Sustainable Agriculture Reviews 56

Ajay Rana
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Bioconversion of Food and Agricultural Waste into Value-added Materials

Springer

Sustainable Agriculture Reviews

Volume 56

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Sustainable agriculture is a rapidly growing field aiming at producing food and energy in a sustainable way for humans and their children. Sustainable agriculture is a discipline that addresses current issues such as climate change, increasing food and fuel prices, poor-nation starvation, rich-nation obesity, water pollution, soil erosion, fertility loss, pest control, and biodiversity depletion.

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Because most actual society issues are now intertwined, global, and fast-developing, sustainable agriculture will bring solutions to build a safer world. This book series gathers review articles that analyze current agricultural issues and knowledge, then propose alternative solutions. It will therefore help all scientists, decision-makers, professors, farmers and politicians who wish to build a safe agriculture, energy and food system for future generations.

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ISSN 2210-4410 ISSN 2210-4429 (electronic)
Sustainable Agriculture Reviews
ISBN 978-3-030-84404-2 ISBN 978-3-030-84405-9 (eBook)
https://doi.org/10.1007/978-3-030-84405-9

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Preface

Respect for food is a respect for life, for who we are and what we do – Thomas Keller

The future of goods will be circular because earth resources are limited, and any waste should be recycled in a way or another. For instance, there is actually a huge "golden mine" of waste produced by the agricultural and food sectors, where many practices are emission intensive and generate yearly huge quantities of waste biomass. This book reviews the recycling of valuable nutrients and bioactive molecules from major food and agro industries, such as the recycling of apple pomace into food products (Fig. 1).

The first chapter by Kumar et al. reviews strategies for utilization of agro-industrial biomass, and biomass conversion into high value products, which helps reducing greenhouse gas emissions. In Chap. 2, Rana et al. discuss the immense potential of recycling industrial apple pomace as food, feed, and bioabsorbent. In Chap. 3, Ruchica et al. review the potential of active phytochemicals from apple pomace in various drug delivery systems for augmenting drug bioavailability and therapeutic efficacy. Kaur et al. in Chap. 4 discuss lignin and its applications in photocatalysis. Chapter 5 discusses about β-sitosterol extraction from agro-industrial waste and its therapeutic uses and implications for drug delivery systems. In Chap. 6, Sharma et al. highlight the phytochemical value of underutilized tea plant parts and their possible applications into various products. In Chap. 7 Ghoshal explains the potential of agricultural waste as a substrate for bioprocessing of highly valuable products and additives. In Chap. 8, Galali and Sajadi review the extraction and processing of food by-products for further utilization in various sectors. Vanoh et al. discuss the untapped potential of phytochemicals in fruits, nuts, and vegetables wastes in Chap. 9.

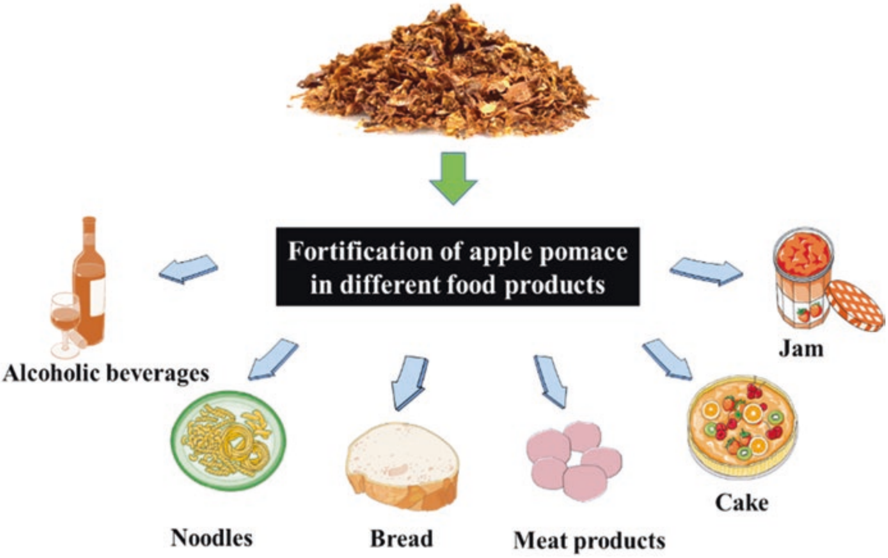

Fig. 1 Apple pomace fortification into various food products. (From Rana et al., Chap. 2)

We extend our sincere gratitude to all the contributors who had made substantial contribution to prepare high-quality chapters. We also extend our thanks to Melanie van Overbeek, Assistant Editor at Springer Nature, for her support during this whole process.

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Ajay Rana is presently working as Project Scientist at Dietetics and Nutrition Technology Division of CSIR–Institute of Himalayan Bioresource Technology, Palampur. In the past 12 years, he has published several research articles in peer-reviewed international journals based on his research work with various international patents to his credit. He has successfully transferred few of the technologies from his research work to industries for commercialization. He has huge passion for new product and process technology development, sustainable valorization of agro and forestry bioresources using green and sustainable process/bioprocess technologies, and post-harvest value addition. He has extensive experience in phytochemicals exploration, downstream processing, process optimization, and bioprocessing of bioactive phytochemicals from medicinal and aromatic plants.

Ankit Saneja obtained his PhD from the Academy of Scientific and Innovative Research (AcSIR) at CSIR–Indian Institute of Integrative Medicine, Jammu. He was a postdoctoral research associate at National Institute of Immunology, New Delhi, India, from September 2017 to September 2019. Presently, he is working as Scientist at CSIR–Institute of Himalayan Bioresource Technology, Palampur. He has been recipient of several international awards such as the CEFIPRA-ESONN Fellow, Bioencapsulation Research Grant, and PSE Travel Bursary. Dr. Saneja has to his credit several international publications. His research interest includes exploring different types of formulations for various biomedical applications. He has also edited *Pharmaceutical Technology for Natural Product Delivery* published by Springer Nature.

Sanjay Kumar is serving as Director at, Palampur, since June 2015. He is an eminent scientist in the field of plant sciences. His key research accomplishments include discovery of a novel carbon fixation pathway, discovery of an autoclavable superoxide dismutase enzyme and deciphering the mechanisms of winter dormancy and drought stress in tea, and enumerating molecular aspects of secondary metabolism in medicinal plants for catechins, picrosides, steviosides, shikonins, and podophyllotoxin biosynthesis. He is Fellow of National Academy of Sciences (NASI), National Academy of Agricultural Sciences (NAAS), and Crop Improvement Society of India. He is bestowed with prestigious VASVIK Industrial Research Award 2013 for Agricultural Science and Technology. He has guided 25 MSc/PhD students with several international patents and commercial technologies and has more than 150 peer-reviewed research/review articles/edited book/book chapters to his credit.

Eric Lichtfouse is Professor of environmental sciences and scientific writing at Aix Marseille University, Xi'an Jiaotong University, and the University of Shanghai for Science and Technology. He has invented carbon-13 dating, a molecular-level method allowing to study the dynamics of organic compounds in temporal pools of complex environmental media. He has discovered temporal pools of individual substances in complex media such as soils. He is Chief Editor and founder of the journal *Environmental Chemistry Letters*, and the book series Sustainable Agriculture Reviews and Environmental Chemistry for a Sustainable World. He is the author of the book *Scientific Writing for Impact Factor Journals*, which includes an innovative writing tool: the micro-article. He has awards in analytical chemistry and scientific editing.

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Chapter 1
Efficient Utilization and Bioprocessing of Agro-Industrial Waste

**Aman Kumar, Sareeka Kumari, Kiran Dindhoria, Vivek Manyapu,
and Rakshak Kumar**

Abstract The rising population and industrialisation produce a huge amount of waste, in particular from agro-industries, thus inducing environmental pollution. Therefore, waste should be better recycled into materials and energy, e.g. by incineration, gasification, and pyrolysis. Valuable by-products include enzymes, pigments, biofertilizers and edibles. Here we review the conversion of agro-waste, with focus on fermentation, composting, anaerobic digestion, enzymes, bioethanol, biofertilizers, microbial treatment and greenhouse gases.

Keywords Agro-industrial waste · Bioenergy · Biofertilizer · Sustainable · Bioconversion · Renewable

1.1 Introduction

The rapid growth of the population generated significant investment in the food and agricultural industries. Every year, approximately 1.3 billion tonnes of agro-industrial food waste is produced worldwide. Fruits, vegetables, roots, and tubers account for the bulk of this (40–50%), making for 520–650 million tonnes (Ravindran et al. 2018), and destined for landfills or uncontrolled disposal, resulting in damage to the environment and financial loss. Therefore, sustainable

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable
Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_1

management of them must be established. Population rise also calls for increased global energy demand, currently supported by fossil-fuels, which prevents long-term sustainability. The biggest and most often used source of renewable energy globally is biomass, which is increasingly used. The world biomass production is expected to 1500 Exajoules in 2050 and can be used sustainably from 200 to 500 Exajoules, accounting for 40–50% of the estimated primary energy demand (Popp et al. 2014). The energy demand is expected to rise by about 48 percent between 2012 and 2040 (Avcıoğlu et al. 2019). Government assistance is a pillar in accessing funding and technology and reducing the cost of producing green energy to promote the application of biomass-based energy technologies (Gutiérrez et al. 2020).

High-strength residues like livestock slurry, manure, crop remains, by-products of the agri-food such as coffee dregs, bagasse, degummed fruit, legumes, milk serum, sludge from wool, cellulose generated from agricultural and industrial sectors may be used to produce electricity, composting, biogas, biofuels and many other by-products by the action of microbes. (Yusuf 2017). For this purpose, advanced biorefinery becomes a promising option with several outputs (biofuels, biomaterials). The circular economy is based on a biorefining concept and approach to reducing, reusing, and recycling waste to recover waste products considered renewable resources (Peng and Pivato 2017).

This chapter discussed various kinds of waste generated from the agro-industrial sectors, such as agricultural residues, industrial residues, and different forms of wastewaters generated from agro-food industries. Well-established methods such as solid-state fermentation, Anaerobic digestion, and the composting process can be used to treat these various organic wastes. The action of different microbial communities can result in the production of various value-added products such as enzymes (alpha and beta-amylase, β-glucanase, cellulase, hemicellulase, xylanase, mannase, pectinase, inulinase, laccase, phytase, invertase, protease, pullulanase, and lipase), bioethanol, biodiesel, biogas and microbial biofertilizers with their potential applications in industrial or agricultural sectors. Increased industrialization and improper agro-waste management lead to greenhouse gas generation at a high rate, which has a toxic effect on the atmosphere and the human race. So, proper management practices can be helpful in the reduction of greenhouse gases and also dependency on fossil fuels.

1.2 Generation and Utilization of Agro-Industrial Biomass

A vast amount of waste is generated from agriculture-based industries in the form of agriculture and industrial residues, and wastewaters. Poor and unorganized disposal of these wastes adversely affects the environment and human health. These agro-based wastes have great potential to generate various kinds of value-added products such as biofuels, enzymes, and biofertilizers. Different type of biomass wastes generated from these industries are discussed below.

1.2.1 Agricultural Residues

Agriculture residues can be classified into field residues and process residues. Field residues are residues present in the field during the crop harvesting process, such as seed pods, stems, leaves, and stalks. Process residues are present till the crop has been turned into a profitable replacement commodity. These residues consist of husks, nuts, straw, leaves, shells, peel, pulp, roots, molasses, bagasse, and other waste biomass. They are used for animal feed, soil enhancement, fertilizers production, and various other uses (Sadh et al. 2018). Five million metric tons of agricultural biomass are generated annually from agro-based industries (Bharathiraja et al. 2017), which is underutilized, and their controlled use will improve irrigation abilities and erosion management. Barley and wheat are the main crops in the Middle East region. Moreover, many other crops are also produced worldwide, such as Fruits, vegetables, rice, corn, lentils, and chickpeas. The availability and characteristics of agricultural residues distinguished them from other solid fuels such as charcoal, char briquette, and wood.

1.2.2 Industrial Wastes

An immense quantity of organic waste and associated effluents are produced annually by food processing industries such as fruits, chips, garments, juices, and meat. These organic residues may be used as multiple sources of energy. The continually increasing population has raised the demand for food and its uses. Thus, in most of the nations, numerous food and beverage industries in this region have greatly expanded to satisfy food needs. These food and fruit industries lost around 20–40% of fruit and vegetable production annually (Dora et al. 2020). These agro-food-based waste materials show different compositions of lignin, ash, moisture, carbon, nitrogen, cellulose, and hemicellulose, which are useful for biogas production, biofuels, and some other valuable products by biochemical conversion. With increasing production by food industries, the percentage of waste generated also increased with a high value of chemical oxygen demand (COD), biological oxygen demand (BOD), and other suspended solids in it. Many of these wastes are discarded or untreated, resulting in harmful natural, human, and animal health effects, but their composition involves many organic compounds providing a range of value-added goods and reducing the manufacturing costs (Madureira et al. 2020).

After extracting oil from the seeds, enormous quantities of refined residues are made in oil industries called oil-cakes. Different varieties of oil cakes are generated after processing, such as coconut oil cake, mustard oil cake, soybean cake, cottonseed cake, rapeseed cake, palm kernel cake, olive oil cake, groundnut oil cake, sunflower oil cake, sesame oil cake, and canola oil cake. (Ramachandran et al. 2007). These industries pollute water, air, and other solid waste because these residues have vast amounts of grease, oil, suspended solids, fat, and dissolved solids. These agro-industrial residues are comparatively inexpensive, containing vast quantities of components, and can be used as substitute substrates for fermentation in an infinite prospect.

1.2.3 Drainage from Agro-Food Industries

In India, roughly 65–70% of organic contaminants are released into water bodies by food and agricultural sectors, such as distilleries, sugar mills, milk, fruit canning, and pulp and paper milling industries. The production of wine has also reached prominence in other parts of the world and is one of the leading food-processing industries in Mediterranean countries such as Australia, South Africa, Chile, China, and The US with its rising economic impact (Ganesh et al. 2010). According to the international organization of vine and wine (OIV), in 2020, global wine production was estimated at approximately 258 million hectoliters. Wine produces large amounts of wastewaters primarily from various washing procedures, e.g., when the grapes were crushed and squeezed, fermentation tanks, barrels, other machinery, and the surfaces were washed (Badshah et al. 2012). Moreover, for many Mediterranean countries, the olive oil industry has become of fundamental economic value. Malaysia currently represents 28% of the world's palm oil production and 33% of world exports (MPOC 2020). Because of its surplus production, a large amount of contaminated wastewater is generated, commonly referred to as palm oil mill effluent (POME). An estimated 1750 million metric tons of olive oil are produced worldwide annually, with Portugal, Greece, Italy, Tunisia, and Spain are the leading producers. About 30 million cubic meters of waste oils are produced annually in the Mediterranean region in seasonal olive oil extraction (Meksi et al. 2012). The final effluent produced after the processing of coffee industries in the regions such as Colombia, Brazil, and Vietnam has created a huge environmental impact, which requires low-cost and efficient techniques for treating wastewater generated (Fia et al. 2012). Also, some agro-food wastes such as yogurt waste, milled apple waste, beverages waste, fat and oil from dairy wastewater treatment, and cattle manure have great potential for the production of methane and other biofuels.

1.3 Different Methods Used for Bioconversion of Agro-Industrial Waste

Various microbial treatments such as solid-state fermentation, composting, anaerobic digestion may employ to manage waste generated from the agro-industries. These treatment technologies are eco-friendly, cost-effective, and produce many value-added products to overcome future demand. Some of the treatment methods are discussed below:

1.3.1 *Solid-State Fermentation*

When non-soluble or solid organic wastes are processed in biotechnological ways in the absence or lack of water by microorganisms, it is called solid-state fermentation (Soccol et al. 2017). Residues of rice bran, rice straw, wheat bran, wheat straw, barley straw, corn, legume seeds, sawdust, wood shavings, fruits and vegetable peels, and other plant and animal products constitute the substrate for the solid-state fermentation (Singhania et al. 2009). Though these substrates are polymeric and barely soluble in water or barely soluble, they are available easily and cheaply. The process of solid-state fermentation has been given in Fig. 1.1.

Both at the lab and pilot scale, the solid-state fermentation process can occur, which results in bioconversion of organic agro-industrial waste leading to the production of active biological metabolites. The bio-products produced by the solid-state fermentation method are organic acids, aromatic compounds, enzymes, biosurfactants, bio-pesticides, bio-fertilizers, feed for animals, vitamins, antibiotics, and pigments (Thomas et al. 2013). Different industries like agriculture, paper, beer

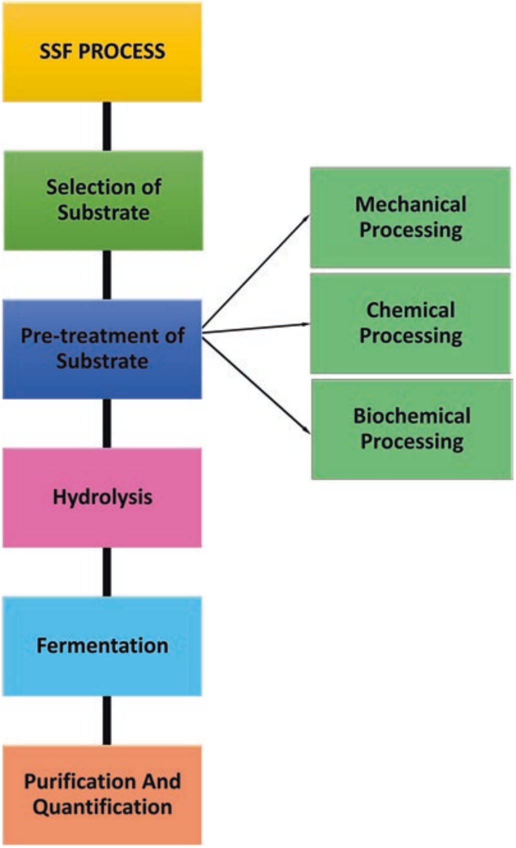

Fig. 1.1 Solid-state fermentation (SSF). The first step in solid-state fermentation is the selection of substrate and its pretreatment, which can be done through mechanical, chemical, and biochemical processes. The substrate undergoes hydrolysis followed by fermentation by the action of the microorganism. The fermented by-product is purified and quantified for further usage. (Modified from Sadh et al. 2018)

and wine, detergent, textile, food, animal feed generate large substrates for solid-state fermentation. Though the substrates used in solid-state fermentation are solids, the moisture level is low. The low-level moisture is sufficient for the fermentation process. Because of their high-water absorbing capacity, many agro-industrial wastes are being used as carriers in solid-state fermentation that help in the immobilization of fungus (Orzua et al. 2009). This helps in the efficacious growth of required microorganisms.

Through the process of solid-state fermentation, from the cheap substrates of agro-industrial solid wastes, many varieties of value-added products like tempeh, oncom, animal feed, biofuels, biogas are being prepared and sold for economic benefits (Fig. 1.2).

1.3.2 Composting

It is a managed process of converting organic matter into nutrient-rich and pathogen-free end product, i.e., compost (Fig. 1.3) (Onwosi et al. 2017). The end product is dark brown with a humus-like substance that may be stored and used as a beneficial

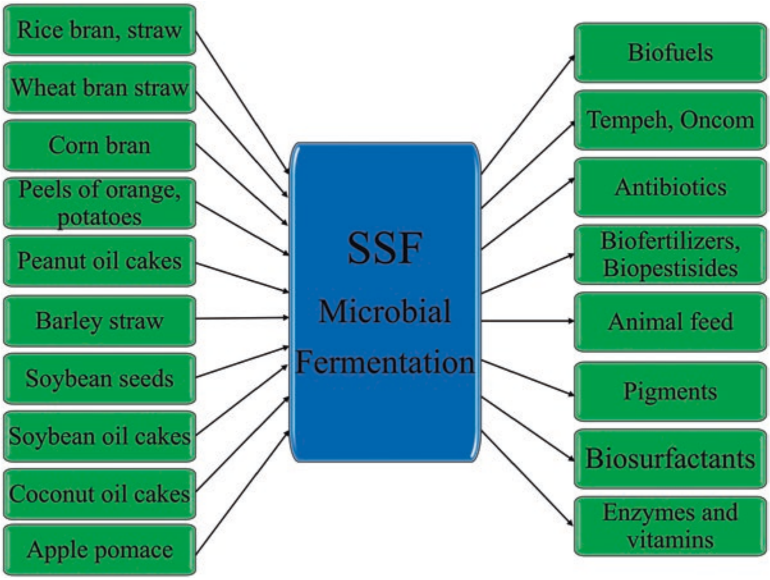

Fig. 1.2 Common agro-industrial wastes and by-products derived through solid state fermentation (SSF). The common agro-industrial wastes such as rice bran and straw, wheat bran and straw, corn bran, peels of orange, peels of potatoes, oil cakes of peanut, soybean, coconut, barley straw, seeds of soybean, apple pomace when subjected to solid-state fermentation can yield beneficial by-products like biofuels, edibles like tempeh and oncom, antibiotics, biofertilizers and biopesticides, nutrient-rich feed for animals, several pigments, biosurfactants, enzymes, and vitamins. (Modified from Sadh et al. 2018)

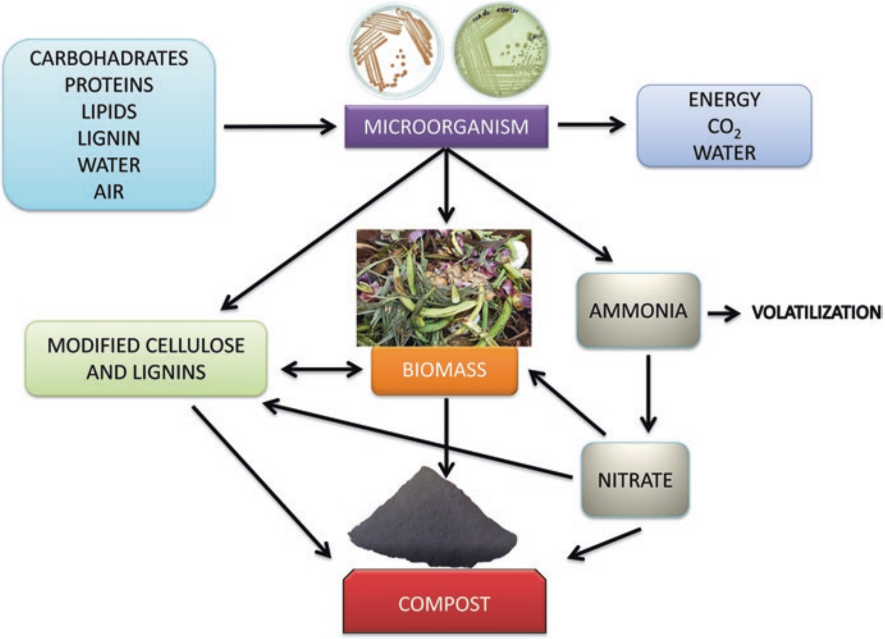

Fig. 1.3 Microbial decomposition of biomass into compost. Microorganisms in the conducive parameters act efficiently on the biomass with complex organic matter transform it into nutrient-rich compost having an agricultural application. The action of microorganisms results in converting lignocellulosic biomass into simpler ones and the available nitrogenous components into ammonia and nitrate/nitrite, further enhancing the overall compost quality

soil amendment for agricultural applications (Onwosi et al. 2017). To carry out an efficient composting process, the temperature is the main parameter that regulates the overall composting process. According to Kulikowska (2016), the substrate's ambient temperature and nature decide the composting process's effectiveness and the final compost's quality. Based on temperature gradient, there are four stages of the composting process viz.; mesophilic phase, thermophilic phase, cooling phase, and the maturation phase (Fig. 1.4) (Onwosi et al. 2017). In each phase, the microbial biomass varies within the composting pile (Hou et al. 2017).

Such temperature variation during the composting process defines the benefits of microbial populations involved in transforming available substrates into value-added products. In the initial phase, i.e., mesophilic phase, the complex organic matters get converted into simpler ones by the synergistic action of different microbial populations, which further accelerates the compost temperature and drives the composting process into the thermophilic phase (Van der Wurff et al. 2016). In the composting process, the thermophilic stage plays an important role because it eliminates pathogens, weeds, and parasites from the compost pile (Zhang et al. 2012; Hou et al. 2017). Thus, it results in pathogen-free compost (Varma and Kalamdhad 2014). Due to the limited bioavailability of substrate, the microbial population's

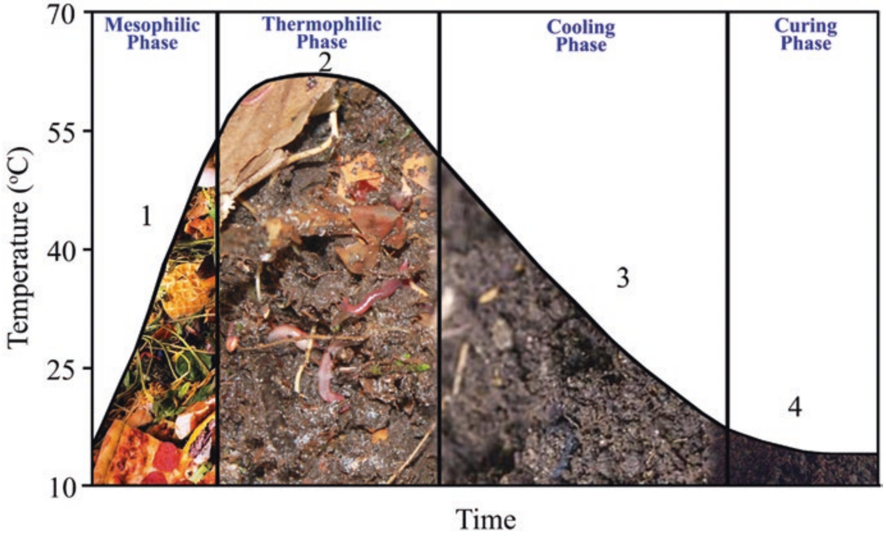

Fig. 1.4 Phases of the composting process. Composting process consists mainly of four phases, namely mesophilic, thermophilic, cooling, and curing or maturation phase. The composting process starts with a mesophilic phase where the temperature reaches up to 40–50 °C. After that, it is dominated by the thermophilic phase. Here the temperature may rise to 60 °C. Then gradually, due to complete utilization of energy and reducing microbial population, the temperature retards, which depicts the cooling phase. Finally, the compost reaches to room temperature, at which it is kept for some more time to get matured completely. Thus, the final phase is called as curing or maturation phase. (Adapted from Alsanius et al. 2016)

activity slows down in the cooling phase. As a result, this takes the composting temperature to a declining stage. Now at this phase, the microbial community, for their survival, they will compete with each other by developing strategies such as antibiotic productions (Van der Wurff et al. 2016). In the last stage, i.e., the maturation phase, there is a slow transformation in the composting pile's microbial population. In this stage, the compost gets colonized by the microorganisms that readily depend on the available substrate (Van der Wurff et al. 2016).

1.3.2.1 Composting of Agro-Industrial Waste

Urbanization and rapid industrialization have led to increased exploitation of resources and the generation of waste in bulky volumes (Gonzalez-Salazar et al. 2016). The huge amount of nutrients rich biomass waste generated from agro-industries is disposed of and underutilized (Abdel-Shafy and Mansour 2018). With the advancement in technology and increased global research standards, scientific tools have taken place. The emerging interest in research is to control agro-industrial waste by proposing green value-added technologies focused on traditional approaches, including harsh and hazardous chemicals at high processing and waste treatment costs (Chen and Lee 2018). The biological processing of agro-industrial wastes is exciting green biotechnology with minimal harmful effects on the environment while balancing it (Zakaria et al. 2020). Microorganisms, primarily from bacterial and fungal species, are used for biological treatments to fix those problems. Bran and cereal straw (Hart et al. 2003); horticultural wastes (Lu et al. 2004; Lopez et al. 2006); Cotton, lemon tree prunings, and brewery wastes (García-Gómez et al. 2005); Grapes, olive, and palm wastes (Arvanitoyannis and Kassaveti 2007) are ideal substrates for the processing of humus-rich compost.

