZI(mm)**	(Mirhosseini and Firouzabadi 2013)
			0	*	
			0.5	*	
			2	**Gr	
			5	10 ± 0.3	
			10	12 ± 0.3	
		Iron oxide	**Concentration**	**ZI(mm)**	(Behera et al. 2012)
			50 mg/ml	12 ± 0.35	
		Gold	**Dose (μL)**	**ZI(mm)**	(Shamaila et al. 2016)
			5	13	
			15	20	
			30	22	

(continued)

Table 15.3 (continued)

S.No	Food borne pathogens	NPs	Antimicrobial activity			References
5.	*Enterobacter cloacae*	Zinc oxide **VS** Zinc powder	**Concentration**	**ZI(mm) for ZNO NPs**	**ZI(mm) for ZNO powder**	(Tayel et al. 2011)
			Disc diameter (6 mm) which carried 10 mL from1 M Zinc oxide suspension.	19 ± 1.4	14 ± 0.9	
6.	*Pseudomonas Aeruginosa*	Zinc oxide **VS** Zinc powder	**Concentration**	**ZI(mm) for ZNO NPs**	**ZI(mm) for ZNO powder**	(Tayel et al. 2011)
			Disc diameter (6 mm) which carried 10 mL from1 M Zinc oxide suspension.	17 ± 1.2	11 ± 0.4	
7.	*Salmonella enteritidis*	Zinc oxide **VS** Zinc powder	**Concentration**	**ZI(mm) for ZNO NPs**	**ZI(mm) for ZNO powder**	(Tayel et al. 2011)
			Disc diameter (6 mm) which carried 10 mL from1 M Zinc oxide suspension.	22 ± 1.2	11 ± 0.5	
		Magnesium oxide	MIC – 8 mg/ml			(He et al. 2016)
8.	*Salmonella typhimurium*	Zinc oxide NPs **VS** Zinc oxide powder	**Concentration**	**ZI(mm) for ZNO NPs**	**ZI(mm) for ZNO powder**	(Tayel et al. 2011)
			Disc diameter (6 mm) which carried 10 mL from1 M Zinc oxide suspension.	21 ± 1.4	12 ± 0.6	
		Silver	MIC – 3.12 mg/ml			(Zarei et al. 2014)

9.	*Campylobacter jejuni*	Magnesium oxide	MIC – 2 mg/ml		(He et al. 2016)
10.	*Vibrio parahaemolyticus*	Silver	MIC – 3.12 μg/mL		(Zarei et al. 2014)
	Fungus				
	Organism	NPs	Concentration	Diameter of the colony	References
11.	*Claviceps purpurea*				
	Aspergillus flavus	Zinc oxide	12 μg/ml	1.6 cm	(George et al. 2014)
	Mucor circinelloides				
	Penicillium expansum	Zinc oxide	>3 mM/l	Inhibit the growth	(He et al. 2011)

* No inhibition zone
** Growth reduction

15.3 Conclusion

The nanoparticles are the most effective nanotechnology products which as lot of applications in the controlling of many disease causing pathogens in different biomedical and industrially important areas. The microorganisms are the very major food spoiling agents may cause severe effects to consuming peoples as well as the animals. Controlling of the food borne pathogens using very advanced nanoparticles such as aluminium, iron oxide, silver, zinc oxide, gold, magnesium oxide, titanium dioxide, Silicon and copper oxide are trending now and may acts efficiently against the pathogens. The development of nanotechnology for food technology may reduce the cost and eco-friendly. In future the nanoparticles are used in the food packaging and safety processes will very much helpful to the food based industries. Already some research and development departments of some industries are started working on nanoparticles for the food industries developments it move on to next level vigorously in coming days.

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Index

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S. M. Roopan, G. Madhumitha (eds.), *Bioorganic Phase in Natural Food: An Overview*, https://doi.org/10.1007/978-3-319-74210-6