1.3.2.2 Various Microbial Community Involved in Carrying out the Composting Process

Conventional chemical methods for agro-industrial waste treatment have led to increased environmental pollution hampering human and animal life. Therefore, there is a demand for eco-friendly approaches to tackle such waste. In such conditions, microorganisms' function can't be ignored as they play a vital role in the biological method of composting to treat agro-industrial wastes into value-added products. Various microorganisms are reported to yield better compost products under improved composting conditions. These microorganisms possess various enzymatic activities directly involved in decomposing organic materials into a valuable product (Eida et al. 2009). These microbes have great potential to rapidly convert cellulosic and lignocellulosic compositions of wastes into nutrient-rich biological matter (de Souza 2013). This nutrient-rich decomposed organic matter is fruitful to enhance the activity of native important microorganisms in the soil (Meena et al. 2014; Rashid et al. 2016).

The mixture of bacterial communities, i.e., *Ureibacillus thermosphaericus,* S*treptomyces thermovulgaris, and Bacillus shackletonni* are proved to enhance the process of composting (Vargas-García et al. 2007). The inoculum of lignocellulolytic fungi (e.g., *Trichurus spiralis*) can be used before composting process, which will help reduce the resistance to biodegradation substrates (Hart et al. 2003; Vargas-García et al. 2007).

A decomposed product by the action of earthworm *Eisenia fetida,* i.e., vermicompost, is also considered to increase indigenous soil microbial diversity and encourage plant growth (Lim et al. 2015). The mixture of sawdust, guar gum waste, and cow dung in the substrate has been reported to humify by a new strain of earthworm *Perionyx sansibaricus* (Suthar 2007). Composting may also be viewed as a cheap technology for transforming agro-industrial waste into a value-added commodity.

1.3.3 Anaerobic Digestion

Anaerobic digestion is a method of decomposition of organic waste under anaerobic conditions with low energy requirements. It produces biogas and leftover digestate as the by-products used as renewable energy sources and fertilizer for agricultural lands. The application of anaerobes in waste management has been identified for more than hundreds of years (McCarty 2001). Generally, the waste disposal methods are employed to avoid contamination of the environment; however, anaerobic processes are used for the treatment of high organic waste content for the generation of energy in the form of biogas or biofuels. The current scenario of global greenhouse gas emission and energy disasters is encouraging green energy and advances in biotechnology to generate a new economy based on environmental and energetic factors (Holm-Nielsen et al. 2009). In this regard, principles like biorefining and energy extraction are introduced based on the biotechnological transformation of biomass. From this point of view, anaerobic digestion plays a vital role in these situations, as it generates various by-products such as methane and hydrogen at the different metabolic stage, which can be used as power sources, i.e., either in boilers, internal combustion engines, or fuel cells.

The fermentation of methane is a dynamic mechanism separated into four stages: hydrolysis, acidogenesis, acetogenesis, and methanogenesis (Pereda Reyes and Sárvári Horváth 2015) (Fig. 1.5). Diverse microorganisms execute the degradation

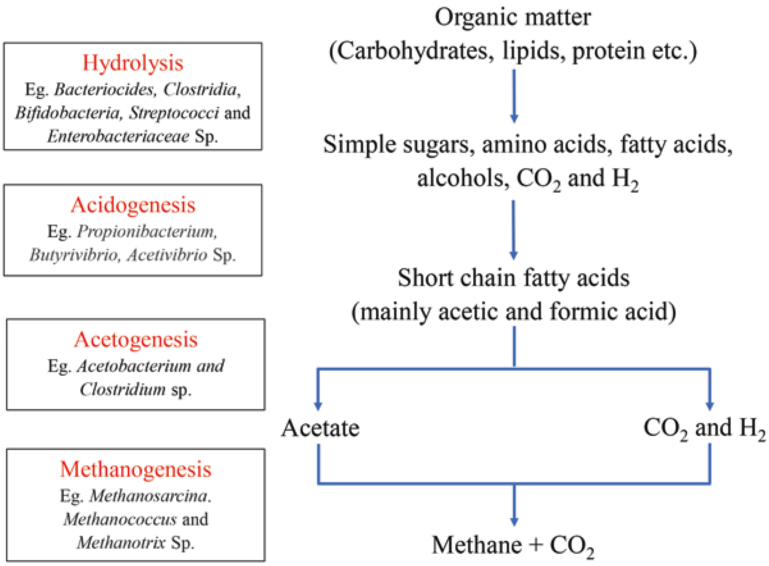

Fig. 1.5 Degradation process involved during anaerobic digestion. Anaerobic digestion of organic waste includes four major steps, i.e., hydrolysis, acidogenic fermentation, hydrogen-producing acetogenesis, and methanogenesis, which results in the formation of methane and carbon dioxide

steps, which are partially interrelated syntrophically and have different environmental requirements. Hydrolytic bacteria were the first group of microorganisms. These species hydrolyze polymeric compounds by extracellular hydrolytic enzymes (cellulase, xylanase, amylase, protease, lipase) into monomers such as glucose and amino acids (Weiland 2010). These microbial communities include some strict anaerobes such as *Clostridia, Bifidobacteria, Bacteriocides,* and some facultative anaerobes also take parts, such as *Streptococci* and *Enterobacteriaceae*. The acidogenic bacteria are the second category of microorganisms that transform carbon dioxide, hydrogen, ammonium, and other organic acids from sugars and amino acids. The third type of bacterial species involved is hydrogen-producing acetogenic bacteria, such as *Clostridium acetium, Acetobacterium woodii,* which converts volatile fatty acids into acetate and hydrogen. Two different groups of strictly anaerobic bacteria produce methane as a final product from acetate (Acetotrophic pathway) or hydrogen and carbon dioxide (hydrogenotrophic pathway) at the end of the degradation process. Very few microorganisms, i.e., *Methanotrix soehngenii, Methanosarcina barkeri, and Methanococcus mazei* can degrade acetate into methane and carbon dioxide, whereas hydrogen can be used to form methane by all methanogenic bacteria such as *Methanobacteriales* and *Methanomicrobiales* (Batstone et al. 2002).

Anaerobic digestion occurs at three different temperatures depending on the climate conditions, thermophilic (55–60 °C), mesophilic (35–37 °C), and psychrophilic (below 20 °C). Thermophilic and mesophilic temperatures are often used for industrial applications due to higher process stability, methane yields, and fewer energy requirements (Alatriste-Mondragón et al. 2006). The proper implementation of anaerobic digestion relies heavily on how the composition of waste to be digested (Murto et al. 2004). Solid waste treatment varies from liquid waste treatment, as solubilization and hydrolysis of particle material may be the limiting step in the process. To enhance mass transfer phenomena and ensure the proper interaction between the biomass and the substrate, waste mixing must be carried out correctly. If the microorganisms involved in the process are not separated from the solid wastes to be decayed, the retention time is generally 50–60 days in the digester; otherwise, microorganisms may wash out from it. On the other hand, in the wastewater bioreactor system, microorganisms' retention time will be decoupled from liquid retention results into reduced hydraulic retention time to a few hours. The microbial treatments of agro-industrial waste generally remove pathogens and other organic compounds from the effluent, but due to high particulate and fat contents, anaerobic digestion is complicated in slaughterhouse industries (Batstone et al. 1997). Still, anaerobic digestion remains a viable alternative for the treatment of these kinds of waste materials, as they have a high potential to generate biogas only because of their high protein and fat content.

On the other hand, agro wastes are composed of major biodegradable components, i.e., cellulose and hemicellulose linked with lignin. Compared to carbohydrates, these organic compounds produce low amounts of methane (up to 50% methane) under anaerobic conditions due to the low biodegradability and sheltering effect of lignin. But several agro wastes are favorable for anaerobic digestion as they can degrade 80% of their fiber content, such as paper and rice residues (Esposito et al. 2011) (Contreras et al. 2012). For the anaerobic treatment of agro-industrial drainages, several reactor configurations are used:

1.3.3.1 Completely Stirred Anaerobic Digester

The continuous stirred tank reactor is the earliest and basic high-rate system for the anaerobic treatment of wastewater with a high amount of suspended solids and organic industrial waste. It a stable and reliable anaerobic treatment system with an equally solid retention time and hydraulic retention time of 15–40 days for the proper treatment and process (Del Real Olvera and Lopez-Lopez 2012). In this system, alternate and continuous mixing is helpful to suspend the microorganism in the digester, which results in better substrate-sludge contact, but it requires a significant amount of energy and is labor-intensive (Mao et al. 2015). Another drawback of this method is that only high volumetric waste sources with a biodegradable COD content range between 8.000 and 50.000 mg/L attain a high loading rate, but many waste sources are diluted considerably. A single continuous stirred tank reactor system is easy to operate but produces poor quality effluent. So, a two-phase treatment system is employed and is most common these days. The two-stage continuous stirred tank reactor system is comparatively simple in design and cost-effective for the treatment of wet digesters. However, the system's sensitivity to substrates with high organic loads and the complicated operation leads to fewer alternatives to increase the two-phase system's digestive efficiency (Boe and Angelidaki 2009). Different variants of continuous stirred tank reactors are currently constructed to enhance the reactor's performance by optimizing the reactor volume. To increase the reactor's microbial load, gravity sedimentation tanks or membrane bioreactors are used in series with continuous stirred tank reactors for a more effective digestion process. For the treatment of dairy wastewater, a two-phase anaerobic system of continuous stirred tank reactor and up-flow anaerobic filters are used under various operating conditions, but a high concentration of suspended solids affects treatment efficiency (Mao et al. 2015).

1.3.3.2 Upflow Anaerobic Sludge Blanket Reactor

Upflow anaerobic sludge blanket reactor is a compact system that requires a small area to operate with low maintenance and expenditure costs, low energy usage, and low production of sludge continuously feeding the up-flow anaerobic sludge blanket reactor from the bottom, creating an up-flow stream towards the upper outlet through the sludge bed consisting of aggregated microbes and granular biomass. With the upward movement of effluent, its velocity decreases, providing greater area and enhancing the process's solid retention time and efficiency. Upflow anaerobic sludge blanket reactor systems can achieve better settlement ability, high biomass concentrations, short retention time, strong solids/liquid isolation, cost removal of packaging content, and very high loading rate operations. The removal efficacy of chemical oxygen demand is about 65%, and biochemical oxygen demand is 75% in up-flow anaerobic sludge blanket reactor type reactor system. Also, highly concentrated sludge is produced with better dehydration capacity. Although the sludge acclimation is vital for start-up only, after long periods of disrupted functioning, reactor output can be resumed. This method is generally restricted by the high solid suspended content in wastewater to be treated, which prevents the production of dense granular sludge, and sometimes foul smell occurs due to the inappropriate nature or installation of the gas collection system and low tolerance of toxic charge.

1.3.3.3 Fluidized and Expanded Bed Reactors

In an anaerobic fluidized bed reactor, bacteria are grown and attached on small granular particles such as alumina or sand and activated carbon. These particles are suspended by a fast-upward flow of wastewater, allowing resistance to inhibitors and a higher organic loading rate level. Organic loading rate of 10–20 kg COD/ m^3d^{-1} can be used in an anaerobic fluidized bed reactor (Siqueira et al. 2013). The high rate of flow around the particles covered with a thin biofilm layer of methanogens results in good mass transfer. Less clogging of the latter allows the short-circuiting and larger surface to volume ratio of the carrier in the reactor, making the anaerobic fluidized bed reactor more efficient than up-flow anaerobic sludge blanket reactors. Also, an anaerobic fluidized bed reactor is cheaper due to the reduced volume of the reactor, and it is better than an up-flow anaerobic sludge blanket in terms of removing the suspended solid particles from wastewater (Mao et al. 2015). However, the key disadvantages of this method are the difficulties of producing a tightly attached biofilm containing the right mix of methanogens, the risk of detachment of microorganisms, the harmful consequences of dilution near the inlet due to high recycling rates more cost of energy. The expanded granular sludge bed reactor is a variant of the anaerobic fluidized bed reactor with a variation in the fluid's upward flow rate (Del Real Olvera and Lopez-Lopez 2012).

1.3.3.4 Anaerobic Filters Reactors

The Anaerobic Filters are designed to support the intimate interaction between the waste and bacterial population, thereby providing a longer retention time for biomass than hydraulic retention time. They are used to treat various wastewaters produced from dairy, beverages, chemical, and food processing industries. Anaerobic filters are a widely used anaerobic digestion process due to the high organic loading rate. The anaerobic filter is generally made up of different materials such as ceramic, charcoal, plastic materials, sintered glasses, seashells, limestones, and pumice clay (Karadag et al. 2015). These are designed with at least two filtration compartments arranged in a manner. At the anaerobic filters, biomass can degrade the organic material found in wastewater and then bind outside the filter material. Furthermore, these anaerobic filters are commonly used as an optional treatment to increase solid elimination. The anaerobic filters need to be able to use sufficient packaging media because the media's chemical and physical properties have a crucial influence on biomass and its reactor efficiency. The anaerobic filter is generally packed with various packaging materials to contain the bacteria in the voids. The ideal packaging media increases the surface area and extends anaerobic filters' porosity, increasing the biomass link, decreasing the reactor's volume, and restricting channel obstruction. Some researches show that anaerobic filters remove 80% of chemical oxygen demand with a maximum organic loading rate capacity of 19 and 17 g COD $L^{-1}d^{-1}$ of wastewater generated from cheese, dairy, and fruit canning industries (Rajagopal et al. 2013). These days, researchers concentrate on using industrial by-products for the natural application of anaerobic filters, as it is more efficient for the treatment of wastewaters with a low level of suspended solids. Also, anaerobic filters have some advantages like minimum nutrients reduction and require further treatment of effluents.

1.4 Recycled Value-Added Products from the Microbial Treatment of Agro-Industrial Waste

The scientific community uses various agro-industrial wastes and effluents through green and recycling technologies to overcome the existing global environmental health. The agro-industrial wastes are used for the production of many value-added products such as biofuels, enzymes, and biofertilizers based on their composition, i.e., lignocellulose, proteins, polyphenols, and carbohydrates. Some of the products are discussed below:

1.4.1 Some Important Enzymes from Agro-Industrial Waste

1.4.1.1 Alpha and Beta-Amylase

Alpha-amylases (E.C 3.2.1.1) cleave α-D-(1,4) glycosidic linkages between the glucose subunits in starch, glycogen, and other related polysaccharides. They have a wide variety of applications in food, detergent, textile, paper, pulp, distilleries, and pharmaceutical industries (Ramachandran et al. 2004). They are derived from many organisms, such as plants, animals, and microorganisms (Far et al. 2020). At the industrial level, they are produced by both submerged fermentation and solid-state fermentation using genetically improved microorganisms such as *Bacillus* and *Aspergillus* species (Sundarram and Murthy 2014). Agro-industrial residues act as a favorable substrate for the production of α-amylases, mainly due to their high lignocellulosic content and low economic cost. In literature, the production of this enzyme is primarily emphasized by solid-state fermentation. In some of the earlier studies, banana waste, rice husk, coconut oil cake, sugarcane bagasse, corn cob, and spent brewer's grain has been used for the production of amylase (Ramachandran et al. 2004; Anto et al. 2006; Aliyah et al. 2017).

β-amylases (E.C. 3.1.2.3), also known as glucoamylases, cleave the α-1,4linkages found in starch and other carbohydrates to release glucose molecules. It also hydrolyses α-1,6 glycosidic bonds at slower rates. Thus, an exoamylase releases glucose moieties from the non-reducing end of the carbohydrates (Espinosa-Ramírez et al. 2014). They are very useful in the bakery and brewery industry (Diler et al. 2015). They are produced by several bacterial and fungal species like A*spergillus, Bacillus, Saccharomyces,* and *Rhizopus* (Singh and Soni 2001; Shin et al. 2000). Vegetable waste such as cassava, yam, and banana peels has been used as a carbon source for glucoamylase production (Adeniran et al. 2010).

1.4.1.2 β-Glucanase

β-glucans are polysaccharides made of D-glucose monomers linked through β-1,3 and β-1,4 glycosidic linkages. They form a major part of the cell wall polysaccharide of cereal endosperm and comprise approximately 5.5% of the dry weight of grains (Dais and Perlin 1982). Besides cereal endosperm, they can also be found in natural products like mushrooms, yeast, oats, and algae (Zhu et al. 2016). Fungi produce glucans with β-1,3, β-1,4, and β-1,6 bonds, which also exhibit antitumor activity (Latgé 2010). Based on the cleavage of glycosidic bond, β-glucanases are classified as β-1,4-glucanase (EC 3.2.1.4), β-1,3(4)-glucanase (EC 3.2.1.6), β-1,3-glucanase (EC 3.2.1.39), and β-1,3-1,4-glucanase (EC 3.2.1.73) (Ueda et al. 2014). Microorganisms like *Fusarium oxysporum, Bacillus subtilis,* and *Penicillium echinulatum* have been reported to produce high endo and exoglucanase levels when grown on biomass sources (Ravindran et al. 2018). They have applications in brewing, detergent, and animal feed industries (Chaari and Chaabouni 2019).

1.4.1.3 Cellulase

Cellulases are a group of enzymes involved in the depolymerization of cellulose. They comprise three enzymes endoglucanase (E.C. 3.2.1.4), exoglucanase or cellobiohydrolase (E.C. 3.2.1.176) (E.C. 3.2.1.91), and β-glucosidase (E.C. 3.2.1.21). They play a very important role in biofuel production using different lignocellulosic materials (Castro and Pereira Jr 2010). Besides bioethanol, they have applications in food, detergent, paper, pulp, and textile sectors (Ferreira et al. 2014). They are secreted by several microorganisms like bacteria, fungi and actinomycetes (Zverlov et al. 2015). *Clostridium thermocellum*, *Proteus vulgaris, Bacillus circulans, Escherichia coli*, *Klebsiella pneumonia*, and *Cellulomonas* are the bacteria involved in the production of Cellulases (Ravindran et al. 2018). Simultaneously, fungal species such as *Melanocarpus*, *Schizophyllum, Penicillium, Aspergillus, Trichoderma* and *Fusarium* produce these enzymes (Juturu and Wu 2014). Studies have been conducted in the literature to use fruit peels and spent brewer's grain to be used as a substrate for cellulase production by *Trichoderma* sp. (Sim and Oh 1990; Nadar and Rathod 2019).

1.4.1.4 Hemicellulase

Hemicellulose is a branched heteropolysaccharide consisting of different hexoses and pentoses, including glucose, fructose, galactose, arabinose, xylose, mannose, glucuronic acid, and galacturonic acid. It accounts for 20–30% of the total wood (Collins et al. 2005) and is generally amorphous in nature. Hemicellulases are the enzymes that break β-1,4-glycosidic bonds present in the backbone of hemicellulose. They are produced both by bacterial and fungal strains, namely *Clostridium, Bacillus, Geobacillus, Trichoderma,* and *Aspergillus* (Shallom and Shoham 2003). The most common hemicellulases are xylanases, mannanases, glucuronidases, galactosidases, and arabinofuranosidases (Obeng et al. 2017). They also play a crucial role in the paper, pulp, biofuel, food, and pharmaceutical industries. Studies have been conducted on using corn cobs, apple pomace, and palm oil effluents as a substrate for hemicellulases production (Zainudin et al. 2013; Dhillon et al. 2012; Kheiralla et al. 2018).

1.4.1.5 Xylanase

Xylan is a complex polysaccharide made of β-1,4-linked xylose residues. It is the most abundant type of hemicellulose present in nature (Beg et al. 2001). The backbone made of xylan residues have the side branches of d-glucuronic acid and d-glucuronic acid (4-*O*-methyl α-1,2 linked) or d-arabinofuranose (α-1,2 or α-1,3 linked), and *O*-acetyl groups (Bastawde 1992). The branches play an important role in the cross-linking of cellulose microfibrils and lignin through ferulic acid residues. The extent of branching depends on the source of xylan. Because of its heterogenous nature and complex structure, xylan requires several enzymes, namely endoxylanases, β-xylosidases, ferulic acid esterase, p-coumaric acid esterase, acetyl xylan esterase, and α-glucuronidase (Bhardwaj et al. 2019). They all form a class of xylan degrading enzymes called xylanases (E. C. 3.2.1.8). Xylanases have been isolated from different microorganisms, such as Aspergillus *Chytridiomyces, Streptomyces, Trichoderma, Phanerochaete, Clostridium, Fibrobacter, Bacillus,* and *Pichia* (Collins et al. 2005). Several agro-industrial wastes such as wheat straw, wheat bran, rice husk, and sugarcane bran have been used to produce xylanases at very low cost (Pandya and Gupte 2012; Membrillo Venegas et al. 2013).

1.4.1.6 Mannase

Mannan is the second most abundant hemicellulose in nature. It comprises linear mannan, glucomannan, galactomannan, and glactoglucomannan. The enzymes involved in the depolymerization of linear mannan are β-mannanase (EC 3.2.178), β-mannosidase (EC 3.2.1.25), β-glucosidase (EC 3.2.1.21), acetyl mannan esterase (EC 3.1.1.6), and α-galactosidase (EC 3.2.1.22) (Moreira 2008). β-mannanases cleave the internal glycosidic bonds and release short-chain manno-oligosaccharides, whereas β-mannosidases hydrolyze mannan from the non-reducing end releasing individual mannose unit (McCleary and Matheson 1983; Gomes et al. 2007). They are produced by several bacterial and fungal species: B*acillus circulans, Clostridium cellulolytic, Trichoderma reesei, Agaricus bisporus, Aspergillus aculeatus* (Moreira 2008). They have applications in paper, pulp, food, and textile industries (Clarke et al. 2000; Naganagouda et al. 2009). Abdeshahian et al. has used palm kernel to produce β-mannanases using the fungi *Aspergillus niger* (Abdeshahian et al. 2010). Apple pomace, cottonseed powder, and locust bean have also been observed as excellent substrates for the production of mannases (Gomes et al. 2007; Yin et al. 2013).

1.4.1.7 Pectinase

Pectin is a widely distributed carbohydrate polymer in plants. It is a complex polysaccharide made of galacturonic acid residues linked by α-1,4 linkage. The acid groups along the chain are largely esterified with methoxy groups in the natural product. There can also be acetyl groups present on the free hydroxy groups. Pectinases are a group of enzymes that degrade pectic substances and release comparatively simpler compounds based on their mode of action. The linear pectin chain is generally cleaved by endo-polygalacturonases (EC 3.2.1.15) and exo-polygalacturonases (EC 3.2.1.67) from inside and at the terminal, respectively (Rytioja et al. 2014). Pectinlyases (EC 4.2.2.10) and pectate lyases (EC 4.2.2.2) also cleave the pectin backbone. Whereas the branched region is degraded by rhamnogalacturonan acetylesterase (EC 3.1.1), pectin acetyl esterase (EC 3.1.1), and pectin methylesterase (EC 3.1.1.11) (De Vries and Visser 2001). Pectinases are produced by bacterial, fungal, and yeast strains, namely *Bacillus, Paenibacillus, Chryseobacterium, Pectobacterium, Aspergillus, Fusarium, Penicillium, Rhizopus, Botrytis, Fusarium, Trichoderma, Rhodotorula* (Singh et al. 2019). They have applications in the fruit, paper, pulp, textile, and animal feed industries. They have also been used in coffee and tea fermentation (Sharma et al. 2013).

1.4.1.8 Inulinase

Inulin is produced by several plants such as banana, garlic, chicory, onion, garlic, barley, wheat, barley, and rye (Kaur and Gupta 2002). It is classified as an oligo or polysaccharide, depending upon its chain length. It consists of D-fructosyl moieties linked by β-2,1 glycosidic bond terminating with α-1,2 bonded D-glucosyl group (Ronkart et al. 2007). Inulinases are defined as a group of enzymes involved in the degradation of inulin. They mainly consist of exo-inulinases (β-D-fructanfructohydrolase, EC 3.2.1.80) and endo-inulinases (2,1-β- D -fructanfructohydrolase, EC 3.2.1.7) based on their mode of activity (Vijayaraghavan et al. 2009). They are shown to produce by *Streptococcus, Pseudomonas, Xanthomonas, Chrysosporium, Actinomyces, Penicillium, Aspergillus, Kluyveromyces* species. They have applications in lactic acid production, 2,3 butanediols, biofuel, sugar alcohols, fructose syrup, and inuloorligosaccharides (Liu et al. 2013; Chi et al. 2009). Recently, coconut oil cake, sugarcane baggase, and rice bran have been used for the synthesis of inulinases (Onilude et al. 2012; Singh and Chauhan 2018; Mazutti et al. 2006).

1.4.1.9 Laccase

Laccases (E.C. 1.10.3.2) are aromatic compounds oxidizing enzyme which belong to a multi-copper oxidase family. They oxidize a wide variety of phenols, heterocyclic compounds, and aromatic amines. They catalyze the oxidation of their substrates with the help of molecular oxygen. They play a crucial role in dye, bleaching, pulp, and industrial effluent treatment. They have also been explored for the degradation of lignin, herbicides, and pesticides (Ravindran et al. 2018). They are produced by bacteria, fungi, plants, and insects. The bacterial and fungal species involved in the production of laccases are *Bacillus subtilis*, *Streptomyces lavendulae*, *Azospirillum lipoferum*, *Pleurotus ostreatus, Trametes versicolor.* (Kiiskinen et al. 2004). They can be produced using groundnut, banana peel, rice straw, orange peel, and wheat bran from agro-industries as substrate (Singh and Gupta 2020).

1.4.1.10 Phytase

Phytates are defined as naturally occurring phosphate-rich compounds found in cereals, oilseeds, and legumes. The enzyme that catalyzes the release of phosphates from phytates is known as phytase (EC 3.1.3.8) (Hussin et al. 2007). Phytases are classified based on their stereospecificity of hydrolysis. The enzymes that cleave at the C3 and C6 positions of phytic acid are classified as 3-phytases (EC 3.1.3.8) and 6-phytases (EC 3.1.3.26), respectively. Mostly, 3-phytases are produced by the microorganisms; on the other hand, 6-phytases by plants. They are produced by different bacterial, fungal, and yeast genera, namely *Klebsiella, Bacillus*, *Shigella*, *Selenomonas, Rhodotorula, Aspergillus* (Pandey et al. 2001). Ruminants produce phytases for the proper digestion of phytate-rich food, whereas monogastric animals do not produce this enzyme. Treatment of animal feed with phytases increases the bioavailability of minerals, thus improving its nutritional value. The phytases are important for poultry, pig, baking, and bioethanol industries. They can be produced using residues from agricultural industries and fruit peels as substrate, thus pointing towards their low-cost synthesis (Bajaj and Wani 2011).

1.4.1.11 Invertase

Invertase (EC.3.2.1.26) is a glycoprotein that catalyzes the hydrolysis of sucrose into glucose and fructose. They mainly hydrolyze β-1,2 linkage present between the glucose and sucrose units. They are also known as β-D-fructofuranosidase because of their ability to release fructose from the non-reducing terminal of β-D-fructofuranoside substrates (Linde et al. 2009). Sucrose hydrolysis is generally carried out using hydrochloric acid with only 50–60% efficiency, whereas the employment of invertase enzyme improves the efficiency of this reaction up to 100% and without yielding any impurities (Ravindran et al. 2018). Invertase is shown to be present in *Bacillus cereus, Lactobacillus reuteri, Brevibacterium* sp., *Arthrobacter* sp., *Streptomyces* sp., *Zymomonas mobilis*, *Saccharomyces cerevisae, Candida utilis, Aspergillus niger, and Penicillium chrisogenum* (Lincoln and More 2017). Recently, wheat bran, fruit waste, and bagasse waste have been observed as excellent carbon sources for the low-cost production of invertase (Ravindran et al. 2018).

1.4.1.12 Protease

Proteases (EC 3.4.21.62) are a group of enzymes that perform the hydrolysis of peptide bonds and release small peptides or free amino acids. They are also known as proteinases. They are a crucial industrial enzyme that accounts for approximately 70% of the total enzymes produced worldwide (Meena et al. 2013). They are widely distributed in living organisms as they are crucial for various physiological processes. They can be classified as acidic, alkaline, and neutral proteases. The alkaline (EC.3.4.21–24.99) and acidic proteases cleave proteins between pH range 9–11 and 3–4, respectively (Razzaq et al. 2019). They are found in plants, animals, and microorganisms. Among microbes, they are produced by *Bacillus licheniformis, Bacillus stearothermophilus, Pseudomonas aeruginosa, Lactobacillus acidophilus, Aspergillus oryzae, Penicillium, Rhizopus* (Singh et al. 2019; Razzaq et al. 2019). They are important in the food, feed, leather, silk, and textile industries. Alcalase, Neutrase, and protease are some of the commercially available proteases. Tomato pomace, soybeans, and jatropha seed cakes have been used as a substrate for protease production (Ravindran et al. 2018).

1.4.1.13 Pullulanase

Pullulan is a maltotriose trimer made up of α-1-4 and α-1-6-linked triglucosides. Due to the existence of both α-1-4 and α-1-6 in this compound, it is seen as an intermediate between the amylose and dextran structure. Pullulan is insoluble in non-polar compounds but is soluble in water. It has high mechanical strength thus can be used for a gelling agent, capsule, and thin-film formation (Farris et al. 2014). The enzymes used to depolymerize pullulan are mainly classified as pullulanase (EC. 3.2.1.41), isopullulanase (EC.3.2.1.57), and neopullulanase (EC.3.2.1.35). The pullulanase is further divided into type-I and type-II, which cleave only α-1,6-glycosidic linkage and α-1,4 & α-1,6-glycosidic linkages, respectively. They are essential for the baking and starch industries (Hii et al. 2012). They are synthesized by *Klebsiella pneumoniae, Bacillus cereus, Bacillus macerans, Streptomyces mitis, Clostridium* sp.., *Thermus aquaticus, Thermoanaerobacter* sp*., Saccharomyces* sp*., Aspergillus* sp*., Cladosporium* sp. (Saha and Zeikus 1989; Tomasik and Horton 2012). Agricultural waste materials such as wheat, rice, and corn bran can be used for its cheap production (Zhang et al. 2020; Reddy et al. 2000).

1.4.1.14 Lipase

Lipases (EC 3.1.1.3) are a group of hydrolases that catalyze the breakdown of triglycerides to glycerol and fatty acids. They also carry out hydrolysis, transesterification, alcoholysis, aminolysis, acidolysis, and esterification, which are important industrial processes (Ravindran et al. 2018). They are crucial in the cosmetic, food, detergent, and pharmaceutical industries. They are well distributed in plants, animals, and microorganisms. Among microbes, they are produced by bacterial, yeast, and fungal strains such as *Bacillus, Serratia, Burkholderia, Candida, Rhodotorula, Aspergillus,* and *Penicillium* (Treichel et al. 2010). They are extracellular enzymes and are greatly influenced by physicochemical factors like pH and temperature. They are inducible enzymes and are synthesized when an inducer such as fatty acid, oil, and triglycerols are present in the medium. Agricultural residues like oil cake, fruit peels, and bean waste have been used for the cheap production of lipase (Godoy et al. 2011; Pereira et al. 2019).

1.4.2 Bioethanol Production

Due to the rise in population and rapid industrialization, energy demands have increased worldwide. The excessive consumption of fossil fuels, such as natural gas, oil, coal, and petroleum, has resulted in higher pollution levels. The increased pollution, especially due to the accumulation of large amounts of greenhouse gases, causes a change in the earth's climate. It has also been suggested that petroleum-based fuels will deplete in the near future; thus, due to their harmful effects and limited supply, these non-renewable sources should be replaced with better environment-friendly energy resources. Biofuels are the most feasible alternate for traditional fuels as they reduce our dependency on fossil fuels and do not disturb the balance of the earth's atmosphere. Both bioethanol and biodiesel have been seen as a supplement of gasoline and diesel, respectively. The global bioethanol production was approximately 66.77 billion liters in 2008, which was increased to 90.38 billion liters in 2014 (Gupta and Verma 2015).

The countries like the USA and Brazil produce bioethanol using corn and sugarcane, respectively, which account for 62% of the total global production (Kim and Dale 2004). The utilization of sugars and starch is not widespread in bioethanol generation, mainly due to their high food value. Recently, it has been observed that lignocellulosic biomass and agricultural crop waste can be used for bioethanol production. They are cheap sources and present in large amounts, so their employment for bioethanol production provides a route for their effective utilization. Agro-residues like wheat straw, rice straw, corn straw, fruit peels, sugarcane bagasse, and oil cakes now have significant interests. Rice straw is the highest agricultural waste and can produce 205 billion liters of bioethanol per year (Sarkar et al. 2012). Physical, chemical, and biological pre-treatments are required to generate bioethanol from agricultural waste materials.

Lignocellulosic material consists of cellulose and lignin linked with hemicellulose chains. A pre-treatment process is required for the breakdown and release of these components. It makes lignocellulose susceptible to hydrolysis and makes the release of monomer sugars easy (Mosier et al. 2005). There are three types of pre-treatment processes, i.e., physical, chemical, and biological treatments. The physical pre-treatment process for bioethanol production involves mechanical methods such as milling, grinding, and chipping. The amount of power used to crush the material mainly depends on the particle size, nature, and moisture content of the waste (Buaban et al. 2010). The mechanical processes disrupt the structure of lignocellulose and decrease its particle size to increase the surface area for enzymatic hydrolysis (Kumar et al. 2008). Besides mechanical processes, physical pre-treatment also includes uncatalyzed steam-explosion, high-energy radiation, and liquid hot water treatment (Fig. 1.6). The steam explosion aids in the loosening of lignocellulosic structure and releases pentose, but it has a disadvantage of generating cellulase inhibitory compounds, which later interfere with enzymatic hydrolysis of this substrate (Gupta and Verma 2015). The high-energy treatment is provided by heating in a microwave oven or electron beam irradiation. The microwave irradiation leads to the vibrations in the bonds present in the exposed biomass and heats it from inside. It leads to the explosion effect, thus disrupting the recalcitrant structures of lignocellulose (Hu and Wen 2008). The liquid hot water treatment employs compressed hot water to hydrolyze the lignocellulosic biomass and release sugar monomers (Sarkar et al. 2012).

Chemical pre-treatment methods make use of dilute acids, alkali, organic solvents, and ammonia. This process utilizes a chemical impact to access the lignocellulosic matrix. However, this method produces certain inhibitors that later interfere with enzymatic activity in downstream processing and affect the entire economy of

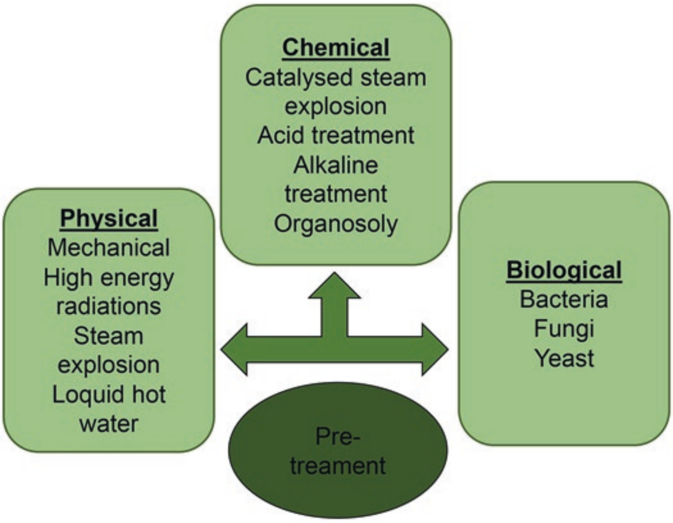

Fig. 1.6 Pre-treatment processes used for bioethanol production. Physical, chemical, and biological processes are the three main types of pre-treatment processes used to degrade the lignocellulosic matrix

bioethanol production. On the other hand, the biological treatment uses microorganisms like brown rot, white rot, and soft rot fungi. White and soft rot fungi degrade both cellulose and lignin, whereas brown rot fungi only attack cellulosic material. The hydrolysis rate is lower in biological treatment, but it requires low energy and mild environmental conditions. Most of the sugar released after biological treatment are still in the form of oligomers and still needs to be hydrolyzed by specific microbes before fermentation (Prasad et al. 2007). Enzyme hydrolysis is also necessary to convert sugars to simple monomers. The cellulases and hemicellulases producing microorganisms such as *Clostridium, Cellulomonas, Thermonospora, Bacillus, Streptomycetes, Bacteriodes, Acetovibrio, Ruminococcus, Erwinia, Microbispora, Trichoderma, Penicillium, Fusarium, Phanerochaete, Humicola, Schizophillum,* release hexoses and pentoses upon acting on lignocellulosic substrate materials (Gupta and Verma 2015). The cellulases which are involved in the degradation are endoglucanase (E.C. 3.2.1.4), degrading the low crystallinity regions, exoglucanase (E.C. 3.2.1.91) removing the cellobiase units from the free chain terminal, and finally, βglucosidase (E.C. 3.2.1.21), which cleave cellobiose units into glucose (Castro and Pereira Jr 2010). The hemicellulases consist of a mixture of enzymes, namely xylanases, mannases, glucuronidases, galactosidases, and arabinofuranosidases (Obeng et al. 2017). Fermentation and distillation are the final steps for the production of bioethanol. For industrial purposes, microbes with a broad substrate range, higher temperature tolerance, and high ethanol yields are essential. As such microbes' recognition becomes difficult, genetically modified microorganisms are employed to utilize the sugars spent for efficient bioethanol production. It has been reported that *Saccharomyces* can theoretically yield around 90% ethanol from glucose (Spindler et al. 1992).

The most common fermentation processes are simultaneous saccharification and fermentation and separate hydrolysis and fermentation. Other agricultural remains like bagasse, fruit peels, wheat straw, almond shells, rice straw, sorghum, and corn cobs can be used to efficiently produce bioethanol (Quintero et al. 2011; Gupta and Verma 2015).

1.4.3 Biofertilizers

Targeting agro-industrial waste represents a possible source for developing biofertilizers that can be used as a soil conditioner in agro-ecosystem to yield high crop productivity (Sadh et al. 2018). The term biofertilizer is defined as the preparations which contain living microorganisms that play a crucial role in providing nutrients to the plants. These biofertilizers accelerate specific microbial processes such as nitrogen fixation, ammonia production, indole acetic acid production, siderophore production, phosphate solubilization, and potassium mobilization into the soil and boost up the nutrient availability for easy assimilation by the plants (Devi and Sumathy 2017). Hence biofertilizer plays a vital role in nutrients management (Devi and Sumathy 2017). To develop biofertilizers, several microbial populations and their close association with plant hosts are being exploited.

1.4.3.1 Diversity of Microbial Biofertilizers

The biodiversity of microbial biofertilizers includes nitrogen fixers, phosphate mobilizers, phosphate solubilizers, phosphate mobilizers (Devi and Sumathy 2017), potassium solubilizers, potassium mobilizers (Parmar and Sindhu 2013; Yadav 2018), and plant growth-promoting rhizobacteria (Devi and Sumathy 2017) (Table 1.1).

1.4.3.2 Production of Biofertilizers Using Agro-Industrial Waste

The generation of agro-industrial waste is a huge problem, and at the same time, its maintenance is a major concern. The agro-industrial wastes can be an alternative source to derive biofertilizers for agro-ecosystem and sustainable development (Sadh et al. 2018). solid-state fermentation and submerged fermentation are substrate-based fermentations processes, which are extensively used for producing biofertilizers at a large scale. Agro-industrial waste like soluble sugars, liquid synthetic media, extracts of fruit and vegetable, and dairy by-products are used in biofertilizer production (Suthar et al. 2017). Such waste contains high nutritional components in the form of proteins, sugars, and minerals, which offers a hostile

Table 1.1 Biofertilizers

	Groups	Examples	References
Nitrogen fixers			
1.	Free-living	*Azotobacter, Beijerinkia, Clostridium, Klebsiella, Anabaena, Nostoc*	Singh et al. (2016), Verma et al. (2014), and Meena et al. (2017)
2.	Symbiotic	*Rhizobium, Frankia, Anabaena, azollae*	Singh et al. (2016) and Meena et al. (2017)
3.	Associative symbiotic	*Azospirillum*	Singh et al. (2016) and Meena et al. (2017)
Phosphate solubilizers			
1.	Bacteria	*Bacillus megaterium* var. *phosphaticum, Bacillus subtilis Bacillus circulans, Pseudomonas striata*	Singh et al. (2016) and Nath et al. (2017)
2.	Fungi	*Penicillium* sp, *Aspergillus awamori,*	Singh et al. (2016) and Ma et al. (2016)
Phosphate mobilizers			
1.	Arbuscular mycorrhiza	*Glomus* sp., *Gigaspora* sp., *Acaulospora* sp., *Scutellospora* sp. & *Sclerocystis* sp.	Singh et al. (2016)
2.	Ectomycorrhiza	*Laccaria* sp., *Pisolithus* sp., *Boletus* sp., *Amanita* sp.	Singh et al. (2016)
3.	Ericoid mycorrhizae	*Pezizella ericae*	Singh et al. (2016)
4.	Orchid mycorrhiza	*Rhizoctonia solani*	Singh et al. (2016)
Potassium mobilizers			
1.	Fungi	Mycorrhiza	Yadav (2018) and Singh et al. (2016)
2	Bacteria	*Acidothiobacillus ferrooxidans, Bacillus mucilaginosus, Bacillus edaphicus, Burkholderia* sp., *Frateuria* sp., *Pseudomonas* sp., *Rhizobium* sp., *Azotobacter chroococcum*	Lian et al. (2008) and Liu et al. (2012)
Potassium Solublizers			
1.	Bacteria	*Bacillus, Pseudomonas, Aspergillus, Burkholderia, Paenibacillus* sp., *Bacillus mucilaginosus, Acidothiobacillus ferrooxidans, Acidothiobacillus ferrooxidans*	Yadav (2018), Parmar and Sindhu (2013), and Singh et al. (2016)

environment for the growth of several microorganisms (Sadh et al. 2018). The agro-industrial waste such as corn steep liquor, molasses, deproteinized leaf extracts, jaggery, wastewater sludge is utilized as a substrate for the cultivation of *Rhizobium* species (Suthar et al. 2017). Moreover, agricultural waste such as bagasse, paper pulp, wheat bran, vegetable, watermelon, papaya, pineapple, custard apple, guava, rice straw is also being used routinely as a source for biofertilizer production using the fermentation process (Devi and Sumathy 2017; Suthar et al. 2017; Sadh et al. 2018).

1.5 Potential Outcomes from Microbial Treatment of Agro-Industrial Waste

Improper management of high-value waste from agro-industries will lead to many environmental and health-related issues. Proper treatment of these waste residues can be helpful in many aspects, such as reducing greenhouse gases, being used as a renewable energy source, and improving environmental and human health.

1.5.1 Greenhouse Gases Emission Reduction

Greenhouse gases that consist of CO_2, CH_4, NO_x, SO_x, H_2O are natural temperature regulators for the Earth by trapping solar radiation's heat. In the lacuna of these gases, the earth would be a cold planet. But excess of these gases along with synthetic gases like CFCs, HFCs, PFCs, SF_6, and NF_3 (Department of Environment and Energy 2018). These greenhouse gases are increasing at an alarming rate due to massive industrialization and improper agricultural practices. As it is aptly said, excess of anything is toxic or has a catastrophic effect. This is the reason the earth and earthlings are suffering from global warming.

Currently, the agro-industrial waste with a very high potential energy recovery is being dumped in landfills or left on the fields. These methods of waste disposal lead to an incessant generation of GHGs, mainly CO_2 and CH_4. Anaerobic decomposition is the prevailing process through which the anaerobic microorganisms generate methane. The crop leftovers release nitrous oxide (N_2O) by the microbial action, which involves nitrifying and denitrifying microorganisms (Portugal-Pereira et al. 2015). One of the mains sources of greenhouse gases in milk production industries comprises enteric fermentation (CH_4), feed purchased (N_2O, CO_2, CH_4), manure management (N_2O), manure fertilizers, and energy (fuels and electricity). Instead of utilizing the agro-industrial waste for animal feed, it is more effective if it is put to energy production because the milch animals, when fed with the waste, will generate more greenhouse gases. The waste, when used as biofuel, will be carbon neutral (Fig. 1.7). There is a drastic decrease in enteric methane production through the feed involving tomato waste (Pardo et al. 2016).

There is an immediate need for abatement to reduce the emission of greenhouse gases. One of the eminent steps to do so is through bioprocessing of agro-industrial waste. Fossil fuels are the greatest source of greenhouse gases. The combustion of fossil fuels emits massive CO_2. Moreover, fossil fuels are diminishing at a very proliferating rate. To curb this burden, bioenergy from agro-industrial waste helps in dual ways.

Firstly, it reduces the dependency on fossil fuels. Secondly, it reduces the emission of greenhouse gases. The trash from crops like sugarcane, maize, and soybean is a readily available substrate for bioenergy production in Brazil, where it was estimated that around 141 TWh/year of environmentally sustainable potential is

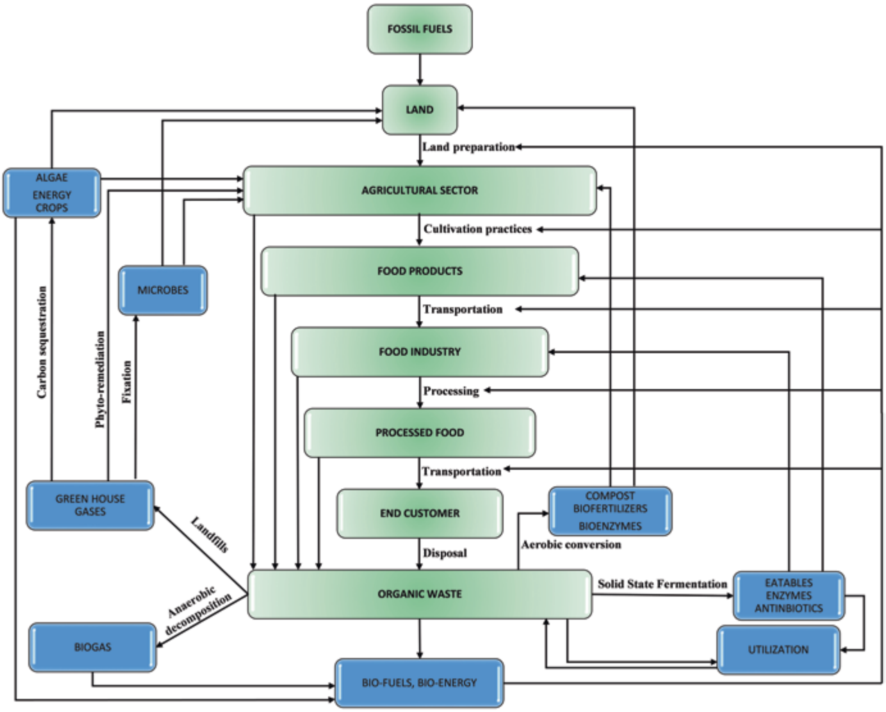

Fig. 1.7 Life cycle assessment of greenhouse gas reduction from the utilization of agro-industrial waste. To meet the heavy energy demand in the agro-industrial sector, many fossil fuels are consumed for various purposes. This, in turn, exaggerates the greenhouse gases in the atmosphere. A large amount of organic waste is generated in each sector, starting from the land preparation (cradle) to the plantation, food production, food processing, and consumption by the consumers. This organic waste can be treated effectively through different bioprocessing techniques to produce different by-products to serve the energy demand. Thus, the greenhouse gas emission can be reduced to a very large extent making the agro-industrial sector a cradle-to-cradle system

achieved in different regions, mainly the South, Southeast, and Midwest regions of Brazil (Portugal-Pereira et al. 2015).

1.5.2 *Renewable Source of Energy*

Today's global economy relies mainly on a range of fossil fuels such as oil, natural gases, and coal used to manufacture fuel, electricity, and other uses. A sustainable alternative needs to be sought for the world's increased energy demand due to population growth. As fossil fuel stocks are limited, world annual petroleum production will start to decrease in the coming future, leading to the use of renewable sources as alternative options. As the energy industries rely on solar, water, wind, and geothermal heat as renewable sources of energy, biomass generated from agro-industries can be an alternative source for fuel production and chemical industries (Sarkar et al. 2012). These fossil fuels may be replaced by bioethanol production as a renewable source through waste generated from agro-industries. In 2004, Kim and Dale reported that lignocellulosic biomass would generate 442 billion liters of bioethanol, and 491 billion liters can be generated from total waste crop residues every year, 16-folds greater than the current world bioethanol supply. This can be accomplished through different processes, such as enzymatic decomposition, physiochemical treatments, pyrolysis, and solid-state fermentation (Yusuf 2017). The use of agro-industrial biomass for electricity generation appears to be an energy option and mitigates carbon dioxide emissions as fossil fuels are minimal and non-renewable. The Inexpensive agricultural biomass wastes such as oil residues, energy crops, and other organic materials generated from agro and food-based industries may be utilized to produce renewable energy (Guldhe et al. 2017).

1.5.3 Improvement in the Environment and Human Health

A massive amount of agro-industrial wastes are dumped in landfills, left on the fields, or drained into rivers and other water bodies, which pollute the soil, air, and water. Improper management of waste in the landfills will lead to various health problems such as asthma, cancer, bacterial infections, increased cardiovascular risk, some vector-borne diseases, i.e., dengue and cholera, improper reproductive disorders, and other diseases due to exposure to carcinogenic and non-carcinogenic pollutants (Giusti 2009). Microbial degradation of some organic compounds in the landfills results in the emission of greenhouse gases such as methane and carbon dioxide, carbon monoxide, and nitrogen. Greenhouse gas emitted through landfills has great potential for global warming, whereas the pollutants released in the lower soil and groundwater in the form of leachate cause soil and water pollution. So, the leachate, greenhouse and toxic gases, and other toxic substances released from the unorganized landfills are adversely affecting humans and environmental health (Swati et al. 2018).

To overcome these problems, a proper system should be established for the treatment of waste biomass. The bulk of garbage is dumped freely and is now turned into an enormous mountain of waste, leading to significant environmental pollution and depletion of natural resources. The health and ecological resources, including groundwater, soil fertility, and air quality, can be covered by building properly engineered sanitary landfills (Kumar et al. 2009). Additional issues such as pollution pollutants, smelling, litter, fire hazards, and pest breeding can also be eliminated where waste is disposed of at appropriately built landfill sites. Sanitary landfills can also be used to store methane by installing vertical wells on the top, which can generate heat and electricity and eliminate the exponential harm to the atmosphere and public health. Instead of dumping the waste in the ground, it can be transferred to waste-to-energy plants where a high calorific fraction of the waste can be utilized as a resource with present technologies. Generally, heat and power can be generated by the combustion of waste in waste-to-energy plants. These waste-to-energy plants use waste material as a resource collected in the dumping ground. For energy recovery, the waste composition is of considerable significance as present technologies use a high calorific fraction of the wastes that provide heat and power upon combustion. In the future, waste-to-energy technologies are crucial in treating various industrial wastes (Swati et al. 2018). New waste management technologies will play an essential role in future waste treatment, positively affecting the environment and human health.

1.6 Conclusion

In the current scenario, the global view for agro-industrial waste changes quickly to protect the environment and human health. Various kinds of wastes generated in the form of agricultural residues or wastewaters have been utilized to produce value-added products. These waste residues have enormous potential for the production of various important products such as biofuels, enzymes, biofertilizers, and many other bioactive compounds by using different microbial treatments. As these products are profitable, eco-friendly with an optional alternate for fossil fuels, and have potential applications in new sectors, it is important to establish more regulatory systems and investments to commercialize these products in the market. Transforming agro-industrial waste residues into efficacious compounds provides researchers a new way of sustainability for the next generation and eliminates established environmental risks.

Acknowledgment RK is thankful to DST, Govt. of India for financial assistance under the DST INSPIRE Faculty Scheme [DST/INSPIRE/04/2014/001280], Science and Engineering Research Board Start-up research grant no. SRG/2019/001071, NMHS project of MoEF&CC grant no. GBPNI/NMHS-2018-19/SG/178, and DST-TDT project no. DST/TDT/WM/2019/43. KD is thankful to CSIR, Govt. of India for 'Research Fellowship' Grant [CSIR-NET JRF award no: 31/054(0139)/2019-EMR-I/CSIR-NET JRF JUNE 2017]. Authors also acknowledge financial support from CSIR MLP 0137, MLP 0143, and MLP 0201.

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Chapter 2
Industrial Apple Pomace as a Bioresource for Food and Agro Industries

Shalika Rana, Smita Kapoor, Ajay Rana, Y. S. Dhaliwal, and Shashi Bhushan

Abstract Apple fruit juice industries produces large quantity of waste biomass annually. This biomass, named pomace, includes fruit peel, seeds, stem and pulp. Apple pomace is a rich source of bioactive ingredients such as micronutrients, carbohydrates, dietary fibres, phenolics and other phytochemicals. These by-products make apple pomace a credible source for development of wide range of functional food and feed products. Here we review the conversion of apple pomace into value-added products, with focus on apple pomace composition, fermentative and non-fermentative utilization, fertilizers, mushroom substratum, biofungicide, metal adsorbent, ethanol, and bioactive compounds in the management of diabetes.

Keywords Apple pomace · Dietary fiber · Bioactives · Value added products

2.1 Introduction

Apple (*Malus domestica*) is the most widely cultivated pomaceous fruit crop all over the world. The global production of apples in 2017 reached 83.1 million metric tons with major apple producing countries are China, US, Turkey and Poland (Lyu et al. 2020). Currently, India stands at fifth position in apple production in the world

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_2

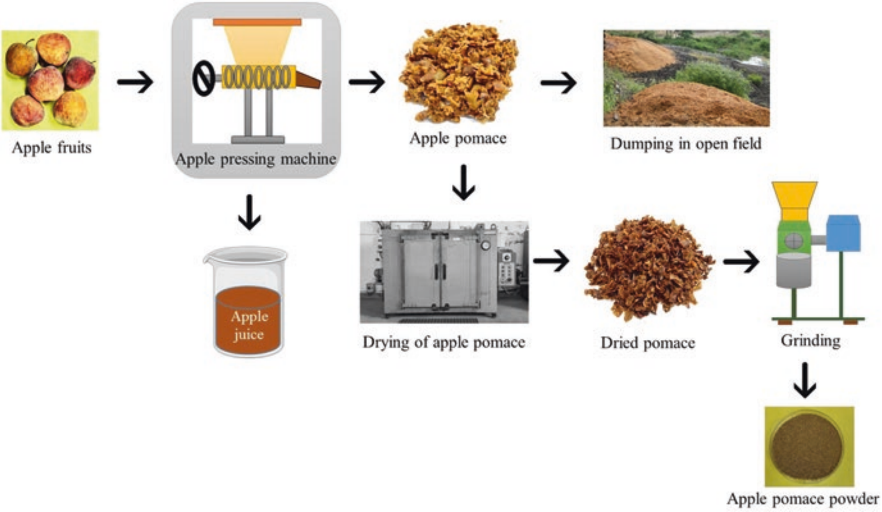

Fig. 2.1 Processing of apple fruits and production of apple pomace

with major contribution from Jammu and Kashmir, Himachal Pradesh and Uttrakhand (Kumar et al. 2018). In India, apple processing is mostly done for the extraction of juice and preparation of its concentrate. Apple processing includes sorting, cleaning and washing fresh fruits with water, followed by processing for juice extraction in fruit pressing unit. Thereafter, the juice is filtered and clarified. The remaining pressed fruit residue is known as 'apple pomace' and generated in huge quantity around the world (Fig. 2.1).

This residue, if dumped in open, may cause environmental hazards. There are reports that revealed about generation of one million tonne of apple pomace every year in India, and only a small fraction is utilized for various purposes (Manimehalai 2007; Shalini and Gupta 2010).

It is well documented that this biomass contains various nutritive constituents having huge health potential (Bhushan et al. 2008; Rana and Bhushan 2016; Lyu et al. 2020). Nevertheless, we are still far from developing workable approach for its effective utilization. Unexpectedly, the high demand for natural bioactive food by consumer has impelled an expansion in research and development activities for judicious application of natural bioresources. Henceforth, the apple pomace is still under consideration as a prospective source of bioactive constituents and enormous efforts for their scientific validation are on to develop health promoting supplements.

2.2 Nature

Apple pomace is a fruit processing waste that is biodegradable in nature and have high biological oxygen demand. However, it's high moisture content makes this residue more prone to enzymatic and chemical oxidation along with microbial contamination (Bhushan et al. 2008; Shalini and Gupta 2010). Because of the harmful impact of this biomass on environment and sensitivity to degradation, its profitable utilization is a big challenge. Thus, a safe, sustainable and cost effective technology is required.

2.2.1 Nutritional Composition

Apple pomace contains considerable amount of carbohydrates (44.5–57.4%), protein and lipids (3.8%) (Wang et al. 2019; Lyu et al. 2020). Apple pomace is reported to have 4.4–47.3% total fiber with 33.8–60.0% insoluble fiber and 13.5–14.6% soluble fiber (Bhushan et al. 2008; Queji et al. 2010). Apple pomace also rich in minerals such as sodium, potassium, calcium, phosphorus, magnesium and zinc that are essential for normal human body function (Skinner et al. 2018; Antonic et al. 2020).

2.2.2 Phytoconstituents

Polyphenols are natural antioxidative compounds, provides protection against various chronic ailments. A number of comprehensive reports available that advocates apple pomace as a potential ingredient for extraction of such phenolic constituents (Rana and Bhushan 2016). Apple pomace contains about 0.17–0.99 g/100 g polyphenolic constituents with dominance of flavanols, di-hydrochalcones, hydroxycinnamic acids, flavonols and anthocyanins (Barreira et al. 2019; Rana and Bhushan 2016; Antonic et al. 2020). Among flavanols, quercetin derivatives are most common such as quercetin-3-galactoside, quecetin-3-glucoside, quercetin-3-xyloside, quercetin-3-rutinoside, quercetin-3-arabinoside, quercetin-3-rhamnoside (Schieber et al. 2003; Barreira et al. 2019), whereas 3-hydroxyphloridzin, phloretin-2′-xyloglucoside phloridzin and phloretin are reported to be the most predominant dihydrochalcones in apple. Moreover, cyanidin 3-galactoside, cyanidin 3-glucoside, cyanidin 3-arabinoside and cyanidin 3-xyloside are the major anthocyanins present in apple fruits (Mazza and Velioglu 1992). Among phenolic acids, the key compounds are caffeic acid, p-coumaroylquinic acid, p-coumaric acid and chlorogenic acid were reported (Schieber et al. 2003; Barreira et al. 2019).

2.2.3 Biocontaminants

Currently, the research efforts are going on to evaluate the health hazards associated with apple pomace consumption as food ingredient. The risk factors associated with apple pomace consumption are natural toxins and pesticides. Seeds of apple pomace known to contains significant amount of amygdalin, which is a cyanogenic glycoside, a naturally occurring plant toxin. However, quantitative variation in amygdalin content due to difference in environmental factors and type of cultivars was also reported. The seeds of Royal gala apple stated to have about 2.9 mg/g amygdalin (Bolarinwa et al. 2014). Nevertheless, the amount of amygdalin present in apple seeds is normally indicated to be safe for human consumption (Opyd et al. 2017).

In addition, apple crop is heavily sprayed with pesticides such as methyl parathion chlorpyriphos, endosulfan, fenazaquin. Dichlorvos and lindane to control various insect-pest throughout the developing period (Sharma and Nath 2005). The apple scab, premature leaf fall, mites and the woolly apple aphid are some of the most common pests and diseases of apple (Sharma and Nath 2005). Moreover, fungicides are also gradually used in order to improve the quality and productivity of apple fruit. Mancozeb, bitertanol, myclobutanil, dodine, antracol, thiophanate, carbendazim and pyrimethanil are most common fungicides used during cultivation of apple crops (Liu et al. 2016). Reports revealed that quantity of pesticides residues (chlorpyrifos, cypermethrin, tebuconazole, acetamiprid and carbendazim) after harvest in apple fruits parts such as apple peel, core, flesh, juice and pomace (Kong et al. 2012). It was suggested that processing conditions i.e. washing, peeling, coring and juicing process affect the pesticide residue and apple peel and core contains higher pesticide residue levels compared to apple flesh. Apple pomace concentrates reported to have chlorpyrifos, cypermethrin and tebuconazole, whereas acetamiprid residue was not detected in it (Kong et al. 2012). Pesticide residue present in fruits and vegetables impose adverse effects on human health. Therefore, different food processing techniques must be utilized to significantly diminish the pesticide residues in fruits and vegetables (Keikotlhaile et al. 2010).

Furthermore, patulin is considered to be carcinogenic lactone metabolite and is found in cider and unfermented apple juice. Patulin (4-hydroxy-4H-furo[3,2-c]pyran-2(6H)-one) is a secondary metabolite produced by *Penicillium* and *Aspergillus*, including *A. clavatus, P. patulum, P. aspergillus, P. byssochlamys* and *P. expansum* (Beretta et al. 2000). Apple and apple based products have been showed to get contaminated by *Penicillium, aspergillus, Paecilomyces, Byssochlamys and Scopulariopsis* (Sajid et al. 2019). Patulin is associated with adverse human health issues mainly neurological, immunological and gastrointestinal outcomes and it shows different levels of toxicity like general toxicity, acute toxicity, sub-acute toxicity and genotoxicity (Puel et al. 2010).

2.3 Value Addition of Apple Pomace

2.3.1 *Fermentative Utilization*

2.3.1.1 Deployment of Apple Pomace as Substrate

Apple pomace being rich in pectin, carbohydrates, fibers, minerals and vitamin could act as a good substrate for the production of alcoholic beverages, enzymes, aroma compounds, ethanol, heteropolysaccharide, citric acid and bio-color (Joshi et al. 2006; Parmar and Rupasinghe 2013; Bhushan et al. 2008; Vendruscolo et al. 2008) (Fig. 2.2).

Due to the presence of fermentable sugars (glucose, fructose and sucrose) in high quantity, apple pomace can be a good substrate for alcoholic fermentation to prepare products such as wine, beer and cider (Kruczek et al. 2016). Pomace usage in beverage industry is known to concomitant with improved flavor of alcoholic beverage. Li et al. (2015) used fermented apple homogenates ciders with abundant volatile components. Ricci et al. (2019) suggested the use of fermented apple pomace as aromatizer in beverage industry. In this study, lactic acid bacteria used to produce fermented apple pomace, which was further added to supplement beer. It was reported that addition of fermented apple pomace to beer enhanced its aroma. *Lactobacillus* fermentation modified the volatile composition of apple pomace and enhanced the aroma characteristics of beer (Ricci et al. 2019).

Bioconversion of apple pomace into useful ingredient is one of the best way for feasible utilization of pomace. Villas-Bôas et al. (2003) worked on bioconversion of apple pomace to animals feed by selecting under specific conditions using *Candida*

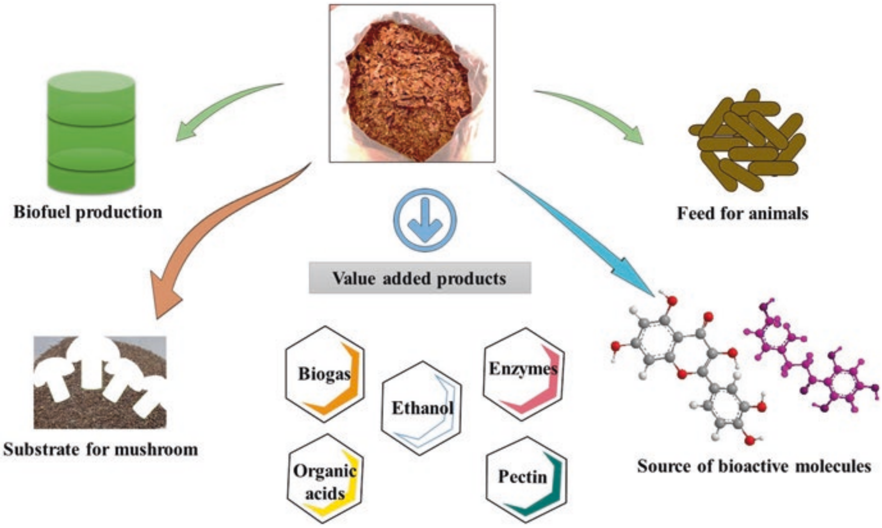

Fig. 2.2 Fermentive and non fermentive utilization of apple pomace into valuable products

utilis and *Pleurotus ostreatus*. Fermentation using *C. utilis* found to increase the protein and minerals content, and even improve its digestibility (Villas-Bôas et al. 2003). Considering the fermentability of pomace, it can be easily used for generation of ethanol. Gulhane et al. (2015) used apple pomace as a substrate in solid fermentation process employing different microbial species *Saccharomyces cerevisiae*, *Aspergillus foetidus* and *Fusarium oxysporum* for the production of ethanol. The highest yield of ethanol is observed in the combinatorial usage of all the three microorganisms (*Saccharomyces cerevisiae*, *Aspergillus foetidus* and *Fusarium oxysporum)* (Gulhane et al. 2015). Recently, addition of apple pomace to the soil by Oszust and Frąc (2020) led to improvement in the bioavailability of polyols. In addition, *Trichoderma* G79/11 strain found to grow well on apple pomace and exhibited antagonistic activity against fungal plant pathogens such as *Colletotrichum* sp., *Botrytis* sp., *Verticillium* sp., and *Phytophthora* sp. It was suggested by researchers that apple pomace with *Trichoderma* G79/11 spores and with metaferm biopreparation, may possibly be an efficient bioagent against pathogenic fungus. Apple pomace was also utilized as a substrate for growth of entomopathogenic fungi (*Lecanicillium lecanii, Beauveria bassiana* and *Paecilomyces fumosoroseus),* which is used as biopesticide in the management of insect pests (Reddy and Bhardwaj 2020). Earlier, toxicity was reported against *Aphis craccivora* of *Lecanicillium lecanii* cultivated on apple pomace (Reddy and Sahotra 2020).

Apple pomace being rich in carbohydrate polymers (lignin), minerals (nitrogen) is considered to be the best substrate for the production of mushroom. In previous studies, scientist have done comparative analysis by using sawdust and apple pomace alone and also both in combination as a substrate for the growth of shiitake (*Lentinula edodes*) and oyster mushrooms (*Pleurotus ostreatus* and *P. sajor-caju)* (Worrall and Yang 1992). *Agaricus brasiliensis* is a remedial mushroom that have various human health promoting effects. Study conducted by Mokochinski et al. (2015) showed that apple pomace as a substrate yield good mycelium growth of *Agaricus brasiliensis* during solid state and submerged fermentation (Mokochinski et al. 2015). The addition of pomace (2.5%) for the cultivation of *P. ostreatus* in solid culture, liquid culture and solid-state fermentation was reported to increase the mycelial growth by 34.5%, 20% and 26% respectively (Park et al. 2012). *Flammulina velutipesis* is another important mushroom which was grown in modified substrate i.e. fermented apple pomace and produces effect on fruiting bodies yield and its quality (Hiramori et al. 2017). Pathania and coworkers showed significant increase in the yield of oyster mushrooms using different ratio of apple pomace and wheat straw mixed substrate (Pathania et al. 2017). A lot of work on using apple pomace as a substrate for mushroom cultivation has been done and needs to be validated at commercial scale for assessing its feasibility.

2.3.1.2 Animal Feed

One of the way to reduce environment load is the use of pomace like residues as animal feed (Maslovarić et al. 2017; Vendruscolo et al. 2008) (Fig. 2.2). A number of investigations are available, where dried pomace (post fermentation) was found to be rich in fat (1.5–2.0 times), crude proteins (3 times) and vitamin C (2 times). Moreover, the minerals, crude fibre and ash content of apple pomace also reported higher (Joshi and Sandhu 1996). Factually, study conducted by Alarcon- Rojo et al. (2019) related the properties of meat those have consumed fermented apple pomace rich diet (feed). It was demonstrated in this study that consumption of fermented apple pomace led to the decreased oxidation of meat without affecting its quality characteristics. Tosun and Yasar (2020) reported a significant enhancement in crude ash and protein content through *Pleurotus ostreatus* and *Phanerochaete chrysosporium* fermentations of apple pomace, hence, suggested its potential usage in animal nutrition.

2.3.1.3 Biofuel Production

Production of biofuel using carbohydrate present in apple pomace could also be an effective method to reuse and reduce the waste (Fig. 2.2). Molinuevo-Salces et al. (2020) in their study showed the production of bioethanol using different microorganisms such as *Kluyveromyces*, *Saccharomyces*, *Scheffersomyces* and *Zymomonas*. A complete process was delineated in detail for the production of biofuel using apple pomace as a feed stock (Magyar et al. 2016). Furthermore, potential usage of apple pomace was also done for the production of butanol using *Clostridium beijerinckii* (Hijosa-Valsero et al. 2017; Jin et al. 2019).

2.3.2 Non-fermentative Utilization

2.3.2.1 Apple Pomace Usage in Food Products

The high dietary fiber contents in apple pomace are considered as important functional ingredients, which can be added in different food products such as bakery products, cakes, noodles, bread, extruded products, meat products and dairy products (Table 2.1) (Lyu et al. 2020). Pomace is also utilized for the preparation of jelly products owing to presence of soluble fiber, especially pectin (Royer et al. 2006). The jam prepared from apple pomace gained highest acceptability due to its fruity flavor and appearance. The soluble fibers present in pomace reported to be as good gelling agents, emulsifier, stabilizer and even as a fat replacer in various food processing industries (Min et al. 2011; Thakur et al. 1997). Figure 2.3 showing different valuable products prepared by addition of apple pomace (Product images were adapted from smart.servier.com). Earlier, Issar et al. (2017) prepared fiber-enriched

Table 2.1 Effect of apple pomace fortification into various food products

Food Product	Apple pomace Percentage	Effect on product	References
Cookies	5, 10, 15, 20 and 25% of apple pomace with wheat flour	Enhanced sensory and compositional attributes of cookies prepared with 10% apple pomace	Usman et al. (2020)
Noodles	10, 15 and 20% of apple pomace powder	Increase in dietary fibre and content of protein, also improvement in anti-oxidant activity and swelling index	Yadav and Gupta (2015)
Bread	Addition of 1, 3, 5, and 7% of apple pomace	Enrichment of fibre in the final product	Jannati et al. (2018)
Buffalo meat patties	2 to 8% apple pomace	Dietary fiber got enhanced; cooking yield got improved along with texture and fat binding property.	Younis and Ahmad (2018)
Chicken sausages	Substituting pork fat with 1–2% apple pomace	Reduction in the fat level, increase in caloric energy, chewiness improved.	Choi et al. (2016)
Apple puffed snacks	Addition of 7.7% of apple pomace	Improvement in texture, reduction in hardness of product and producing crisper end product.	O'shea et al. (2014)
Apple pomace flour cookies	15 and 20% apple pomace flour substituted for wheat flour.	Color change of cookies and enhanced caramelization.	Jung et al. (2015)
Wet apple pomace fortified meat products	Wet apple pomace (10 and 20%) was substituted for chicken meat	Product with improved fiber and antioxidant activity. Decreased hardness, springiness and cohesiveness, improved chewiness	Jung et al. (2015)
Acidophilus yoghurt	2.5, 5, 7.5 and 10% apple pomace fiber	5% fiber containing yoghurt showed good quality and sensory characteristics	Issar et al. (2017)
Yogurt	1% apple pomace	Apple pomace at 1% level increased gelation and decreased fermentation time	Wang et al. (2019)
Biscuits	5, 10 and 15 mass % of apple pomace powder	5 mass % of apple pomace powder did not affect quality of biscuits. Higher amount (10 and 15% mass) of apple pomace powder decreased the overall acceptance	Kohajdová et al. (2014)
Cookies	25, 50 and 75% of apple pomace flour	The cookies with 50% apple pomace flour retained phenolic and flavonoid constituents along with antioxidant activity. Sustained aroma and texture.	Zlatanović et al. (2019)
Chevon rolls	2, 4 and 6% levels	Water holding capacity, emulsion stability and phenolic content increased	Parkash et al. (2016)
Yogurt	1, 3 and 5% apple pomace flour	Supernatants showed increased phenolic content, antioxidant activity, and inhibition of cancer cells.	Jovanovic et al. (2020)

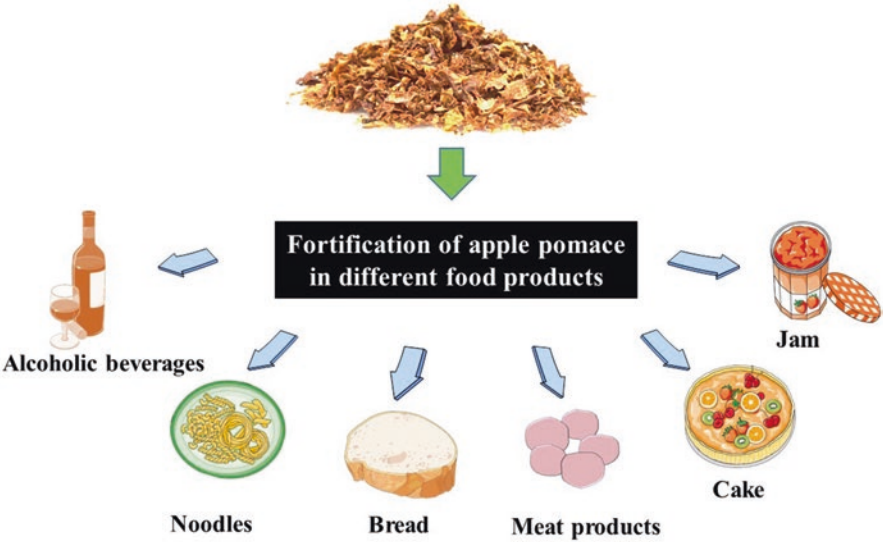

Fig. 2.3 Food products prepared by fortification of apple pomace

yoghurt using 2.5, 5, 7.5 and 10% apple pomace fiber in milk. Authors reported decrease in acidity and fat contents with increase in concentration of apple fiber.

It is suggested that incorporation of 5% apple fiber was acceptable in terms of sensory attributes for the preparation of acidophilus yoghurt. Recently, freeze dried apple pomace was efficiently utilized in yoghurt gel preparation (Wang et al. 2019). Its addition on one hand increased the gelation, while led to decrease in fermentation time on other. Jovanovic et al. (2020) fortified probiotic yogurt with 1%, 3% and 5% apple pomace flour and revealed high phenolic content and antioxidant activity in yoghurt's supernatant. It also found to inhibit the proliferation of cancer cells. Hot water extract of apple pomace added with yogurt formulations showed increased *in vitro* antioxidant activity compared to control (Fernandes et al. 2019). Thus, it is clear from above discussion that apple pomace has potential to be used as a natural functional ingredient in variety of products.

Nowadays, extrusion cooking has turn out to be a well-recognized processing technology that have wide food applications including the transformation of functional characteristics of food ingredients (Singha and Muthukumarappan 2018). In order to increase the nutritive value of extruded snack products, apple pomace has been successfully added to improves the quality without influencing their physical properties (Stojceska et al. 2010). Extrusion of freeze dried apple pomace powder showed increase in total flavanols, phenolic acids and dihydrochalcones, when subjected to gastric phase digestion. Moreover, the antioxidant activity was considerably increased by extrusion upon *in vitro* intestinal digestion (Liu et al. 2019). Earlier, Singha and Muthukumarappan 2018 optimized process to produce apple pomace-enriched extruded snacks using different parameters. Also, the extrusion process showed to influence degradation of pectic polysaccharides that has significant impact on final product (Schmid et al. 2020).

Efforts were also made to prepare fiber enriched bread using apple pulp powder in a ratio of 70:30 (flour: pomace). Authors suggested that it can be used as an alternative source of dietary fiber (Gupta 2006). In another study, 5, 10, 15% of whole and ground pomace was used for the preparation of bread fortified bread was also evaluated for the chemical constituents, physical characteristics and sensory evaluation (Gumul et al. 2019). Addition of 5% whole pomace in bread during its preparation improve its volume and reduce the hardness. Preparation of bread by mixing both wheat flour and apple pomace powder have showed significant improvement in the gluten content and moisture absorption along with the increase in the ash and dietary fiber content (Lu et al. 2017). Different percentages of apple pomace powder (1, 3, 5 and 7% w/w) has been added to the flour to find its effect on the rheological properties of dough and observed that apple pomace addition reduced hardness, and also enhanced the aroma of the bread (Jannati et al. 2018).

Gluten free cake production by replacement of wheat flour with apple pomace powder was also attempted (Azari et al. 2020). In addition of apple pomace, dietary fiber rich pomaces generated from orange and, carrot were also used for gluten free batter and cake production (Kirbaş et al. 2019). Even replacement of wheat flour with apple skin powder upto 24% to manufacture muffins reported to have better sensory properties and overall acceptance (Vasantha Rupasinghe et al. 2009). Formulation of muffins having 20% apple pomace powder exhibited normal shape symmetry and scored high in sensory tests (Sudha et al. 2016). However, the application of apple pomace like residue in such products still needs more experiments to be implemented at marketing scale.

Cookies is another bakery product prepared by incorporating apple pomace with enhanced quality. The organoleptic properties of cookies prepared using 10% of apple pomace with wheat flour found to improve their sensory as well as compositional attributes (Usman et al. 2020). In an another report, cookies prepared with 50% coarse apple pomace flour able to retain higher phenolic, flavonoid and antioxidant activity and found acceptable (Zlatanović et al. 2019). The addition of apple pomace improved the spread factor and sugar content in cookies (Oh and kang 2016). The replacement of wheat flour (10% and 20% w/w) by apple pomace in biscuits manufacturing lead to significant decrease in the glycemic index, thus, exhibited its potential use as functional food ingredient (Alongi et al. 2019). Apple pomace has also been incorporated in noodles. Its addition reported to increase the total dietary fibre (from 6.0% to 13.28%) and protein (10.20% to 11.80%) content as compared to control (Yadav and Gupta 2015). Pomace enriched noodles also had improved anti-oxidant activity and swelling index. Overall, the apple pomace mixed bakery products (bun, muffin and cookies) shown to have high free radical scavenging activity with prevention of oxidative DNA damage (Sudha et al. 2016).

Introduction of apple pomace into the meat was done to reduce the fat content of diet. Choi et al. (2016) incorporated apple pomace fiber into chicken sausages and reported to have significant fat reduction in final products. It also seems to be a good approach to improve dietary fiber content in meat. Similarly, Huda et al. (2014)

prepared mutton nuggets by addition of different apple pomace (5, 10 and 15%) concentration. Data showed that apple pomace incorporated nuggets had high crude fiber content and also help in decreasing the hardness as compared to control products. Apple pomace powder also used to replace the fat in goshtaba and showed improvement in its texture, physiochemical and sensory properties (Rather et al. 2015). Increased percentage of apple pomace have been related to the improved cooking yield, water holding capacity of meat. Similarly, various meat attributes such as hardness, firmness and toughness also reported to increase with addition of apple pomace. Buffalo meat patties were also prepared with 6% incorporation of apple pomace powder and found acceptable (Younis and Ahmad 2018).

In addition, the effect of apple pomace addition in different ratios with maize and sunflower meal into the feed stuffs was also investigated on pellet quality (Maslovarić et al. 2017). It was reported that addition of apple pomace improved the quality of pellets such as durability index, hardness and quantity of fines in pellets. Its addition to the cow feed also showed higher milk yield with improved protein content (Tiwari et al. 2008).

2.3.2.2 Source of Bio-Fungicide in Agriculture

The industrial fungicides are generally reported harmful to humans and also affect health of the animals (Sanzani et al. 2009a, b). Therefore, use of apple pomace like residue can be considered to extract phytochemicals that exhibit such properties can be used as fungicides in agriculture In support of this notion, apple pomace extract and its bioactive fractions were reported to possess strong activity against *Botrytis* sp., *Fusarium oxysporum, Petriella setifera* and *Neosartorya fischeri*. The highest amount of anti-fungal activity was reported by apple pomace containing significant amount of phloridzin (Oleszek et al. 2019). In addition, dihydrochalcone, phloretin isolated from apple fruits was also reported to inhibit the growth several plant pathogenic fungi such as *Magnaporthe grisea*, *Phytophthora capsici*, *Alternaria panax*, *Magnaporthe grisea*, *Rhizoctonia solani* AG4, *Sclerotinia sclerotiorum* (Shim et al. 2010). According to the published reports of Parvez et al. (2004), isoquercitrin and quercetin-3-methyl ether are capable of inhibiting the conidial germination of *Neurospora crassa*. Furthermore, quercetin found toxic to the growth of *Penicillium* and patulin accumulation on Golden Delicious apples (Sanzani et al. 2009a, b) Therefore, the extracted phytoconstituents present in pomace like biomass could be used as substitute to chemical fungicides for control of pre and post-harvest diseases.

2.3.2.3 Natural Fertilizer

There are reports to suggest that apple pomace can be utilized as a fertilizer ingredient. It is demonstrated that the aerobic composting of pig manure with fortification of apple pomace resulted in improved quality of manure and also reduces the gaseous emission of NH_3 and N_2O (Mao et al. 2017). The usage of different additives in the swine manure is linked with the improved nitrogen content. The addition of bentonite, calcium superphosphate and apple pomace found to influence the transformation of nitrogen, phosphorus, carbon along with the maturity of compost (Jiang et al. 2014). A combinatorial of orange, sweet lime, pomegranate pomaces reported to promote the growth of plants owing to their richness in organic matter and nutrients (Röös et al. 2018). Halpatrao et al. (2019) demonstrated the use of waste generated from fruits as a natural fertilizer for improving the growth and production of crops.

Dried apple pomace contains 36.8% fiber composed of water soluble and insoluble fractions, but is treated as a waste in apple processing industries. The present study was conducted to prepare fiber-enriched yoghurt by using 2.5, 5, 7.5 and 10% apple pomace fiber in whole milk and milk without fiber was kept as the control. All the treatments were inoculated with combined culture (1%) of Lacto- bacillus acidophilus and Bifidobacterium longum. The yoghurts were evaluated in terms of sensory quality, pH, acidity, total solids and fiber contents. The addition of fiber in yoghurt resulted in a decrease of acidity (0.15–0.09%) and fat contents (1.65–1.59%) with increase in fiber concentration. Further, on the basis of sensory analysis, yoghurt containing 5% apple fiber was judged as the best and hence opti-mized for preparation of fiber-enriched acidophilus yoghurt with desirable quality and sensory attributes.

2.3.2.4 Apple Pomace as Adsorbents for Removal of Heavy Metals

Nowadays, environmental pollution is the major concern which is mainly caused by toxic heavy metal contamination. Its prime cause is fast expansion of fertilizer, dye and pesticides industries. Among heavy metals, lead (Pb), mercury (Hg), copper (Cu), arsenic (As), cadmium (Cd), chromium (Cr) are of most apprehension due to their high risk in development of cancer and other respiratory, cardiovascular, hepatic and renal diseases (Tchounwou et al. 2012). To overcome this problem, there is need for preparation of highly efficient and environment-friendly adsorbents.

Recently, a lot of research efforts are going on for the use of industrial apple pomace for removal of heavy metals from water (Fig. 2.4). In pursuit of this, efforts were made to chemically modify the apple pomace by succinic anhydride (Chand et al. 2014). The results revealed a 50-fold increase in cadmium removal by modified pomace based absorbent than the control. Earlier, xanthate was also used to modify apple pomace surface to produce new sulphur containing binding sites with increased surface area for adsorption of Cd, Ni and Pb (Chand et al. 2015). Similarly, the biosorption prospective of apple peel immobilized on sodium alginate beads was studied and compared with that of non-immobilized sodium alginate control beads using a solution of seven toxic metal ions i.e. Pb, Hg, Cu, As, Cd, Cr and Ni. It was reported that the biosorption of heavy metals by apple peel beads was considerably greater than control beads (Singh et al. 2019). In addition, the synthesized hydroxyapatite nanoparticles impregnated on apple pomace surface demonstrated

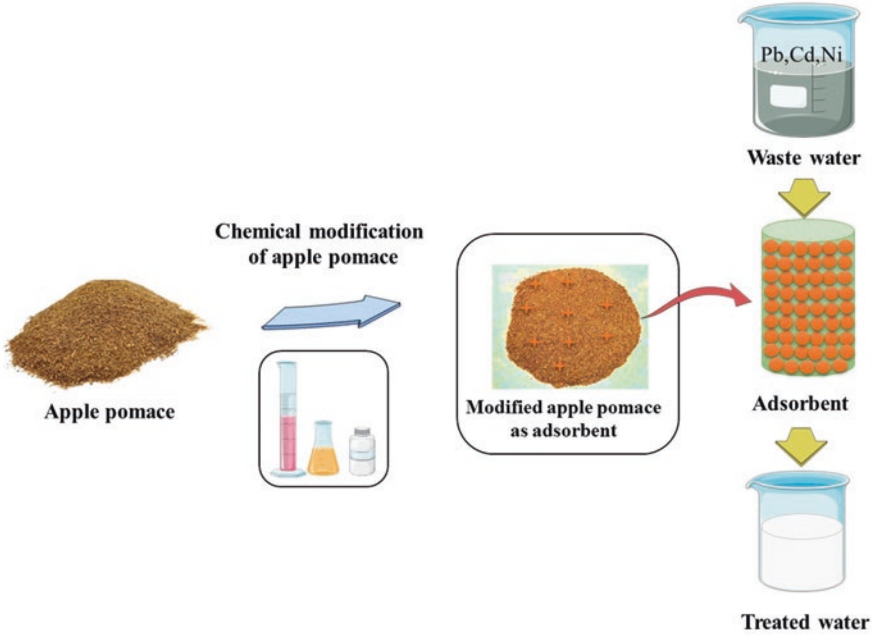

Fig. 2.4 Use of apple pomace as adsorbent for heavy metals

100% removal of Pb, Cd, and Ni ions from industrial waste water (Chand and Pakade 2015).

2.4 Phytoconstituents in Management of Diabetes

Diabetes mellitus is a group of metabolic disorders particularly recognized by elevated blood glucose level either due to defect in insulin secretion because of the destruction of insulin-producing beta cells (type 1) or increased insulin resistance (type 2) (Atkinson and Eisenbarth 2001; Olokoba et al. 2012). There has been an increasing understanding of the relationship between consumption of fruits and management of diabetes. Numerous evidences showed the impact of bioactive molecules present in fruits and vegetables in modulating the processes leads to the development of metabolic diseases. Apple (Malus domestica) bioactives such as phloridzin, phloretin, quercetin and epicatechin were reported to play significant role in management of metabolic disorder particularly diabetes (Fig. 2.5). Various epidemiological studies have showed that apples bioactives decreases the onset risk of diabetes mellitus and play significant role in the management of diabetes (Table 2.2). Apple phenolics also reported to decrease the postprandial glucose level by inhibiting the α-glucosidase enzyme which is involved in carbohydrate digestion (Adyanthaya et al. 2010). *Diabetes mellitus* is further associated with high oxidative

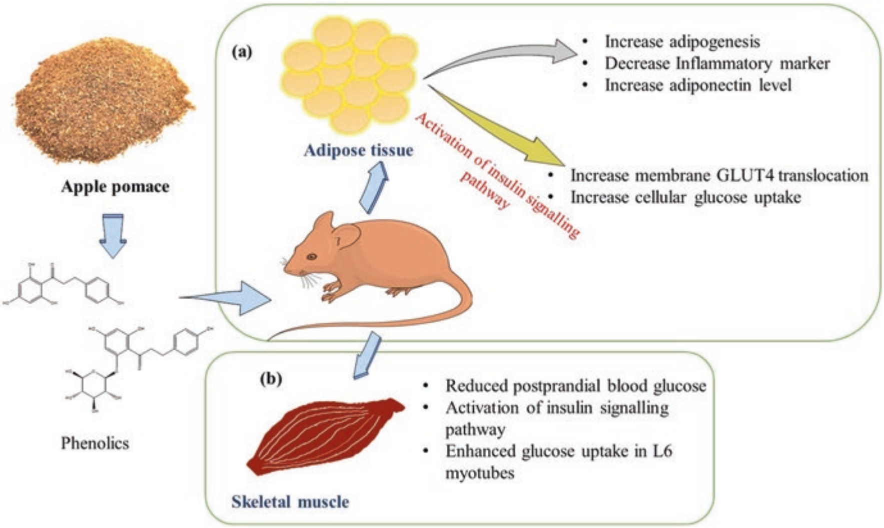

Fig. 2.5 Effects of apple phenolics (phloretin and phloridzin) in the improvement of insulin sensitivity and glucose homeostasis

stress causing damage to DNA. In this regard, phenolics enriched apples pomace found to improve oxidative status in diabetic patients (Grindel et al. 2014).

2.4.1 Phloridzin

There are growing evidences that dietary phenolic constituents play role in prevention of diabetes. Phloridzin is dihydrochalcone mainly present in apple and its plant parts and reported to have possible effects on blood glucose level. Masumoto et al. (2009) showed that phloridzin supplemented diet reduced the blood glucose level of streptozotocin induced diabetic mice. The expression of sodium glucose cotransporter gene elevated during streptozotocin induction was decreased significantly in the small intestine. It also reduced the increased expression of drug metabolizing enzyme genes i.e. Cyp2b10 and Ephx1. Similarly, phloridzin was also reported to reduce blood glucose level and improves serum insulin level in streptozotocin induced mice. It also improved the blood lipid levels i.e. cholesterol, triglyceride, very-low-density lipoprotein, and low-density lipoprotein in streptozotocin induced mice (Najafian et al. 2012). Further, Manzano et al. (2016) demonstrated that phloridzin enhances insulin sensitivity by decreasing lipopolysaccharide with significant effect on gut microbiota. Phloridzin treatment resulted in higher production of short chain fatty acids and also lower lipopolysaccharide load in mice (Mei et al. 2016). Even, the dihydrochalcone was also reported to play a significant role in the treatment of diabetic cardiomyopathy. It reduces the level of serum blood glucose,

Table 2.2 Role of apple bioactives molecules and extract in modulating the expression the genes/proteins involved in diabetes

Bioactives, extracts	Animal model/ Cell line	Genes/ Proteins targeted in the study	Functions	Findings	References
Phloridzin	Streptozotocin-induced diabetic mice	Sglt1and Cyp2b10, Ephx1	Sodium glucose cotransporter and drug metabolizing enzymes	Reduced the blood glucose in diabetic mice	Masumoto et al. (2009)
	db/db Mice	Ttn, DAPK3 and ZIPK	Cardiac contraction and diastolic function proteins	Reduced level of serum blood glucose, triglycerides, total cholesterol and advanced glycation end products	Cai et al. (2013)
	Spontaneously diabetic torii rats	GK,GP, SREBP1, MTP	GK: enzyme of glycolysis pathway, GP: enzyme in glycogen degradation, SREBP1 and MTP: lipid metabolism	Normalizes liver function and level of non-fasted serum triglycerides in rats decreased	Ohta et al. (2012)
Phloretin	Mouse marrow stromal cell line (ST2	PPARγ, C/EBPα, fatty acid synthase, fatty acid-binding protein 4, and adiponectin	Adipogenic markers	Phloretin induced adipogenesis and adiponectin expression	Takeno et al. (2018)
	Porcine preadipocytes	PPARγ, C/EBPα and adipose-related genes, such as fatty acids translocase and fatty acid synthase	Adipose-related genes	Lowered serum glucose level and improved glucose tolerance	Shu et al. (2014)
	3 T3-L1 adipocytes	GLUT4, ACSL1, PEPCK1, lipin-1 and perilipin.	Role in lipogenesis and triglyceride storage	Induced adipocyte differentiation, increased lipogenesis and triglyceride in adipocytes	Hassan et al. (2010)

(continued)

Table 2.2 (continued)

Bioactives, extracts	Animal model/ Cell line	Genes/ Proteins targeted in the study	Functions	Findings	References
Epicatechin/ (+)-catechin	C57BL/6 J mice	IR, IRS1, ERK1/2, Akt	Involved in insulin signalling cascade	Improved insulin sensitivity	Cremonini et al. (2016)
	Wistar rats	IR, IRS-1, Akt and ERK1/2 PKC, IKK, JNK and PTP1B	Components of insulin signaling cascade and negative regulators of insulin signaling cascade.	Reduced the insulin resistance	Bettaieb et al. (2014)
	3 T3-L1 preadipocytes	C/EBPα, PPARγ and HSL, ATGL and PLIN	Involved in differentiation and lipid metabolism	(+)-catechin showed anti-adipogenesis effects on 3 T3-L1 cells	Jiang et al. (2019)
Quercetin	Sprague–Dawley rats	–	–	Decreased the plasma glucose level and increased insulin release in streptozotocin-diabetic rats	Vessal et al. (2003)
	Skeletal muscle cells (L6 myotubes)	GLUT 4, CaMKK, AMPK, MAPK, p38 MAPK, PI3K, Akt and IRS	AMPK pathway and insulin signaling pathway	Enhanced glucose uptake in L6 myotubes through AMPK pathway and its downstream target p38 MAPK	Dhanya et al. (2017)

(continued)

Table 2.2 (continued)

Bioactives, extracts	Animal model/ Cell line	Genes/ Proteins targeted in the study	Functions	Findings	References
Apple pomace extract	Sprague-Dawley rats	CD36 and GLUT4	CD36 involve in etiology of insulin resistance and GLUT4 is the insulin-responsive glucose transporter.	Apple pomace and rosemary extract improves insulin resistance by modulation of CD36 and GLUT-4	Ma et al. (2016)
	Obese Zucker fatty rats and L6 cells	GLUT4, PPARγ, Akt	Involved in insulin signaling	*In vivo* results showed increase of insulin sensitivity; *in vitro* results showed increase in glucose uptake	Manzano et al. (2016)

Abbreviations: *GLUT4* Glucose transporter type 4, *PPAR-γ* Peroxisome proliferator-activated receptor gamma, *Akt* Protein kinase B, *CD36* cluster of differentiation 36, *CAMKK* Calcium/calmodulin-dependent protein kinase, *AMPK* AMP-activated protein kinase, *MAPK* Mitogen-activated protein kinases, *PI3K* Phosphoinositide 3-kinase, *IRS* Insulin receptor substrate, *C/EBPα* CCAAT/enhancer binding protein α, *PLIN* Perilipin, *HSL* Hormone-sensitive lipase, *ATGL* Adipose triglyceride lipase, *ERK1/2* Extracellular signal-regulated kinase 1/2, *PKC* Protein kinase C, *IKK* IκB kinase, *JNK* c-Jun N-terminal kinase, *PTP1B* Protein tyrosine phosphatase 1B, *IRS1* Insulin receptor substrate 1, *IRS2* Insulin receptor substrate 2, *ACSL1* Acyl-CoA synthetase long-chain family member 1, *PEPCK1* Phosphoenolpyruvate carboxykinase 1, *GK* Glucokinase, *GP* Glycogen phosphorylase, *SREBP1* Sterol regulatory element-binding protein 1, *MTP* Microsomal triglyceride transfer protein, *Ttn* Titin, *DAPK3* Death-associated protein kinase 3, *ZIPK* Zipper-interacting protein kinase, *SGLT1* Sodium-dependent glucose transporter 1, *Cyp2b10* Cytochrome P450 2B10, *p38MAPK* p38 MAP Kinase

triglycerides, total cholesterol and advanced glycation end products in db/db Mice. Phloridzin based treatment reversed the decreased expression of cardiac contraction and diastolic function proteins such as cytoskeletal protein titin (Ttn) and death-associated protein kinase 3 (DAPK3 or ZIPK) in diabetic mice (Cai et al. 2013). It also upregulated the expression of other genes that are linked to diabetic cardiomyopathy such as desmin, myosin regulatory light chain 2, lamin A/C, and laminin subunit α-2 compared to diabetic group (Cai et al. 2013). Hyperglycemia play important role in insulin resistance which is a feature of the diabetes. Treatment of diabetic rats with phloridzin regulates insulin sensitivity and improves hyperglycemia (Rossetti et al. 1987). Administration of phloridzin with 5-aminoimidazole-4-carboxyamide ribonucleoside in type 1 diabetic animal model (biobreeding rats) had decreased blood glucose levels and also reversed defects in glucagon secretion (McCrimmon et al. 2002). Moreover, this dihydrochacone have significant glycemic control and normalizes liver function in spontaneously diabetic torii rats. Phlorizin treatment improved the hyperglycemia in non-obese diabetic rats and also showed a considerable decrease in the hemoglobin A1C level. Following treatment, the level of non-fasted serum triglycerides in spontaneously diabetic torii rats decreased significantly. However, there was no significant change in non-fasted serum total cholesterol level was reported (Ohta et al. 2012). The mRNA expression of glucokinase, glycogen phosphorylase, sterol regulatory element-binding protein 1, and microsomal triglyceride transfer protein decreased in spontaneously diabetic torii rats (SDT). However, phloridzin administration reversed the mRNA expression of these targeted genes (Ohta et al. 2012).

2.4.2 Phloretin

The hyperglycemia in diabetes is directly related to hydrolase of carbohydrates by digestive enzymes i.e. amylase and glucosidase. However, the postprandial hyperglycemia can possibly be controlled by inhibition of these enzymes by specific inhibitors. Han et al. (2017) studied the inhibitory effect of important dihydrochalcone 'phloretin' present in apple on alpha-glucosidase and illustrated its potential as therapeutic to the management and improvement of *Diabetes mellitus*. Earlier, phloretin exert antihyperglycemic effect on streptozotocin induced diabetes in adult male albino rats. Phloretin administration significantly reduced blood glucose, glycosylated hemoglobin, serum insulin and glycogen level in streptozotocin induced mice. This dihydrochacone decreased the level of gluconeogenic enzymes i.e. glucose-6-phosphatase and fructose-1, 6-bisphosphatase and increased the activity of hexokinase and glucose-6-phosphate dehydrogenase that are involved in carbohydrate metabolism (Nithiya and Udayakumar 2016).

In different study, authors evaluated the role of phloretin on glycoprotein components in serum of streptozotocin induced diabetic rats. Diabetic rats showed marked decrease in sialic acid level and increase in hexose, hexosamine and fucose level in liver and kidney. Phloretin dose at 50 mg/kg body weight reverted the level of glycoprotein components in serum and tissues of diabetic rats (Nithiya and Udayakumar 2017a). Furthermore, Nithiya and Udayakumar (2018) reported the role of phloretin in kidney markers and liver function enzymes in streptozotocin rats. Authors reported significant improvement in the activities of liver function enzymes i.e. alanine amino transferase, aspartate transaminase, alkaline phosphatase, lactate dehydrogenase and kidney markers (urea, creatinine and uric acid) followed by phloretin treatment which otherwise changed in diabetic rats. Phloretin treatment also attenuated hyperglycemia mediated oxidative stress in diabetic rats by improving the level of antioxidative enzymes i.e. superoxide dismutase, catalase, glutathione peroxidase and non-enzymatic antioxidants (vitamin C, E and reduced glutathione) as well (Nithiya and Udayakumar 2017b). It also decreased the level of lipid peroxidative markers such as thiobarbituric acid reactive substance, lipid hydroperoxides and conjugated diene in in diabetic rat's plasma and tissues. Shen et al. (2017)

studied the antiobesity and hypoglycemic effects of dihydrochancones on streptozotocin-induced diabetic rats and L6 myotubes. Phloretin treatment reduced postprandial blood glucose, serum free fatty acids, triglycerides, total cholesterol and low density lipoprotein level and improved islet injury in type 2 diabetic rats as well. Phloretin administration also showed the upregulated expression of Akt, phosphoinositide 3-kinase, insulin receptor substrate 1, and glucose transporter type 4 (GLUT4) in skeletal muscle and also in L6 myotubes (Shen et al. 2017).

It was reported that regulation of adipogenesis and adipokines expression (adiponectin) prevents the risk of cardiovascular diseases and diabetes. Recently, the adipogenesis promoting effects of phloretin in mouse marrow stromal cell line (ST2) was studied by Takeno et al. (2018). Authors also studied the expression of various adipogenic markers in ST2 cells. Considerable increase in expression of adipogenic markers i.e. peroxisome proliferator-activated receptor gamma (PPAR-γ), CCAAT-enhancer-binding proteins (C/EBPα), fatty acid synthase, fatty acid-binding protein 4, and adiponectin in phloretin treated ST2 cells. Phloretin treatment also inhibited the expression of extracellular signal-regulated kinase1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) confirmed by western blotting technique. Although this molecule activated the p38 MAPK (Takeno et al. 2018). In another study, 3 T3-L1 cells were used to determine the adipogenesis promoting effects of phloretin by assessing increased triglyceride accumulation and glyceraldehyde 3-phosphate dehydrogenase activity. Findings of Hassan et al. (2007) also showed increased mRNA expression of both PPARγ and C/EBPα adipogenic markers followed by phloretin treatment. Furthermore, phloretin treatment found to upregulate the mRNA expression of PPARγ target genes and also enhanced adiponectin secretion and expression. This aglycone also regulates the expression of numerous genes i.e. GLUT4, acyl-CoA synthetase long-chain family member 1, phosphoenolpyruvate carboxykinase 1, lipin-1 and perilipin that play important role in lipid and triglyceride accumulation. This molecule is suggested to improve insulin sensitivity by over expressing genes that are related to insulin signal transduction i.e. Cbl-associated protein, phosphoinositide-dependent kinase 1 and the serine/threonine kinase (Akt2) (Hassan et al. 2010). In another study, Shu et al. (2014) evaluated the mechanism for adipogenesis promoting effect of phloretin. It was showed that phloretin increased the expression of PPARγ, C/EBPα, fatty acids translocase and fatty acid synthase. Administration of phloretin (5 or 10 mg/kg) considerably lowered the serum glucose level and improved glucose tolerance in C57BL BKS-DB mice.

2.4.3 Epicatechin

Epicatechin is a polyphenolic compound belongs to flavan-3-ol type category of molecule. It is one of the representative compound present in apple fruits that contribute to its health beneficial effects. This molecule was reported to exert various health promoting effects such as antioxidant property that provides defense from free radicals, which causes oxidative stress/ damage to cells. Various studies were conducted to explore effective nature of this molecule against diabetes. Cremonini et al. (2016) revealed that administration of epicatechin ameliorated the genes of insulin signaling cascade (insulin receptor, insulin receptor substrate 1, ERK1/2, Akt) in adipose and liver tissues in high fat diet fed mice. It was also clarified that epicatechin improved insulin sensitivity by down regulating the inhibitory genes of insulin signaling pathway i.e. JNK, IκB kinase (IKK), protein kinase δ (PKCδ) and protein tyrosine phosphatase 1B (PTP1B). Furthermore, in different study preventive effects of epicatechin on tumor necrosis factor alpha (TNFα)-induced activation of signals concerned in inflammation and insulin resistance was studied in 3 T3-L1 differentiated adipocytes. TNFα is a main contributor for facilitating the activation of signaling cascades for adipocytes that are vital to insulin resistance and inflammation (Chen et al. 2015). It was demonstrated that epicatechin reduced the TNFα-mediated JNK, ERK1/2, p-38 phosphorylation, and nuclear AP-1-DNA binding in a dose dependent manner. Epicatechin inhibited the TNFα-mediated activation of the NF-κB signaling cascade and also attenuates the TNFα-mediated down regulation of PPARγ expression (Vazquez-Prieto et al. 2012). Its supplementation reduced the insulin resistance developed in rats fed with high fructose diet and leads to the activation of insulin signaling cascade components (insulin receptor, insulin receptor-1, Akt and ERK1/2) that were impaired in high fructose fed rats. Similar to previous report by Vazquez-Prieto et al. (2012), epicatechin treatment also showed down regulation of the expression of negative regulators of insulin signaling cascade i.e. PKC, IKK, JNK and PTP1B in the liver and adipose tissue of high fructose fed rats (Bettaieb et al. 2014). Obesity is also related to diabetes and is characterized by excessive accumulation of fat in adipose tissues. (+)-Catechin decreased the lipid accumulation thereby, suppresses the adipocyte differentiation in 3 T3-L1 cells. This molecule decreased the expression of C/EBPα and PPARγ genes, involved in adipocyte differentiation and also reduced the expression of hormone-sensitive lipase, adipose triglyceride lipase, and perilipin (Jiang et al. 2019).

2.4.4 Quercetin

Among the discussed phytochemicals, quercetin is one of the most abundant phenolic compound present in apple fruits. Alam et al. (2014) reported the significant protective effects of quercetin in alloxan induced type 2 diabetic mice. Its supplementation found to reduce the fasting blood glucose in diabetic group, while increasing the levels of antioxidative enzymes (glutathione, SOD, catalase, and glutathione-S-transferase). Quercetin administration also increases the GLUT4 expression levels in adipocytes and skeletal muscle (Alam et al. 2014). In addition, the antidiabetic effects of quercetin in combination with other bioactives are also reported. Quercetin individually and in combination with resveratrol improved the blood glucose and insulin level in streptozotocin-induced diabetic rats. It also suppressed the liver and kidney injury markers such as alanine aminotransferase, aspartate transaminase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen and creatinine in experimental animal (Yang and Kang 2018).

Acknowledgement Authors are thankful to the Director, CSIR-IHBT for providing required facilities. Shalika Rana acknowledges ICMR, New Delhi, for the research associate fellowship.

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Chapter 3
Nano-delivery of Bioactive Constituents from Apple Pomace

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Abstract Apple, *Malus domestica Borkh.,* a member of Rosaceae family, is one of the most grown, favored and processed fruit worldwide, generating an immense volume of industrial by-products, collectively referred as apple pomace. In general, apple pomace is discarded, which ultimately leads to environmental pollution. Nonetheless, apple pomace is a source of carbohydrates, proteins, amino acids, fatty acids, phenolic compounds, vitamins, and other bioactive compounds that can be used in food and pharmaceutical products. Here we review the nano-delivery of bioactive compounds from apple pomace, with focus on polymer-, lipid- and inorganic-based nanomaterials used to improve bioavailability and therapeutic efficacy.

Keywords Apple pomace · Bio-active constituents · Bioavailability · Phloretin · Phlorezin · Drug delivery system

Abbreviations

NDDS	Nano drug delivery system
PK	Pharmacokinetics
PD	Pharmacodynamics
SEDDS	Self-emulsifying drug delivery system
SLNPs	Solid lipid nanoparticles
FDA	Food and Drug Administration
PLGA	Poly (lactic-co-glycolic acid)
PEG	Polyethylene glycol

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_3

3.1 Introduction

Kingdom plantae has been a birth place of all biologically active compounds which possess numerous functional activities. Not only the main part of plants (fruits, flowers and nuts), their pomace also comprises bioactive constituents which can be utilized for the production of valuable products after their sustainable processing. Increased industrialization in the agricultural area results in increased production of waste and ultimately leads to environmental stress (Fierascu et al. 2019). Usually the waste from vegetables and fruit industries are used as a fodder for animals, utilized in formation of bio-fertilizers, paper and in fermentation industries but these waste can also be utilized for the extraction of natural compounds having biological activities (Ravindran et al. 2018).

Apple is the one of the most consumed fruit cross the world as it is the third most produced fruit, globally after bananas and watermelon. In 2019 china is the largest producer of apple with the production of 41 million metric tons followed by European Union (https://www.statista.com/statistics/279555/global-top-apple-producing-countries/). This huge production and consumption of apple is mainly due to its taste, various food derivative and exhibition of wide range of functional activities such as heart, kidney and liver protection, antioxidant, anti-oncogenic, anti-diabetic, anti-asthmatic and anti-obesity activities. The exhibition of functional activities is mainly due to the active natural compound present in it, especially, catechin, chlorogenic acid, quercetin, phloretin and phloridzin (Boyer and Liu 2004) (Fig. 3.1). Not only apple, side stream product which is usually termed as apple pomace, consist of pulp, skin, seeds, and stalks, often vary on mixture of apple

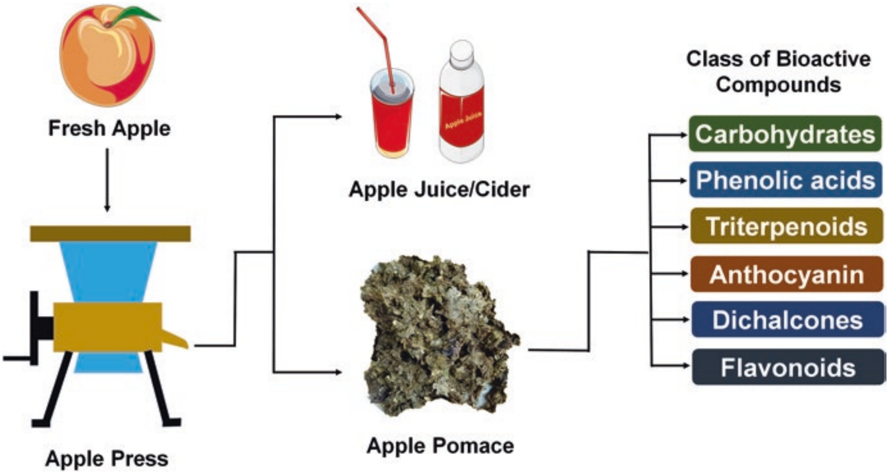

Fig. 3.1 Schematic illustration of apple processing unit. In apple processing industries, along with main stream products, e.g. apple juice, cider and other edible apple derivatives; side stream biomass is also generated which are laden with pharmacologically active phytochemicals (Lyu et al. 2020)

varieties, also have these type of bioactive compounds namely catechins, apigenin, ursolic acid, betulinic acid, phloretin, gallic acid, chlorogenic acid, naringenin, cyanidin, isorhamentin, protocatechuic acid and oleanolic acid (Fig. 3.2). These entire bioactive compounds present in the apple pomace generated from apple industries necessitates its proper utilization so that value added products can be made for the mankind at lowest cost.

The entire set of bioactive constituents in apple pomace has the ability to fight against deleterious health issues by targeting major cellular pathways such as PI3K/Akt pathway, Nf-κB, cell proliferating pathways, apoptosis, insulin receptor pathways, etc. (Djukic 2016; Sharma et al. 2016). However, most of the bioactive constituents from apple pomace are associated with their poor pharmacokinetic properties which is because of poor aqueous solubility, shorter half-life and faster degradation (Sun et al. 2019; Yee Kuen et al. 2020; Zhang et al. 2013a). To tackle these limitations, various delivery systems can be explored to augment their bioavailability and therapeutic efficacy (Castro et al. 2020). This book chapter provides an insight of utilizing various delivery systems for improving the bioavailability and therapeutic efficacy of bioactive constituents of apple pomace.

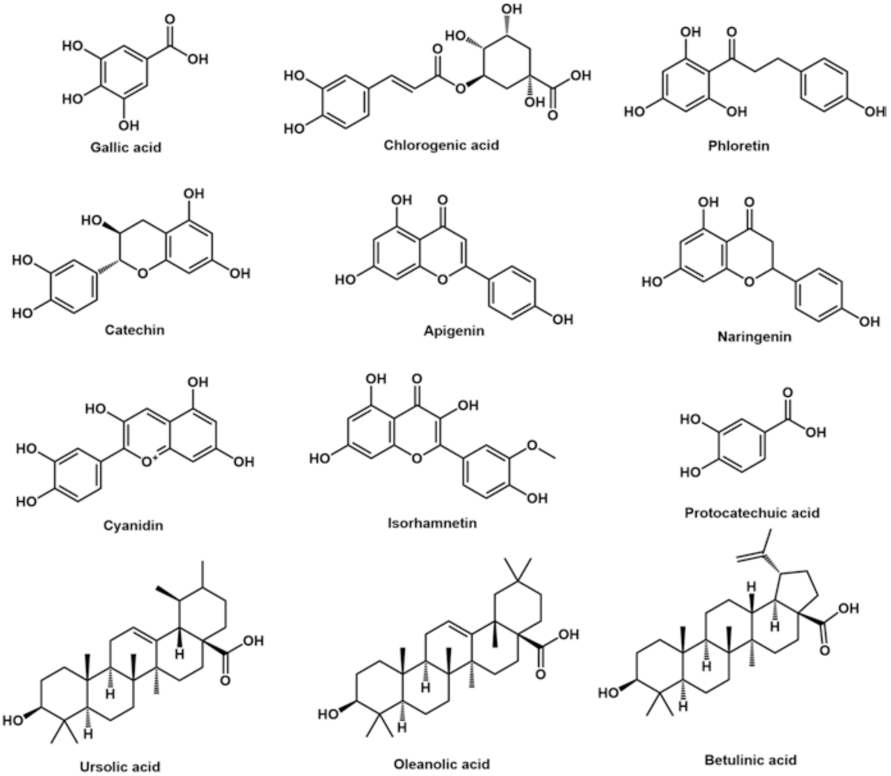

Fig. 3.2 Chemical structures of major bioactive constituent of apple pomace majorly responsible for its pharmacological activities (Barreira et al. 2019)

3.2 Delivery Approaches for Bioactive Constituents of Apple Pomace

Most of the bioactive ingredients obtained from apple pomace are associated with poor aqueous solubility and/or permeability problems such as narigenin, protocatechuic acid, ursolic acid and betulinic acid (Charalabidis et al. 2019; McClements et al. 2015). Poor pharmacokinetic properties of these bioactive compounds lead to the lower clinical efficacies and hinder their proper utilization. Utilization of novel delivery systems have the potential to resolve all these restrains of bioactive compounds as these approaches can enhance the solubility, stability, increases circulation time, controlled release and targeted drug delivery, texture, acceptability and also protect active ingredient from moisture and interaction with the gut microfauna (Fig. 3.3). Moreover, these novel delivery systems also possess the ability to modulate the pharmacodynamics (PD) and pharmacokinetics (PK) of encapsulated molecules (Castro et al. 2020).

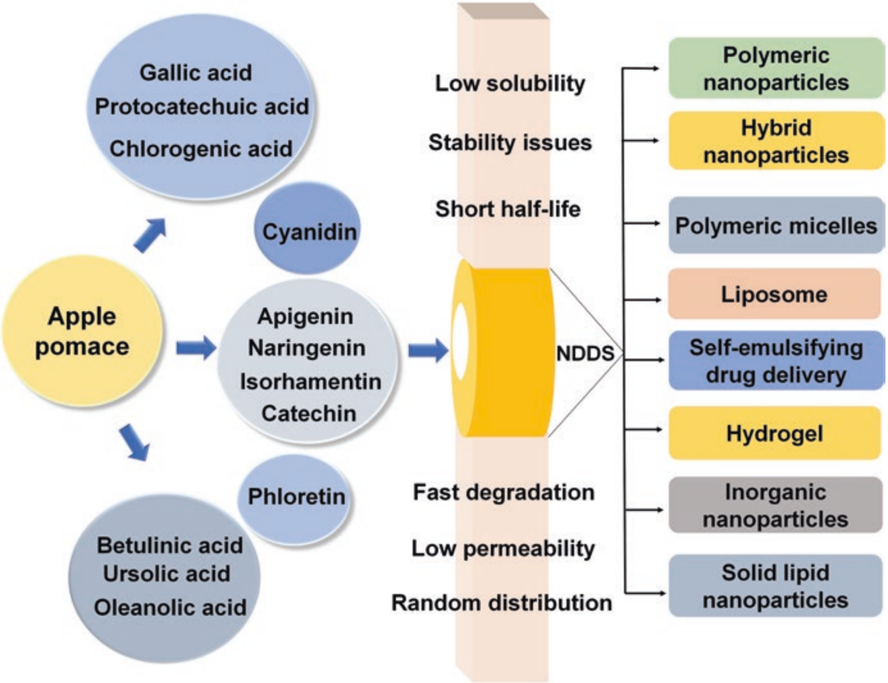

Fig. 3.3 Phytochemicals extracted from apple pomace, their clinical limitations and various nano drug delivery systems which can be explored for enhancing therapeutic efficacy of these phytochemicals. Apple pomace organic molecules exhibit varied types of biological functionalities but have limited therapeutic efficacy which is reasoned by their poor pharmacokinetic attributes. Novel drug delivery system (NDDS) is the most efficient pathway for the liquidation of these limitations
Abbreviations: *NDDS* Nano drug delivery system

In a broad sense, novel delivery systems can be categorized into three major types, namely, polymeric based, lipid based and inorganic based nano-formulations (García-Pinel et al. 2019) (Fig. 3.4). All these three types of nano-formulations have their own pros and cons but lipid based nano-formulations are the one which are extensively studied. In fact, first Food and Drug Administration (FDA) approved nano-based drug was also lipid based named Doxil, against ovarian cancer and further according to a review, about 56% or more of investigating drugs belongs to lipid based formulations (Beltrán-Gracia et al. 2019). The more acceptances of lipid based nano-carriers are may be due their biocompatibility, biodegradability, non-immunogenic, easy modulation and nontoxic nature. Moreover, compatibility with the animal cell membrane may be another reason of their popularity. Numerous clinical trials demonstrated their capability of ameliorating pharmacokinetics and pharmacodynamics of nutraceuticals (Beltrán-Gracia et al. 2019).

3.2.1 Polymer Based Nano-delivery Systems

Polymer nano-carriers are the one of the most extensively studied type of delivery system, in which various approaches ranging from easy nano-capsule formulation to ligand attached targeted delivery approaches has been tried and still advancement

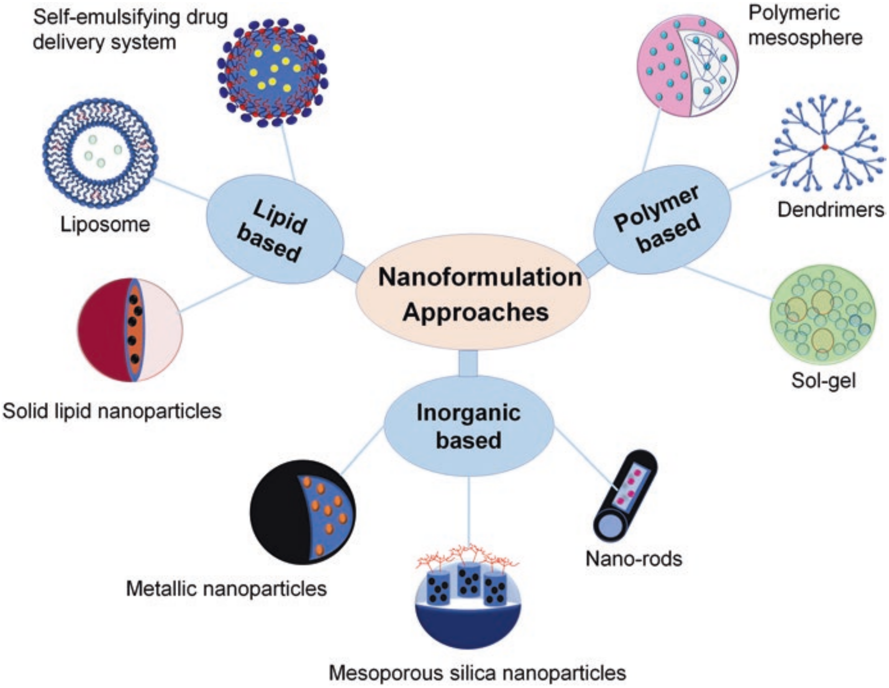

Fig. 3.4 Common nanoformulation approaches for delivery of therapeutic agents. Based on the main excipient used, nano-carriers can be classified in three types, polymeric, lipid and inorganic

in this field is going on in the form of hybrid nano-structures. The ground of its popularity in the area of pharmacology and medicines is its biodegradable, biocompatible and non-toxic nature (Castro et al. 2020). Moreover, they also provides the access of easy modulation in their functional groups present at polymeric backbone position (Wong et al. 2020). Out of two, natural and synthetic, synthetic polymers are highly exploited for efficient delivery of drugs and nutraceuticals via various administration routes.

Natural polymers are the one obtained from natural means, bacteria, fungi, plants and animals and have two main classes, polysaccharides and protein based. Chitosan, hyaluronic acid, dextran, alginates in polysaccharides and collagen, albumin and gelatin as protein based nano-carriers are usual ones. All these natural polymers possess inbuilt properties of being bio-compatible, low-immunogenic, biodegradable and also possess functional activities, moreover, they also solves the problem of nutraceuticals of being in-soluble, fast degradation and poor bioavailability (Castro et al. 2020). Synthetic polymer includes poly lactic-co-glycolic acid (PLGA), poly-ethylene glycol (PEG), poly-lactic acid (PLA) and poly-glycolic acid (PGA) type polymers which are already proven to be safe to use and exploited mostly in the drug delivery formulations of all types (Kakkar et al. 2017). The excessive utilization of synthetic polymers is due to their inherent properties and benefits that they provide as they are bio-degradable, bio-compatible, easy to modify, non-immunogenic (helping drug to bi-pass the opsonisation and attack of immune system) and specificity optimization, moreover, they also help in enhancing the pharmacokinetics and pharmacodynamics of nutraceuticals by enhancing their solubility, half-life, stability, absorption and provides the advantage of targeted drug delivery.

Numerous recent studies demonstrated their effectiveness in the delivery of nutraceuticals; likewise, for the delivery of apple pomace active compounds, several polymeric based drug delivery systems have been tried, including both natural and synthetic polymers (Table 3.1) (An et al. 2020; Arsianti et al. 2020; Karimi et al. 2020; Zhang et al. 2020a). In natural polymers, chitosan (linear amino polysaccharide having β-d-glucosamine and N-acetyl-d-glucosamine monomeric units linked by 1,4-glycosidic linkage) nano-carrier is frequently utilized for enhancing the therapeutic efficacies of various nutraceuticals as it provides the advantage of easy manipulations at functional groups sites. In recent study, hydrophobically modified chitosan nano-carriers has been exploited for the delivery of protocatechuic acid (Yee Kuen et al. 2020). Protochatechuic acid is a phenolic compound, ubiquitously present in most of the plants, commonly used as traditional medicine. It possesses numerous functional activities particularly, anti-oxidant, anti-bacterial, anti-inflammatory, anti-oncogenic, anti-diabetic and anti-ageing but have lower therapeutic efficacy due to its poor solubility, hence poor bioavailability (Kakkar and Bais 2014; Savjani et al. 2012). Hydophobically modified chitosan nanoparticles efficiently helps in improving the anti-cancer potential of protochatechuic acid (Yee Kuen et al. 2020).

Carboxymethyl chitosan and chitosan oligosaccharides are another modified forms of chitosan usually used for the drug delivery system (Fernandes et al. 2008).

Table 3.1 Polymeric nano-formulations for delivery of bioactive constituents of apple pomace

Bioactive constituent	Main excipients/ ingredients	Key outcome	References
Phloretin	Pectin, carboxymethyl phytoglycogen, sodium caseinate	Developed nanocomplex demonstrated enhanced antioxidant activity as compared to native phloretin	Chen et al. (2020)
Apigenin	Poly(lactic-co-glycolic acid)	Developed nanoparticles demonstrated enhanced therapeutic efficacy as compared to native apogenin against hepatocellular carcinoma	Bhattacharya et al. (2018)
Naringenin	Polyvinylpyrrolidone	Developed nanocomplexes demonstrated enhanced in *in-vivo* intraocular permeation and anti-inflammatory efficacy of naringenin as compared to native naringenin	Wang et al. (2020a)
Gallic acid	Alginate; chitosan	Gallic acid nanoparticles showed enhanced cytotoxicity against breast cancer cell line (T47D) in comparison to gallic acid and can be considered as better anti-oncogenic agent in case of breast cancer	Arsianti et al. (2020)
Chlorogenic acid	Chitosan	Chlorogenic acid nanoparticles exhibited better scavenging and anti-proliferating activities than alone chlorogenic acid in human renal cancer cells (786-O)	Kavi Rajan et al. (2019)
Ursolic acid	Gelatin, sodium dodecyl sulfate, ammonium oxalate	Resultant nanocarriers demonstrated improved bio-accessibility, sustained release of drug and stability at higher temperature	Karimi et al. (2020)
Betulinic acid	Polyethylene glycol, folic acid, 2-(3-butenyl)-2-oxazoline	FA-PEG-PBuOx/BA nanostructure exhibited targeted drug delivery with enhanced internalization in tumour cells with controlled drug release	Zhang et al. (2020a)
Protocatechuic acid	Chitosan, palmitic acid, tripolyphosphate	pC-PCANPs demonstrated increased drug cellular uptake in A549 lung cancer cells in comparison with lone protocatechuic acid	Yee Kuen et al. (2020)
Oleanolic acid	Capryol 90®, poloxamer	Polymeric micelles of oleanolic acid are stable and showed effecting wrinkle alleviating activity and can have cosmetic applications	An et al. (2020)
Cyanidin	Chitosan	C3GNPs demonstrated controlled release, improved compatibility with blood cells and was also designated as bio-safe	Sun et al. (2020)

Abbreviations: *CMPG* Carboxymethyl phytoglycogen, *FA-PEG-PBuOx/BA* Folate-polyethylene glycol- poly [2-(3-butenyl)-2-oxazoline]-betulinic acid conjugated nanoparticles, *pC-PCANPs* Hydrophobically modified chitosan-protocatechuic acid nanoparticles, *C3GNPs* Cyanidin-3-O-glucoside chitosan nanoparticles

Modifications in this polymer are done to overcome its limitation of being insoluble in neutral and high pH. –NH_2 (amine) and –OH (Hydroxyl) groups in chitosan linear chain provides lively spot for the modifications (Mohammed et al. 2017). A recent study demonstrated the stability, solubility and sustained release enhancing capabilities of carboxymethyl chitosan and chitosan oligosaccharides encapsulating nutraceutical cyanidin. Cyanidin belongs to the category of anthocyanin, having chronic disorder prevention, anti-cancer and anti-oxidant like biological activities. (Sun et al. 2020). Lower therapeutic efficacy of anthocyanins is due to their unstable nature, as they are sensitive to pH, moisture, temperature and light (Sun et al. 2017; Sun et al. 2019). So, delivery systems used for the cyanidin is mostly related with its stability enhancement.

Sometimes combination of polymers are also tried in order to get combined advantages of both the polymer in one nano-carrier and also to fulfil the limitations of one of the polymer. As in a recent research, combination of alginate and chitosan polymer for the drug delivery of gallic acid was utilized and concluded that dual polymeric nanocarriers exhibited increased cytotoxicity against breast cancer in comparison to drug alone. Here, alginate was used to eliminate the fragile nature of chitosan, by acting as crosslinking agent (Arsianti et al. 2020). Besides this, protein based nanoparticles are also exploited but not as frequent as polysaccharide based and synthetic ones. Protein based nanocarriers enhances the stability, solubility and bioavailability of nutraceuticals and also solves the problem of aggregation of drug as it degraded naturally inside the body (DeFrates et al. 2018). Collagen, gelatin and albumin are the ones in protein based which are most preferred as nano-carriers and in a study, gelatin based nanocarriers of ursolic acid improved its bio-accessibility by converting its crystalline nature into amorphous and also enhances its stability and release (Karimi et al. 2020). Ursolic acid belongs to the family of pentacyclic triterpenoides, known for its functional properties, namely, anti-oxidant, anti-inflammatory, anti-diabetic, anti-microbial, anti-oncogenic and lipid level lowering. However, like other apple pomace organic molecules, its poor solubility and bioavailability acts as a hurdle in its therapeutic pathway. Various clinical studies demonstrated its fast metabolism, poor absorption and random distribution via both oral as well as intravenous administration (Chen et al. 2011; Liao et al. 2005; Zhang et al. 2013a). Therefore, several delivery systems (polymer, lipid and inorganic nanoparticles) has been tried in the way of eliminating limitations of ursolic acid, and demonstrated that it enhances the overall therapeutic efficacy of ursolic acid (Shao et al. 2020).

Poly (lactic-co-glycolic acid) (PLGA), poly-ethylene glycol (PEG), polyvinylpyrrolidone (PVP) and Poly (lactic-co-glycolic acid)- poly-ethylene glycol copolymer (PLGA-PEG) are the most frequent types of synthetic polymers utilized for drug delivery formulations. Till now, numerous polymer based nanomedicines get approval of Food and Drug Administration (FDA) to be sold in the market for clinical use and proved to have better efficacy than the drug alone. In a review, it was concluded that out of all FDA approved nanomedicines, 34% are polymer based and 18% were under investigation (Ventola 2017). Various *in-vitro*, preclinical and clinical studies are the evidence of their capability to modulate the therapeutic aspect of both hydrophobic and hydrophilic drugs and nutraceuticals. As Bhattacharya et al. reported that PLGA nanoparticles loaded with apigenin exhibited enhanced anti-oncogenic activity in case of hepatic carcinomas and also increase the circulation time and release profile of apigenin upon intravenous administration in *in-vivo* models. Apigenin comes under the category of dietary flavonoids have free radical scavenging, anti-mutagenic, anti-viral and anti-inflammatory activities. Need of its nano-formulation arises because of its hydrophobic and lower absorption rate (Bhattacharya et al. 2018). Further Zhang *et al*, formulated a prodrug of betulinic acid by using polyethylene glycol (PEG) as a main excipient for targeted drug delivery against folate positive cancer cell line (HeLa cells) (Zhang et al. 2020a). Like ursolic acid, betulinic acid also comes in the family of natural triterpenoids and possesses wide varieties of health nurturing properties, particularly, Human immune-deficiency virus (HIV) inhibitory, anti-bacterial, anti-malarial, anti-helminthic, anti-oxidant and anti-inflammatory. The main drawback of this compound is its insoluble nature in water, hence poor therapeutic value (Yogeeswari and Sriram 2005). Polyvinylpyrrolidone (PVP) is a synthetic water soluble polymer, forms cross linkage with the hydrophobic or poorly water soluble drug by non-covalent interactions (van der waal or hydrogen bonding) in aqueous medium and help in enhancing the pharmacokinetics (PKs) of drug/nutraceuticals (Chowdhury et al. 2018). In a recent research, Polyvinylpyrrolidone (PVP) was used for the drug delivery of naringenin via ocular route. Resultant formulation of naringenin and PVP demonstrated to have better drug delivery with ameliorated antioxidant activity, stability and permeability (Wang et al. 2020a). Naringenin is a flavanone, naturally present in most of the citrus fruits and also found in apple pomace. Naringenin is well renowned because of its functional properties of being antioxidant, cardio protective, anti-inflammatory, anti-cancer, anti-adipogenic and anti-microbial, although used in preventive medications not for the curing (Salehi et al. 2019). The reason of lower clinical application is its hydrophobicity which limits its pharmacokinetic levels and hence have limited clinical efficacy, moreover, this molecule is not much explored at clinical levels.

3.2.2 Lipid Based Nano-delivery Systems

Lipid based nanocarriers can be categories as liposomes, solid nanoparticles, self-micro-emulsifying drug delivery system and nano-emulsions, depending upon the type of lipid used and method of synthesis. All types have their own advantages and are efficiently proven to enhance the solubility, circulation time, stability and absorption of encapsulating entity (García-Pinel et al. 2019). Likewise, for the effective delivery of apple pomace bioactive molecules, several lipid based formulations have been explored. For instance, in a recent study hyaluronic acid decorated lipid nanocarriers encapsulating apigenin demonstrated to have better cytotoxicity and internalization when administrated in combination with docetaxel than apigenin alone against non-small-cell lung cancer. Lipid nanoparticle enhances the cytotoxicity effect of apigenin (Nrf2-inhibitor) by eliminating its limiting factors of being insoluble and poorly bio-available (Mahmoudi et al. 2019). Similarly, for other organic molecules obtained from apple pomace, lipid based nano formulations have been tried for their sustainable utilization enlisted in Table 3.2.

Likewise, liposomes of cyanidin have been formulated for the enhancement of its anti-proliferating capability against Caco-2 cell lines (Liang et al. 2017). Further, lipid nanocarriers of different apple pomace nutraceutics, particularly, betulinic acid (Shu et al. 2019), naringenin (Hu et al. 2020), protocatechuic acid (Daré et al. 2020) have been synthesized to saw the effect of formulation on their activities and all exhibited significant enhancement in their biological activities and can go further for clinical trials.

Oleanolic acid is also a triterpenoid same as that of ursolic and betulinic acid, has very long past of being used as folk medicine and have far-flung varieties of biological activities, such as, anti-oxidant, anti-oncogenic, anti-inflammatory, lipid and glucose level lowing, anti-viral, immunomodulatory and hepato-protective (Alvarado et al. 2015; Wang et al. 2010). But like other apple pomace active pharmaceutic ingredients, its therapeutic efficacy is also hindered by certain limitations, namely, being hydrophobic, short-half life and poor absorption. Various lipid based delivery systems (such as liposomes, microemulsions etc.) have been tried for the effective delivery of oleanolic acid (Gao et al. 2012; Liu and Wang 2007; Yang et al. 2013; Zhang et al. 2013b), therein, Luo et al. reported multi vesicular liposomes for the worthwhile *in-vitro* as well as *in-vivo* delivery of oleanolic acid against hepatocellular carcinomas (Luo et al. 2016). Multi vescicular liposome efficienly helps in eliminating the limitation of oleanolic acid by providing it spectacular stability and prolonged drug release.

Solid lipid nano-carriers are the another type of lipid based delivery system which includes the utilization of those lipids which remains solid at both room as well as at body temperature, provides advantages like extra stability to unstable drugs, applicable for both hydrophilic and hydrophobic drugs, controlled release, non-toxic and easy to formulate (Duan et al. 2020). These have been utilized much for the delivery of various nutraceutical/drugs (Eskiler et al. 2018; Oliveira et al. 2018; Pindiprolu et al. 2019; Zielińska et al. 2018). Naringenin, Chlorogenic acid and Protocatechuic acid has also been formulated into solid lipid nanocarriers in the pathway of enhancing their therapeutic efficacy. Resultant solid lipid nanoparticles demonstrated improved functional activities, increased oral bioavailability and enhanced therapeutic efficacy of encapsulating nutraceutical (Daré et al. 2020; Hu et al. 2020; Raskar and Bhalekar 2019).

3.2.3 Inorganic Based Nano-delivery Systems

Inorganic nanoparticles are usually synthesized by using metal, metal oxides or silica and can be categorized into metal and metal oxide nanoparticles. These nanoparticles have low toxicity and are more stable than organic ones. Inorganic

Table 3.2 Lipid based nano-formulations for delivery of bioactive constituents of apple pomace

Bioactive constituent	Main excipients/ ingredients	Key outcome	References
Apigenin	Miglyol-812, precirol® ATO 5, DOPE	Developed nanostructure lipid carriers demonstrated higher cytotoxicity and exhibited synergistic effect combined with docetaxel	Mahmoudi et al. (2019)
(+) Catechin	Cholesterol, span 60, dihexadecyl phosphate	Developed niosomes demonstrated enhanced protective effect on the human skin fibroblasts as compared to native drug.	Li et al. (2020a)
Ursolic acid	Hydrogenated soybean phosphatidylcholine, DSPE-PEG2000, cholesterol	Developed liposomes demonstrated reduction in number of MDSCs and Tregs residing in tumor tissues.	Zhang et al. (2020b)
Betulinic acid	Soy phosphatidylcholine, cholesterol, mannosylerythritol lipid-A	Developed liposomes exhibited significant increase in cell apoptosis, destruction of mitochondrial membrane in HepG2 cells and have elevated anti-oncogenic activity in comparison to lone betulinic acid	Shu et al. (2019)
Oleanolic acid	Soya lecithin, cholesterol, triolein and stearic acid	Developed formulations (OA-MVLs) demonstrated higher encapsulation efficiency, sustained release and prolonged circulation time of drug with enhanced cell cytotoxicity against HepG2 cells and have no toxic effects on *in-vivo* model	Luo et al. (2016)
Naringenin	Soya lecithin, monostearin, stearic acid, oleic acid	Formulated solid lipid nanocarriers demonstrated increased anti-NAFLD activity in comparison with lone drug via increasing intestinal absorption and oral bio-availability	Hu et al. (2020)
Cyanidin	Phosphatidylcholine, cholesterol	Cyanidin liposomes exhibited enhanced cell cytotoxicity against Caco-2 cells in comparison with cyanidin and were also stable at 37 °C in simulated gastric fluid	Liang et al. (2017)
Gallic acid	Stearyl amine, lipoid S75	Synthesized RMLNCs exhibited ameliorated anti-proliferating and internalization in HSC cells and have promising anti-fibrotic activities	Radwan et al. (2020)

(continued)

Table 3.2 (continued)

Bioactive constituent	Main excipients/ ingredients	Key outcome	References
Chlorogenic acid	Glyceryl mono stearate	Resultant solid lipid nano-carriers inhibits the proliferation of RSC-364 cells, increased solid lipid nano-carriers uptake from intestine ad concluded to be a better approach to treat rheumatoid arthritis	Raskar and Bhalekar (2019)
Protocatechuic acid	Miglyol® 810 N, precirol ATO® 5	Nano-lipid carriers and solid lipid nanocarriers both exhibited controlled release and can act as better way for treating skin diseases caused by excessive exposure to UV-radiations	Daré et al. (2020)

Abbreviations: *DOPE* 1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine, *MDSCs* Myeloid derived suppressor cells, *Tregs* regulatory T cells, *OA-MVLs* Oleanolic acid-multi-vesicular liposomes, *NAFLD* Non-alcoholic Fatty Acid Disease, *RMLNCs* Reverse micelle lipid nano-carriers

nanoparticles are thoroughly used in both the areas of medicine as well as in imaging, out of which iron oxide (superparamagnetic iron oxide nanoparticles) nanoparticles are used most extensively for imaging (MRI) and also has been used as treatment for anemia under the drug name, Venofer, Dexferrum, Infed and Ferrlecit which are FDA approved and have high clinical demand (Bobo et al. 2016). These are also been used for the enhancement of therapeutic capabilities of nutraceuticals. For instance, recently iron oxide nanoparticles coated with gallic acid exhibited higher cytotoxic levels than the alone gallic acid, and also responsible for the elevated expression of apoptotic genes in treated cell lines (Saleh et al. 2020).

Nanoparticles synthesized by utilizing noble metal elements namely, silver, gold, palladium, copper etc., has also gained much attention of the researchers because of their unique attributes and wide applications. Silver nanoparticles are one which is most frequently utilized among them for drug delivery of various nutraceuticals, as it possesses idiosyncratic physiochemical properties (size, shape, surface Plasmon resonance, colloidal dispersion, low toxicity, stability and easy synthesis) along with biological activities such as anti-bacterial, anti-oncogenic and anti-oxidant (Yaqoob et al. 2020). Similarly, it has been utilized for the delivery of apple pomace bioactive molecules, particularly, chlorogenic acid (Zhu et al. 2020), phloretin (Payne et al. 2018) and naringenin (Gurunathan et al. 2018) and demonstrated potentiate increment in the anti-bacterial and anti-oncogenic properties of these nutraceuticals respectively. Chlorogenic acid belongs to the family of quinic acid esters and has high water solubility and poor pharmacokinetic properties because of short half-life of approximately 0.91 hours and low absorption rate (Li et al. 2020b; Xie et al. 2007). Chlorogenic acid is well known for its functional attributes particularly, anti-oxidant, anti-oncogenic, anti-inflammatory, anti-bacterial, glucose level lowering and neuro-protectant (Agunloye et al. 2019; Santos and Lima 2016). Phloretin is a dihydrochalcone, belongs to the class of phenolic phytochemicals, well demonstrated to have anti-oxidant, anti-oncogenic, anti-aging, anti-inflammatory and cardio protectant activities but have limited therapeutic efficacy (Wang et al. 2020b). Limitations in its clinical abilities is due to its poor water solubility, stability, absorption and rapid metabolism.

Mesoporous silica have been utilized for the formation of nanoparticles encapsulating apigenin and ursolic acid for enhancing their therapeutic efficacy. Mesoporous silica being insoluble in water comes under third generation solid dispersion excipients and provides advantages like, spectacular biocompatibility, biodegradability, small size, large surface area, unique physicochemical attributes, narrow pore size, stability, controlled drug release, high encapsulation efficiency and low toxicity (Hoffmann et al. 2006; Huang et al. 2019). Therein, it has an excellent ability to enhance the bioavailability of hydrophobic drugs via oral administration (McCarthy et al. 2016). Mesoporous nanoparticles exhibited significant increase in the anti-oncogenic activity and also demonstrated sustained release of encapsulating nutraceuticals (ursolic acid and apigenin) (Huang et al. 2019; Jiang et al. 2017).

Further gold nanoparticles and carbon nanotubes have been synthesized for the translational drug delivery of cyanidin and betulinic acid (Table 3.3) and demonstrated to have improved anti-bacterial and cytotoxic effects, respectively (Aazam and Zaheer 2020; Tan et al. 2014).

3.3 Conclusion

The proverb holds true “apple a day, keeps the doctor away”, as not only the main part of apple, its pomace, roots and stems are also loaded with enormous phytochemicals which have wide range of health benefits. It is one of the most consumed and produced fruit worldwide and therefore, also have many food derivatives. The waste generated from the apple factories in the form of apple pomace can be translated into value added product after proper processing and treatment. The bioactive constituents present in apple pomace are well explored in terms of their biological functionalities but still not translated into efficient therapeutic agent because of their pharmacokinetic limitations. Their pharmacokinetic limitations hinder their therapeutic efficacy and may keep us away from getting an efficient way of treating deadly human ailments. Therefore, it is necessitating for developing such methods that can help in eliminating limitations of nutraceuticals. Nanotechnology is a rising technique in the field of pharmacology and showed promising effects in improving therapeutic aspect of nutraceuticals. Here we have discussed some recent studies done in the favor of enhancing therapeutic efficacy of apple pomace bioactive compounds but still gaps are there as there are few nano based formulation of these bioactive constituents have been explored. For getting full-flash benefits of nutraceuticals, their exploration at both pre-clinical and clinical levels is needed.

Table 3.3 Inorganic nanocarriers for delivery of bioactive constituents of apple pomace

Bioactive constituent	Main excipients/ ingredients	Key outcome	References
Chlorogenic acid	$HAuCl_4 \cdot 3H_2O$, trisodium citrate, Chlorogenic acid	Chlorogenic acid gold nano-carriers demonstrated improved antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* in comparison with native chlorogenic acid	Zhu et al. (2020)
Gallic acid	Iron oxide (Fe_2O_3)	Developed inorganic nanostructures exhibited enhanced cell cytotoxic activity against A549 and WI-38 cell lines than alone gallic acid	Saleh et al. (2020)
Phloretin	Potassium tetrachloroaurate	Phloretin silver nanoparticles demonstrated 17.45 times increase in anti-oncogenic activity against HeLa cellsas compared to alone phloretin	Payne et al. (2018)
Catechins	PEGylated silica and CTAB- silica	Modified inorganic nanostructures demonstrated protective effects against oxidative stress and neurodegenerative diseases	Halevas et al. (2016)
Apigenin	Mesoporous silica nanoparticles	Developed nanostructures were efficient in drug release and proved to be a potent oral therapeutic agent	Huang et al. (2019)
Naringenin	Silver nitrate	Synthesized silver nano-carriers proved to be potent in causing cell death in HCT116 cell lines by increasing lactate dehydrogenase leakage,reactive oxygen species and malondialdehyde levels	Gurunathan et al. (2018)
Cyanidin	Gold(III) chloride trihydrate (HAuCl4·3H2O)	Cyanidin gold nanoparticles exhibited improved anti-bacterial and anti-fungal activity against *S. aureus, E. coil,* and Candida fungus	Aazam and Zaheer (2020)
Betulinic acid	MWCNT-COOH	Betulinic acid modified carbon nanotubes demonstrated high compatibility with no cytotoxicity against normal cells and have increased anti-oncogenic activity as compared to drug alone in HLCCs	Tan et al. (2014)
Ursolic acid	Silica based mesoporous nano-sphere	Modified SMNU demonstrated improved anti-cancer activity with sustained release of drug and can be used as better chemo-preventive agent	Jiang et al. (2017)
Oleanolic acid	$Zn_2(bdc)_2(dabco)$	MOF improves sustained release, efficient loading, targeted drug delivery and also enhances the therapeutic efficacy of the drug	Zhang et al. (2018)

Abbreviations: $HAuCl_4 \cdot 3H_2O$ Hydrochloroauric acid trihydrate, *CTAB* Cetyltrimethylammoniun bromide, *MWCNT-COOH* Oxidized multi-walled carbon nanotubes, *HLCCs* Human lung cancer cell lines, *SMNU* Silica based mesoporous nano-spheres of ursolic acid, *MOFs* Metal organic frameworks

Acknowledgement The authors are greatful to Director, CSIR- Institite of Himalayan Bioresource Technology, Palampur for his constent support and encouragement. AS acknowledges financial assitance from Council of Scientific and Industrial Research (CSIR), New Delhi for major laboratory project (MLP-0204). R acknowledges Council of Scientific and Industrial Research (CSIR), New Delhi for providing junior research fellowship (File number: 31/054(0163)/2020-EMR-I) and RKD acknowledges University Grant Commission for providing Junior Research Fellowship (File number: 82-1/2018 (SA-III)). Some figures are drawn from the material provided by Servier Medical Art under the Creative Common Attribution 3.0 Unported License. The book chapter is institutional communication number: 4802.

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Chapter 4
Synthesis and Application of Lignin-Based Metal Oxide Nanocomposites in Photocatalysis

Ravneet Kaur, Sanjam Chandna, Sanjeev K. Bhardwaj, and Jayeeta Bhaumik

Abstract Pollution by fossil fuels is calling for alternative carbon sources and raw materials. For instance, lignocellulosic biomass is promising because it is usually biocompatible, sustainable and abundant, lignin being the next abundant plant polymer after cellulose. Lignin contains polyphenols and displays properties such as adhesive, reducing, and adsorbing, making lignin an interesting starting material for the synthesis of nanomaterials such as metal oxides. Metal oxide nanoparticles are indeed widely used in sensors, fuel cells, and coatings due to their low toxicity, low cost of production, and photocatalytic behaviour. Metal oxide nanomaterials from lignin show properties such as UV protection, antimicrobials, and photocatalytic efficacy. Here we review the synthesis and photocatalytic applications of lignin-based metal oxide composites.

Keywords Lignin · Photocatalysis · Nanoparticles · Zinc oxide · Titanium dioxide · Cerium oxide

4.1 Introduction

Photocatalysis is a light-driven process that executes efficient chemical transformations. By means of photocatalysis, water purification, dye degradation, volatile organic compound removal, chemical conversion, and similar transformations can be achieved (Byun and Zhang 2020; Li et al. 2018a, b). Various light sources

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_4

including sunlight, UV light, visible, and infrared light are used to perform photocatalysis (Levine et al. 2011; Sang et al. 2015; Yoon et al. 2010). This procedure has taken an important place in the consumer market by participating in odor removal, microbial disinfection, pollutant, or toxin removal, etc. (Fig. 4.1) (Chen et al. 2010; Chen and Poon 2009; Likodimos et al. 2010; Ming et al. 2017; Vohra et al. 2006).

Photocatalysts generally absorb light of a particular wavelength to proceed from their ground state to a higher energy level (Yoon et al. 2010). When such molecules come back to their ground state the energy is released, which reacts with various substances to drive chemical reactions. Examples of photocatalysts include metal, metal oxides and the corresponding nanocomposites (Koe et al. 2020; Kumar et al. 2019; Raizada et al. 2020). Among these, metal oxide nanoparticles are widely used due to economic viability, low toxicity, and biocompatibility (Chen et al. 2012; Dong et al. 2015). These nanoparticles take an active part in environmental remediation via the removal of dyes, bacteria, toxic gases, etc. from water or air (Dong et al. 2015). Further, via photocatalysis, metal oxide nanoparticles can perform water splitting, pollutant, or explosive removal (Xu et al. 2019). Thus, metal oxide nanocomposite-based photocatalysts have become very important in the area of photocatalysis.

Lignin, a polyphenolic biopolymer, consists of multiple functionalities (Ahmad and Pant 2018; Chandna et al. 2020a; Paul et al. 2020). Thus, it can easily act as a matrix to develop various nanocomposites (Chandna et al. 2020b; Chandna et al. 2019; Kai et al. 2016; Kaur et al. 2020; Khan et al. 2020). Due to the adhesion and chelation properties of lignin, it easily stabilizes the metal and metal oxide nanomaterials (Paul et al. 2020). Thus, lignin is nowadays being used for the development of a variety of nanomaterials. Moreover, the biocompatible and antimicrobial nature of lignin helps it to contribute to the properties of the

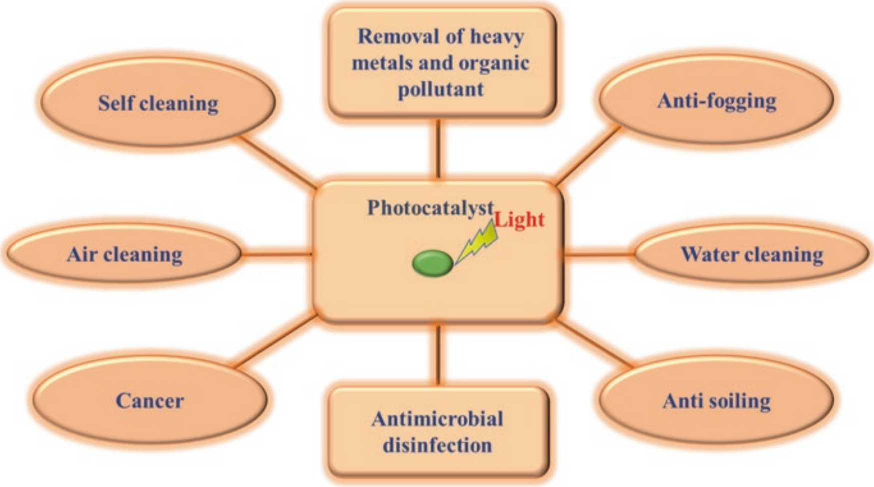

Fig. 4.1 Applications of photocatalysts

photocatalytic nanomaterials developed in its presence (Khan et al. 2020). Likewise, metal oxide nanoparticles prepared with the aid of lignin are being successfully used as versatile photocatalysts.

4.2 Lignin

Lignin derived its name from the Latin word lignum (Khan et al. 2020). Lignin accounts for up to 30% of the total lignocellulosic biomass (plant) (Ahmad and Pant 2018; Kai et al. 2016). It is the most abundant aromatic biopolymer and the second abundant organic polymer present on the earth (Ayyachamy et al. 2013; Khan et al. 2020). Lignin is an amorphous three-dimensional biopolymer consisting of phenylpropane units connected together in diverse ways. It is composed of three monolignols (p-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol) combined in different ratios and combinations (Fig. 4.2a, b) (Bajwa et al. 2019; Kai et al. 2016; Khan et al. 2020). Lignin derived from these monolignols is usually referred to as hydroxyphenyl (H), guaiacyl (G), and syringyl (S) lignin (Espinoza-Acosta et al. 2016).

The amount and arrangement of lignin vary from plant to plant, geographical region, and cell types. Based on its source, lignin is categorized into three basic classes, as defined below:

1. **Guaiacyl lignin:** It consists of a higher amount of guaiacyl alcohol. The ratio of guaiacyl (G): syringyl (S): p-hydroxybenzaldehyde (H) alcohol is 90:2:8. It is mainly present in coniferous trees, so is named softwood lignin.
2. **Guaiacyl–syringyl lignin:** It consists of a higher amount of sinapyl alcohol compared to coniferyl alcohol. It is mainly present in deciduous trees and shrubs, so is named hardwood lignin.
3. **p-hydroxybenzaldehyde lignin:** It consists of a higher amount of p-hydroxybenzaldehyde (approximately 30%). It is mainly present in monocotyledons.

Lignin can also be divided into the following categories, based on the process of extraction (Fig. 4.2c) (Grossman and Vermerris 2019; Upton and Kasko 2016).

1. **Kraft lignin:** This type of lignin is extracted by the processing of wood by the paper and pulp industry through the kraft process. This type of lignin contains sulphur and is insoluble in water.
2. **Lignosulfonates:** It is extracted by the sulphite processing of softwood by the paper and pulp industry. This is the water-soluble form of lignin and is used abundantly in various applications.
3. **Organosolv lignin:** It is extracted by the processing of plant biomass by the organic solvent in the presence of an acid catalyst at a higher temperature.
4. **Alkali lignin:** This is extracted by the processing of plant biomass by alkaline treatment at a moderate temperature.

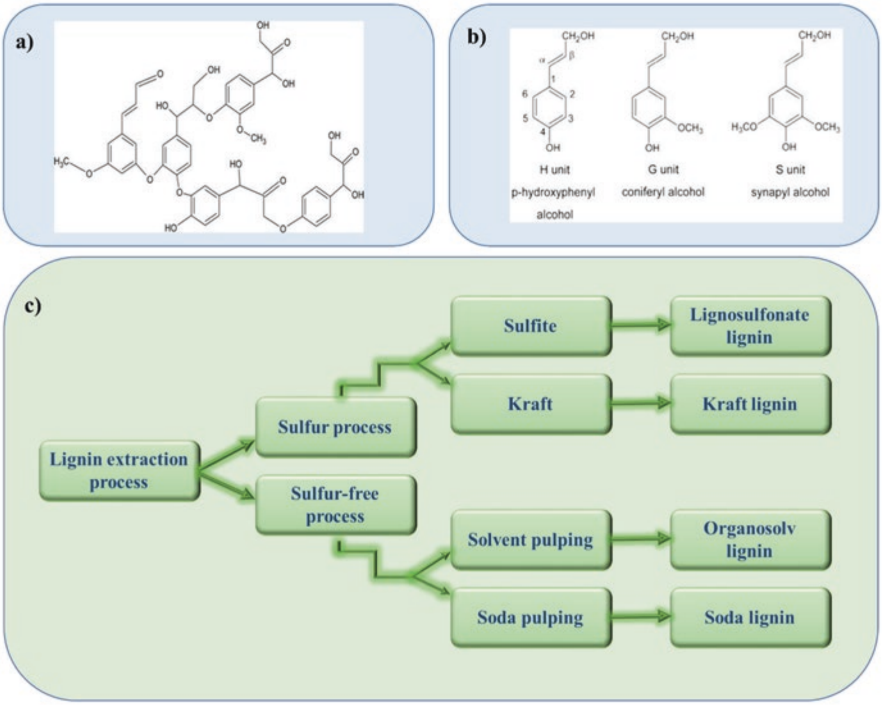

Fig. 4.2 (**a**) Chemical structure of lignin (Mahmood et al. 2018); (**b**) Three monomers of lignin (Yang et al. 2019a, b); (**c**) Types of lignin and isolation processes of lignin (Mahmood et al. 2018)

Lignin is an abundant source of phenolic groups making it a favourable candidate for antimicrobial, anticancer, UV protection, and similar applications (Espinoza-Acosta et al. 2016; Iravani 2020). Due to the inherent adhesive property of lignin, it is used as a good adsorbent for heavy metals, dyes, and gases (Bajwa et al. 2019; Budnyak et al. 2020; Chandna et al. 2020b; Gillet et al. 2017; Liu et al. 2017; Paul et al. 2020; Rahman et al. 2018; Thakur and Thakur 2015; Wang et al. 2019). It is a biodegradable and biocompatible polymer making it the best precursor for fabrication of environment-friendly nanomaterials (Gan et al. 2019; Rahman et al. 2018). Due to biocompatibility, it is further used as a favourable coating material, hydrogel precursor, and wound healing material (Chandna et al. 2020a). Despite the abundant alluring properties (e.g., polyphenolic groups, UV shielding ability, thermal stability, biodegradability, and antioxidant activity), lignin is underutilized properly for creating low-cost and value-added biomaterials (Budnyak et al. 2020; Espinoza-Acosta et al. 2016).

4.3 Metal Oxides and Their Derived Nanoparticles

Metal oxide nanoparticles exhibit unique physical and chemical properties due to their small size and large surface area (Lu et al. 2020; Ray and Pal 2017). Substantial research and subsequent development have allowed the extensive use of the metal oxide nanoparticles in diverse applications (medical, industrial, environmental, and agricultural fields) (Bundschuh et al. 2018; Farner et al. 2020). These metal oxide nanoparticles can be synthesized using physical methods such as ultrasonication, chemical vaporization, spray pyrolysis, etc. (Nikam et al. 2018; Tsai et al. 2004). Various chemical methods have also been reported for the synthesis of metal oxide nanoparticles. These include precipitation of the metal oxide ions precursor in the aqueous phase using various chemical salts or by the oxidation-reduction reactions. These methods are energy-consuming and generate numerous harmful by-products in the atmosphere (Kannan et al. 2016). To combat these problems, researchers are now focussing on greener alternatives for the synthesis of metal oxide nanoparticles which are not only cost-effective but environmentally friendly as well (Nikam et al. 2018). Various chemical, physical and biological methods for metal oxide nanoparticles synthesis are mentioned in detail in Fig. 4.3.

Among the various metal oxide nanoparticles, zinc oxide nanoparticles display high exciton binding energy and large bandwidth (Agarwal et al. 2017). Therefore, these nanoparticles have been immensely used in potential applications, such as anti-diabetic, antifungal, antibacterial, and anti-inflammatory (Agarwal et al. 2017; Bui et al. 2017; Khan et al. 2015; Klapiszewski et al. 2019; Samb-Joshi et al. 2019; Kannan et al. 2016; Mondal 2017; Shateri-Khalilabad and Yazdanshenas 2013). Other applications of these nanoparticles include antioxidants and wound healing (Agarwal et al. 2017; Bui et al. 2017). In the literature, various plant extracts have been reported for the development of zinc oxide nanoparticles. Titanium dioxide is another extensively studied and useful photocatalyst due to its outstanding properties (non-toxicity and high chemical stability) (Weir et al. 2012). Titanium dioxide nanoparticles are versatile and importantly used in various cosmetics, skincare products, pharmaceuticals, paints, toothpaste, and food-colorants (Simonin et al. 2016; Souza et al. 2019; Weir et al. 2012). They have also been studied as antimicrobial agents due to the demonstration of significant microbicidal activity by these nanoparticles (Santhoshkumar et al. 2014).

Being relevant in progressive technologies, researchers have also focussed on the synthesis of copper oxide nanoparticles (CuONPs). CuONPs have been employed in various numerous applications including semiconductors, gas sensors, catalysis, and batteries (Khan et al. 2017; Kumar et al. 2017). Upon exposure to carbon monoxide or hydrogen under high temperature, these nanoparticles can be reduced to metallic copper (Khan et al. 2017; Kumar et al. 2017). Various other metal oxide nanoparticles, such as cerium dioxide (CeO_2) nanoparticles (Siposova et al. 2019), copper hexaferrite ($CuFe_{12}O_{19}$) nanoparticles (Mahdiani et al. 2018), nickel oxide (NiO)nanoparticles, (Nazari et al. 2017), and iron oxide (Fe_3O_4) nanoparticles (Lunge et al. 2014) have also been reported to be relevant in various important

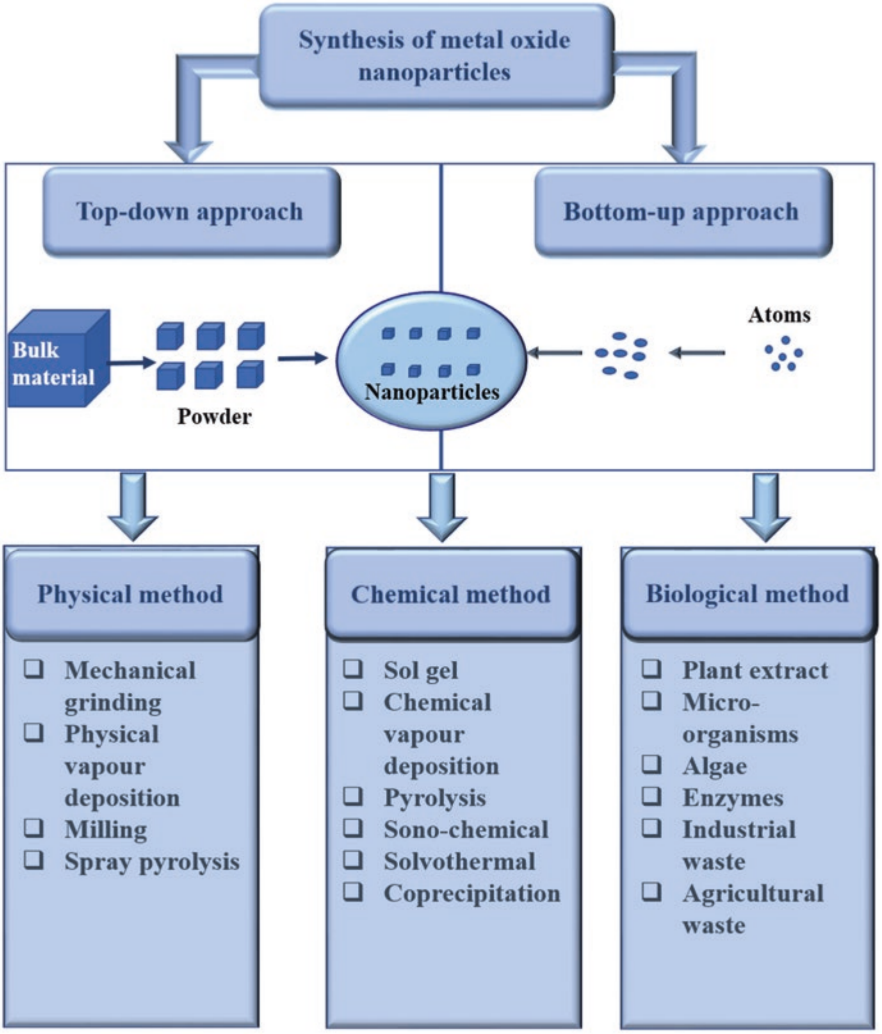

Fig. 4.3 Chemical, physical and biological approaches for the synthesis of the metal oxide nanoparticles (Gebre and Sendeku 2019)

applications, such as catalysis and biomedicine. It has been found that several properties e.g. size and shape conjointly have a vital role in the determination of physical, electrical, catalytic, chemical, and optical properties of the synthesized metal oxide nanoparticles (Wang 2013).

Amongst the various reported biological methods for the synthesis of metal oxide nanoparticles, it has been observed that their microbes mediated synthesis is industrially not feasible given the requirement of high maintenance and aseptic conditions (Santhoshkumar et al. 2014). The use of biomass-based reducing and stabilizing agents is economic and supports the cost-competitive feasibility over the nanomaterial synthesis using microbes or chemical reducing agents (Kaur et al. 2020; Zhang et al. 2019). This hints towards the utilization of other environmentally benign and green methods for the synthesis of metal oxide nanoparticles as better options for improved applicability, cost-effectiveness, and scalability (Yuliarto et al. 2019).

4.4 Lignin-Based Metal Oxide Nanoparticles as New Generation Materials

To overcome the disadvantages offered by the chemical synthesis approach of metal oxide nanoparticles, research has been devoted to developing sustainable, safer, simple, and cost-effective green synthesis methods (Iravani and Varma 2020). The green synthesis approaches eliminate the use of hazardous chemicals and do not produce harmful chemicals as by-products (Singh et al. 2018; Yuliarto et al. 2019). Renewable resources-based nanomaterials are found to be eco-friendly and biodegradable. These bioinspired nanomaterials also have enormous potential for use in broad-spectrum applications ranging from catalysis to therapy (Rahman et al. 2018). The recent advancement in green synthesis approaches has led to the utilization of naturally occurring and biodegradable resources for the synthesis of metal oxide nanoparticles (Singh et al. 2018; Zhu et al. 2019). Lignin is one such naturally occurring biodegradable polymer available in large quantities. Lignin has emerged as a polyphenol-rich starting material for the synthesis of various kinds of nanomaterials (Chandna et al. 2019; Richter et al. 2016).

The green synthesis of metal oxide nanoparticles utilizing lignin is a simple, low energy, and cost-efficient method (Feng et al. 2015; Joshi et al. 2019). Lignin acts as a stabilizing agent as well as a reducing agent for the synthesis of different types of metal oxide nanoparticles (Kaur et al. 2020; Samb-Joshi et al. 2019; Mondal 2017). Many research studies have utilized lignin-based green synthesis methods for the development of metal oxide nanoparticles for further exploring their potential applications. However, the research work utilizing lignin for green synthesis of metal oxide nanoparticles is a comparatively new approach, which is underway and was first initiated in early 2010 (Guo et al. 2013; Miao et al. 2013a, b).

There are various approaches to the utilization of lignin in metal oxide nanoparticles synthesis. One such approach is the use of unmodified lignin for direct one-pot synthesis of the metal oxide nanoparticles (Kaur et al. 2020). In the second approach, lignin is first modified using different chemical treatments, and the modified lignin is then used for the synthesis of metal oxide nanoparticles (Joshi et al. 2019; Wang et al. 2017b, c; Wang et al. 2016). Another approach utilized lignin as a dopant in the already synthesized metal oxide nanoparticles (Dai et al. 2020; Fu et al. 2019; Gutiérrez-Hernández et al. 2016; Morsella et al. 2015). Figure 4.4 demonstrates the synthesis procedure for the synthesis of lignin-titanium dioxide nanoparticles.

Fig. 4.4 Preparation of quaternized alkali lignin/zinc oxide nanocomposites. (Reprinted with permission from American chemical society (Wang et al. 2017a))

Lignin was utilized for the first time for the synthesis of zinc oxide nanoparticles by (Guo et al. 2013). The lignin based metal oxide nanoparticles have been utilized for vast applications including UV protection (Gutiérrez-Hernández et al. 2016; Ibrahim et al. 2019; Kaur et al. 2020; Li et al. 2019; Morsella et al. 2016; Morsella et al. 2015; Wang et al. 2018; Wang et al. 2017a; Wang et al. 2020; Wu et al. 2019; Yang et al. 2019b; Yu et al. 2018), antimicrobial (Kaur et al. 2020; Klapiszewski et al. 2019; Li et al. 2016a, b; Samb-Joshi et al. 2019; Mondal 2017), photocatalytic (Chen et al. 2016; Dai et al. 2020; Feng et al. 2015; Gómez-Avilés et al. 2019; Ju et al. 2015; Li et al. 2018a, b, 2019, 2016a, b; Meshram et al. 2012; Miao et al. 2013a; Nair et al. 2016; Srisasiwimon et al. 2018; Tian et al. 2018; Wang et al. 2015; Zhang et al. 2020), adsorption (Klapiszewski et al. 2017; Ma et al. 2018; Mostashari et al. 2013; Song et al. 2015), supercapacitors (Fu et al. 2019; Wang et al. 2016; Yun et al. 2019) and sensing (Joshi et al. 2019) applications.

4.5 Synthesis and Applications of Lignin-Based Metal Oxide Nanoparticles in Photocatalysis

In the recent decade (i.e. 2010–2020), water reuse is gaining global consideration due to the water inadequacy associated with climate change, inadequate access to clean/potable water assets, and increasing world population leading to a large volume of water demand (Hartley 2006; Ong et al. 2018). To overcome the problem of water scarcity, researchers are developing and using various kinds of materials

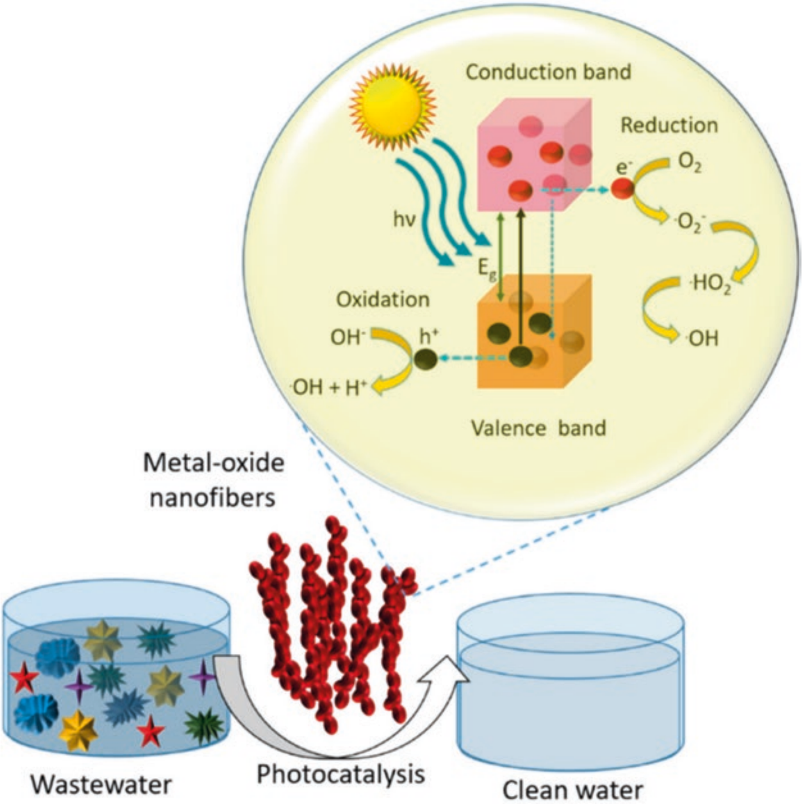

Fig. 4.5 Mechanism of photocatalytic activity utilizing metal oxide nanoparticles. (Reprinted with permission from MDPI (Mondal 2017))

for treating the contaminated water. In the recent research findings, the use of nanoparticles particularly derived from metal oxides has been reported for the removal of environmental pollutants. Figure 4.5 illustrates the mechanism of photocatalysis utilized by metal oxide nanoparticles for the degradation of organic pollutants. The metal oxide nanoparticles particularly zinc oxide and titanium dioxide based ones are of considerable interest as photocatalysts for the degradation of organic matter (Ong et al. 2018; Zhang et al. 2008; Zita et al. 2009).

4.5.1 Lignin-Based Zinc Oxide Nanoparticles

In recent times, zinc oxide nanoparticles have received abundant response due to a wide band-gap of 3.37 eV. zinc oxide is a semiconducting material having a large exciton binding energy (60 MeV) at room temperature. This large exciton binding energy is useful in various fields such as electronics, photoelectronics, and catalysis. In comparison with other photocatalysts, zinc oxide nanoparticles absorb light below 400 nm strongly and are cost-effective. The application of zinc oxide nanoparticles in photocatalytic research has received intensive interest because they effectively eliminate contaminants without causing additional damage to the environment.

For instance, sodium lignosulphonate was used successfully for the first time to synthesize hierarchical zinc oxide nanoparticle structures using the precipitation method (Miao et al. 2013a). The sodium lignosulphonate powder was firstly mixed with sodium hydroxide to make an aqueous solution. The aqueous solution of zinc acetate was prepared and added dropwise to the sodium lignosulphonate solution in an ice bath under stirring. Later, the reaction mixture was refluxed for 5 h at 80 °C followed by calcination to obtain sodium lignosulphonate-zinc oxide nanoparticles. The zinc oxide nanomaterials thus obtained displayed hexagonal wurtzite structure and a size range of 50–200 nm that was tuned by varying the amount of SL during synthesis. Three types of the morphology of zinc oxide nanoparticles namely nanoparticle-bar, nano-mesh-lamina, and quasi-nanosphere particles were obtained by controlling the amount of sodium lignosulphonate.

The zinc oxide nanoparticles were then tested for their photocatalytic activity against methylene blue dye. Zinc oxide possessed good photocatalytic degradation against methylene blue dye (nearly 100% degradation within 1.5 h), under a very low-power UV illumination of 12 watts, allowing the effective treatment of organic pollutants in wastewater. Another interesting study reported the utilization of sodium lignosulfonate for the synthesis of flower cluster-shaped zinc oxide microstructures via a facile hydrothermal method (Hao et al. 2015). During the synthesis, zinc nitrate salt was used as a zinc oxide precursor and was mixed with SL as a structure-directing agent in the presence of sodium hydroxide. The reaction mixture was transferred into a Teflon-lined stainless-steel autoclave and subjected to heating at 100 °C for 22 h in an oven. The precursor solution was then dried at 60 °C for 20 h. The as-synthesized zinc oxide-sodium lignosulphonate nanoparticles displayed flower clustered morphology, hexagonal wurtzite structure, and an extremely high surface area. The photocatalytic activity of nanoparticles was assessed against photocatalytic decolorization of methylene blue dye solution at room temperature. In addition, zinc oxide-sodium lignosulfonate nanoparticles showed exceptional stability even after three cycle of photodegradation**.**

In another interesting study, sodium lignosulfonate-assisted synthesis of zinc oxide was demonstrated following a facile precipitation method (Li et al. 2016a, b). The amount of SL used during the synthesis route was optimized to fine-tune the morphology and porous network in zinc oxide nanoparticles. The synthesized zinc oxide-sodium lignosulfonate nanoparticles exhibited nanoflake-array-flower morphology along with a specific surface area of 82.9 m^2/g. The synthesized zinc oxide nanoparticles were tested for their photocatalytic activity against methylene blue dye under UV light (6 W, 365 nm) illumination. The zinc oxide-sodium lignosulfonate nanoparticles showed good photocatalytic activity under low-power UV illumination (6 W). This activity was attributed to the nanoflake-array morphology and the presence of abundant pores in zinc oxide flakes. The low-cost, simple synthetic route, and high photocatalytic efficiency of the synthesized zinc oxide-sodium lignosulphonate nanoparticles made their application in wastewater treatment effective.

Another type of lignin i.e. lignin-amine was used as a template for zinc oxide nanoparticles synthesis using a solid phase method (Wang et al. 2014). Typically, for the synthesis of nanoparticles, zinc nitrate, sodium oxalate, and lignin-amine (1 g) were grounded for 15 min in a mortar separately. The grounded powders were then mixed and again grounded for another 15 min. The powder thus obtained was dissolved in deionized water and centrifuged. The precipitates were then dried for 12 h at 60 °C to obtain zinc oxide precursors. Lastly, these zinc oxide precursors were calcined for 2 h at different temperatures 400 °C zinc oxide/ lignin-amine(ZL4), 500 °C zinc oxide/ lignin-amine (ZL5), or 600 °C zinc oxide/ lignin-amine (ZL6) in a muffle furnace. Further, it was observed that by increasing calcination temperature average crystallite sizes also increased. The amount of LA was also varied (0.5 g zinc oxide/ lignin-amine (ZL-0.5) and 1.5 g (zinc oxide/ lignin-amine ZL-1.5)) during the synthesis process and calcined at 400 ° C. Among all the nanoparticles synthesized, ZL4 exhibited better UV or sunlight photocatalytic degradation ability for methyl orange than ZL5, ZL6 due to the presence of greater specific surface area. The photocatalytic potential of the nanoparticles was evaluated against methyl orange dye (20.0 mg/L). Under the UV light irradiation for 1 h, 99.26% degradation rate, and under solar radiation for 6 h, 96.48% degradation of methyl orange dye was achieved in the presence of ZL4 catalysts (Fig. 4.6). The results indicated the potential of the zinc oxide/ lignin-amine photocatalyst for dye pollutants removal.

Another study reported the use of aminated lignin as a template for the synthesis of zinc oxide nanoparticles using solid-state reaction (Feng et al. 2015). Firstly, a zinc carbonate precursor was prepared using zinc nitrate and sodium carbonate. This zinc carbonate was then reacted with aminated lignin to get zinc oxide-aminated lignin nanoparticles. The photocatalytic efficiency of zinc oxide-aminated lignin nanoparticles was checked against methyl orange dye and compared with pristine zinc oxide nanoparticles (without aminated lignin). The results of methyl orange degradation pointed out that the zinc oxide-aminated lignin nanoparticles possessed higher photocatalytic efficiency when compared with that of pristine zinc oxide due to smaller size and homogeneous size distribution. The zinc oxide-aminated lignin nanoparticles under UV light irradiation of 90 min showed a maximum degradation efficiency of almost 98% as compared to 75% for zinc oxide nanoparticles. These zinc oxide-aminated lignin nanoparticles showed consistent photocatalytic degradation efficiency even after three cycles of use suggesting their reusability. Figure 4.7 illustrates the mechanism of photocatalytic degradation of pollutants using the lignin catalyst.

In another interesting work lignin-based carbon/zinc oxide (LC/ZnO) hybrid composite was proposed using alkali lignin as a carbon source (Wang et al. 2017b). The lignin-based carbon /zinc oxide hybrid (containing well-dispersed zinc oxide nanoparticles on the lignin-based carbon nanosheet) showed outstanding photogenerated electrons and holes generation. Methyl orange and rhodamine B dyes were degraded (under the illumination of simulated solar light for 50 min)

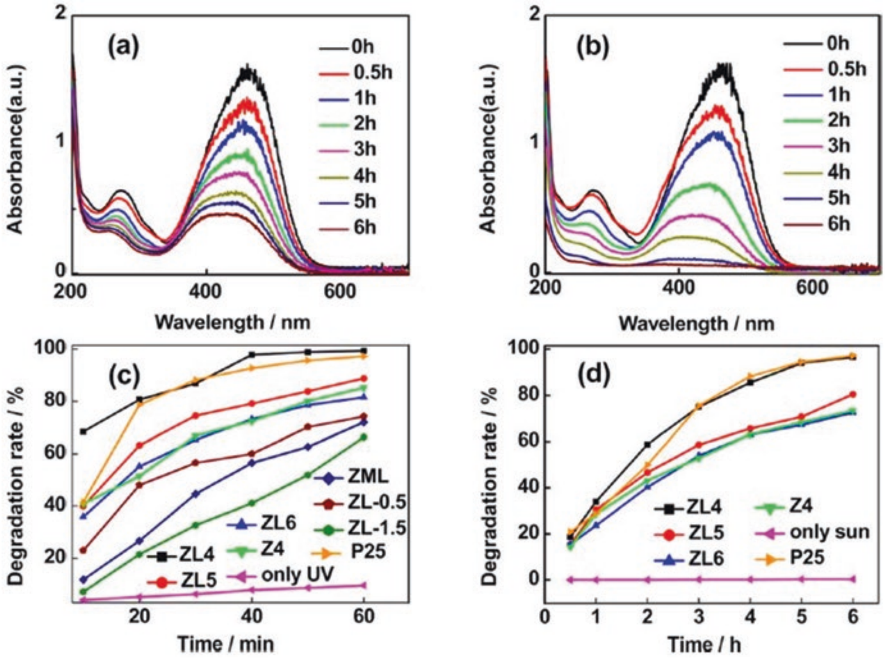

Fig. 4.6 Photocatalytic activity of zinc oxide nanoparticles (**a**) zinc oxide calcined at 400 ° C, (**b**) zinc oxide/ lignin-amine calcined at 400 ° C, under sunlight; degradation of methyl orange under (**c**) UV light and (**d**) sunlight at different time interval. (Reprinted with permission from American chemical society (Wang et al. 2014))

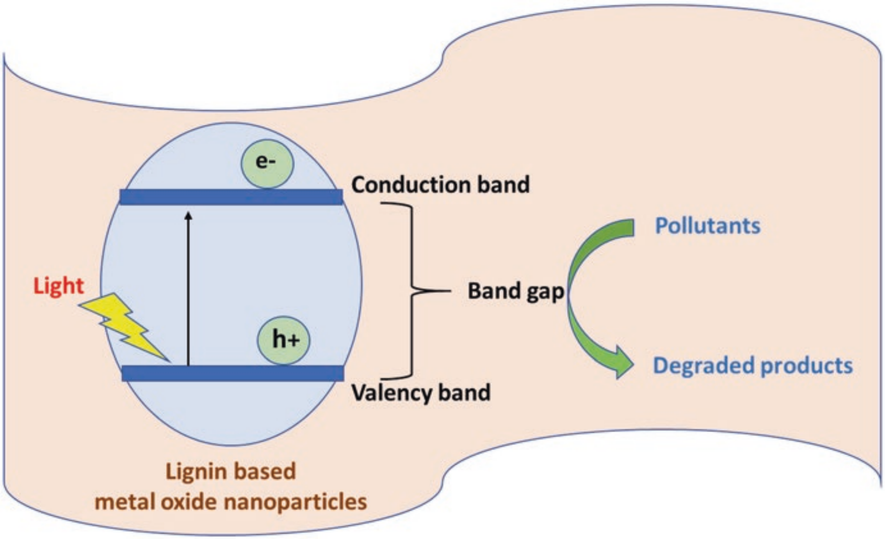

Fig. 4.7 Mechanism of photocatalytic degradation of pollutants using lignin-based metal oxide nanoparticles

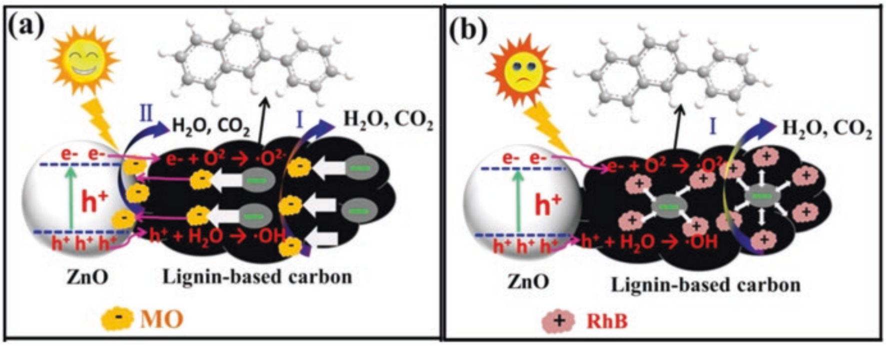

Fig. 4.8 Photocatalytic mechanism for the degradation of methyl orange and rhodamine B dyes by the lignin-based carbon/zinc oxide. (Reprinted with permission from Elsevier (Wang et al. 2017b))

using a lignin-based carbon /zinc oxide hybrid as a photocatalyst. The mechanism of photocatalytic degradation is demonstrated in Fig. 4.8. The lignin-based carbon / zinc oxide hybrid showed much higher photocatalytic activity when compared with pure zinc oxide nanoparticles.

The same authors later reported the synthesis of lignin-based carbon/zinc oxide (LC/ZnO) nanocomposites using a one-pot in-situ approach for utilizing lignin from paper pulping waste (Wang et al. 2017c). Alkali lignin was converted to quaternized lignin using sodium hydroxide solution and 3-chloro-2-hydroxypropyltrimethyl ammonium chloride while zinc nitrate was mixed into the sodium oxalate salt. Quaternized lignin powder was later added in various weights (0.5 g, 1.0 g, 2.0 g, 8.0 g) into the above reaction mixture to give the quaternized lignin /ZnC_2O_4 precursor. The obtained quaternized lignin/ZnC_2O_4 precursor was calcinated under a nitrogen atmosphere at 550 °C for 2 h. The resulting lignin-based carbon /zinc oxide nanoparticles were designated as LC/ZnO-1, LC/ZnO-2, LC/ZnO-3, LC/ZnO-4 having 0.5 g, 1.0 g, 2.0 g, 8.0 g of QL powders, respectively. Their photolytic activity was tested against MO dye that reached a maximum of 98.9% using LC/ZnO-2 nanoparticles under sunlight irradiation for 30 min. All of the synthesized LC//zinc oxide nanoparticles showed better photocatalytic activity than pure zinc oxide nanoparticles. The LC/ZnO-1 showed a slower photocatalytic rate than LC/ZnO-2, due to lower carbon in the nanoparticles. The LC/ZnO-3 and LC/ZnO-4 also showed slower photocatalytic rates than LC/ZnO-2 because of the high carbon content that led to the absorption of more light. The absorption of a large amount of light by the nanoparticles decreased the light irradiated onto the zinc oxide surface, which led to lower photocatalytic activity. This study suggested that the addition of lignin into zinc oxide nanoparticles enhances photocatalytic activity.

Among the metal oxide nanoparticles, copper oxide (CuO) which is an important semiconductor plays a very important role in photocatalysis owing to its low cost, good chemical/thermal stability, and non-toxicity (Liu et al. 2012; Meshram et al. 2012). To enhance the photocatalytic activity of metal oxide nanoparticles, the synthesis of copper oxide/zinc oxide (CuO/ZnO) nanocomposites hybrid was demonstrated using a solid-state grinding technique (Wu et al. 2017). Zinc chloride, sodium carbonate, and sodium lignosulphonate were firstly separately grounded and then again grounded after mixing for 30 min. Finally, the resultant reaction mixture was vacuum-dried at 60 °C to yield $ZnCO_3$- sodium lignosulphonate powder. Similarly, $ZnCO_3$-sodium lignosulphonate powder, copper chloride, and sodium hydroxide were first grounded separately and then transferred into an agate mortar with further grinding for another 30 min. The resulting reaction mixture was then vacuum-dried at 60 °C and further calcinated for 2 h in the air at 400 °C. The CuO/ZnO nanocomposites with different mass ratios of 0, 0.5, 1, and 2 g $ZnCO_3$-SLS were synthesized and denoted as CZ-0, CZ-0.5, CZ-1.0, and CZ-2.0, respectively. The photocatalytic efficiency of the CuO/ZnO nanocomposites samples were evaluated against congo red and rhodamine B dyes under visible light irradiation. Out of all, the CuO/ZnO nanocomposite, CZ-1.0 exhibited a 91.5% and 74.3% degradation efficiency for rhodamine B and congo red respectively under visible light irradiation for 240 min. The CZ-1.0 was found to be the best due to the higher surface area and suitable bandgap. The development of hybrid nanocomposites opens up new opportunities for their exploitation in wastewater treatment and energy storage applications.

In a similar report, hybrid metal oxide nanoparticles i.e. Fe_3O_4/C/ZnO composite was synthesized using lignin amine as a carbon source as well as a bridging ligand (Tian et al. 2018). The synthesized nanocomposite comprised of cubic spinel Fe_3O_4, carbon, and hexagonal wurtzite zinc oxide nanoparticles. The photocatalytic activity of Fe_3O_4/C/ZnO nanocomposite was evaluated for degrading methylene blue dye and antibiotic norfloxacin. The photocatalytic activity of Fe_3O_4/C/ZnO nanocomposite was later compared with Fe_3O_4 and ZnO nanoparticles under ultraviolet and visible light irradiation. Fe_3O_4 nanoparticles exhibited negligible photocatalysis while zinc oxide nanoparticles showed 70% methylene blue dye degradation. In comparison, the Fe_3O_4/C/ZnO nanocomposite showed 97% degradation efficiency for methylene blue dye, which was much higher than zinc oxide nanoparticles. It also showed a very stable catalytic performance (94%) even after a 5-cycle of reuse. The nanocomposite was further explored for photocatalytic degradation of antibiotic norfloxacin and an excellent photocatalytic activity was observed (97%). Owing to good performance and easy recovery, Fe_3O_4/C/ZnO nanocomposite had a good outlook in applications of water treatment. The excellent photocatalytic potential of these lignin-based zinc oxide nanoparticles can be used effectively used for the treatment of organic pollutants from the wastewater (Zhang et al. 2020).

4.5.2 Lignin Based Titanium Dioxide Nanoparticles

Titanium dioxide is the most effective photocatalyst since its discovery in 1791 (Hashimoto et al. 2005). It is widely used in various applications including environmental remediation and energy generation owing to its high photocatalytic

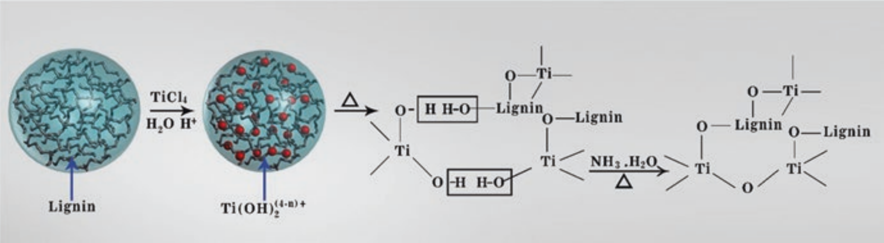

Fig. 4.9 Mechanism of formation of mesoporous utilizing lignin as a template titanium dioxide. (Reprinted with permission from Elsevier (Chen et al. 2016))

activity, high stability, low cost, and safety to the environment and humans (Chen et al. 2016; Gómez-Avilés et al. 2019; Srisasiwimon et al. 2018; Yu et al. 2018).

In order to utilize these unique properties, crude alkali lignin was used for the synthesis of mesoporous titanium dioxide nanoparticles utilizing the hydrolysis precipitation method (Chen et al. 2016). Titanium chloride was added dropwise to the aqueous lignin solution under constant stirring at 25 °C for 30 min. The pH of the reaction mixture was then adjusted to allow precipitation, which was later aged at room temperature for 10 h. The obtained nanoparticles were vacuum dried at 85 °C, then grounded to a fine powder, and finally subjected to calcination at 300–900 °C. The mechanism for the formation of mesoporous titanium dioxide nanoparticles utilizing alkali lignin as a template is demonstrated in Fig. 4.9.

The photocatalytic activity of the synthesized lignin-coated titanium dioxide nanoparticles was tested towards the degradation of phenol under UV light irradiation. The photocatalytic activity of synthesized nanoparticles was compared with titanium dioxide nanoparticles synthesized chemically without lignin under the same condition and the commercially available P25-titanium dioxide catalyst (produced by Degussa, as control). The titanium dioxide nanoparticles synthesized with lignin exhibited the highest photocatalytic activity compared to chemically synthesized and commercial ones. The lignin-coated titanium dioxide nanoparticles showed 97.9% photocatalytic degradation of phenol. In comparison, titanium dioxide nanoparticles without lignin and commercial titanium dioxide nanoparticles showed 76.3% and 86.3% phenol degradation, respectively. The better performance of lignin-coated titanium dioxide nanoparticles was due to the higher specific surface area and smaller grain size. This study also suggested the potential of lignin as a template for titanium dioxide nanoparticles synthesis.

A similar study was performed where titanium dioxide nanoparticles were modified by lignin using the ball milling technique (Nair et al. 2016). The ball milling of lignin and titanium dioxide nanoparticles together improved the contact angle between lignin and titanium dioxide nanoparticles. The ball-milled lignin-titanium dioxide nanoparticles were exploited for photocatalytic conversion of lignin to valuable phenolics and aromatic hydrocarbons under UV irradiation. The lignin decomposition using lignin-titanium dioxide nanoparticles was performed under natural conditions. The ball-milled lignin-titanium dioxide nanoparticles under UV exposure of 3–4 h showed a high yield of phenolic compounds from lignin suggesting the increased lignin depolymerization upon exposure to ball-milled lignin-titanium dioxide nanoparticles due to improved contact between lignin and titanium dioxide.

In another set of experiments, kraft lignin was used to modify titanium dioxide nanoparticles for enhancing the photoactivity of the titanium dioxide photocatalyst (Srisasiwimon et al. 2018). In the first step, titanium dioxide nanoparticles were prepared using titanium butoxide, isopropyl alcohol, and acetylacetone. Then the aqueous solution of kraft lignin was dropped into the titanium dioxide precursor solution leading to the formation of titanium dioxide/lignin photocatalyst. This titanium dioxide/lignin photocatalyst was used to convert lignin into high-value chemicals by the photocatalytic process under UVA irradiation. The photocatalytic activity of the synthesized photocatalyst was compared to pristine titanium dioxide nanoparticles. The titanium dioxide/lignin nanocomposite under UVA irradiation for 5 h showed the highest photocatalytic activity. The titanium dioxide/lignin photocatalyst showed a 40% lignin conversion as compared to only 20% conversion by pristine titanium dioxide nanoparticles. The titanium dioxide/lignin photocatalyst showed better photocatalytic activity due to the presence of carbon from lignin.

In the same year, carbon-modified titanium dioxide was synthesized using lignin as a carbon precursor for the photocatalytic degradation of acetaminophen under solar light (Gómez-Avilés et al. 2019). The titanium dioxide nanoparticles were prepared separately using titanium isopropoxide and isopropanol. These titanium dioxide nanoparticles were then modified by lignin. Briefly, titanium dioxide nanoparticles and lignin were suspended in sodium hydroxide solution, stirred for 10 min followed by sonication for another 10 min to form carbon-modified titanium dioxide nanoparticles. These carbon-modified titanium dioxide nanoparticles were then used to degrade acetaminophen photocatalytically under the illumination of a xenon lamp for 4 h. The 70% photocatalytic conversion of acetaminophen was achieved using the nanoparticles after 4 h illumination. These nanoparticles can be used effectively for photocatalytic applications.

Another type of lignin extracted from reed was used to modify titanium dioxide nanoparticles to form a hydrophobic titanium dioxide/lignin-based carbon nanofibers (TiO_2@CFs) composite with high photocatalytic efficiency (Dai et al. 2020). The TiO_2@CFs composites were characterized using FTIR (Fourier-transform infrared spectroscopy), SEM (Scanning electron microscopy), and EDS (Energy-dispersive X-ray spectroscopy) analysis showing uniform and firm coating of titanium dioxide nanoparticles on the surface of carbon nanofibers. The TiO_2@CFs composites showed enhanced photocatalytic efficiency due to good hydrophobicity and high electrical conductivity of carbon nanofibers. The photocatalytic activity of TiO_2@ composites was checked against methylene blue dye and was compared with the commercial titanium dioxide powder. The TiO_2@CFs composite showed 2.62- and 3.02-times improved degradation rate toward methylene blue under static state and xenon lamp irradiation for 30 and 15 min respectively when compared to the commercial one. Based on all compiled studies, it can be concluded that lignin-based titanium dioxide nanomaterials with unique structures are becoming a promising photocatalytic material.

4.5.3 Other Lignin-Based Metal Oxide Nanoparticles

The zinc oxide and titanium dioxide nanoparticles are the major photocatalysts in industrial and nanotechnological applications but apart from these two, few other metal oxide nanoparticles have also been utilized for photocatalytic applications.

For instance, cerium oxide nanoparticles were synthesized via the co-calcination method utilizing lignin as a template (Wang et al. 2015). The powder form of lignin sulphonate was added into the cerium nitrate ($Ce(NO_3)_36H_2O$) salt for further grinding and mixing on agate stone. The ground mixture was dried using a light lamp and calcined to generate carbon–cerium oxide composites. The synthesized composite was tested for photocatalytic desulphuration of a mixed solution of sulphuric acid and sodium sulphite using a simple device shown in Fig. 4.10. The results of the photocatalytic activity of carbon–cerium oxide composites were compared to cerium oxide composite without lignin. The carbon-cerium oxide

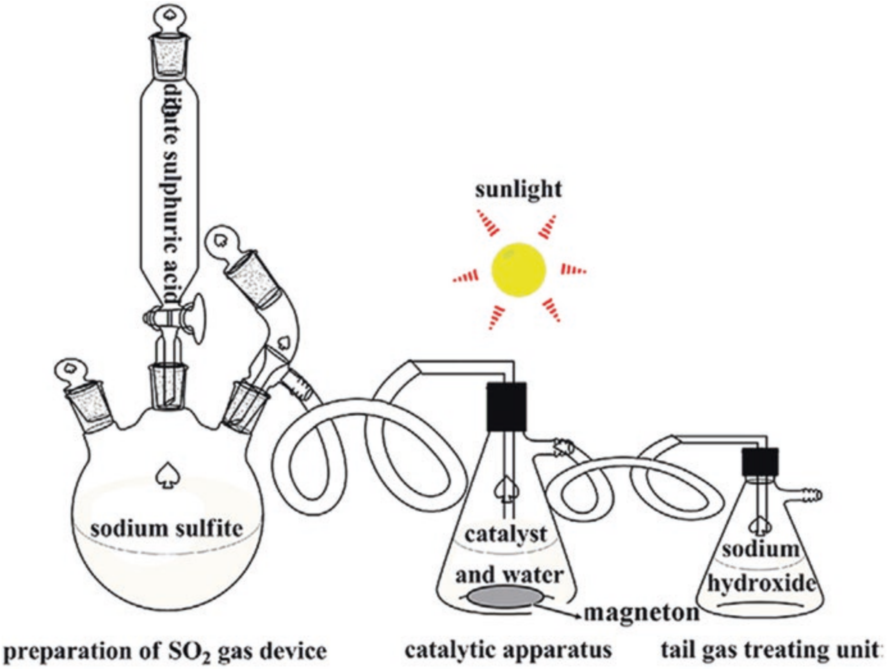

Fig. 4.10 Setup used for the detection of photocatalytic desulphuration. (Reprinted with permission from Elsevier (Wang et al. 2015))

composites showed maximum photocatalytic conversion, which was 51.89% higher due to higher surface area than that of cerium oxide nanoparticles without lignin. The synthesized carbon–cerium oxide composites showed great potential for the photocatalytic removal of SO_2 in actual life.

In separate research, copper oxide nanoparticles were synthesized using aminated lignin and utilized for photocatalytic degradations of methylene blue and methyl orange dyes (Wang et al. 2016). For the synthesis of the nanocomposite, the powdered salt of copper nitrate and sodium hydroxide were grounded separately and later mixed. The powdered aminated lignin was added into the above mixture and further grounded leading to the formation of black powder. This black powder was washed with deionized water and ethanol. The precipitates were dried in a vacuum oven at 60 °C for 10 h and calcined in a muffle furnace to generate copper oxide nanoparticles. For evaluating the photocatalytic activity, copper oxide nanoparticles were incubated with methylene blue and methyl orange dyes separately under UV light irradiation for 1.5 h. The copper oxide nanoparticles showed degradation of ~97.83% for MB and 66.76% for methyl orange under UV light irradiation. Overall, the synthesized nanoparticles showed good photocatalytic activity against both the dyes and the simple and low-cost synthesis methods showed great industrial feasibility. The summary of applications of lignin-based metal oxide nanomaterials in the different photocatalytic areas is tabulated in Table 4.1.

Table 4.1 Applications of lignin-based metal oxide nanomaterials in different photocatalytic area

S.No.	Nanocomposite material	Type of lignin	Targeted material	Efficiency	References
1.	Sodium Lignosulphonate--ZnO nanocrystallites	Sodium lignosulphonate	Methylene blue dye	100% degradation within 1.5 h	Miao et al. (2013a)
2..	Lignin amine-zinc oxide nanoparticles	Lignin-amine	Methyl orange dye	99.26% degradation under UV light irradiation for 1 h, and 96.48% degradation under solar radiation for 6 h	Wang et al. (2014)
3.	Zinc oxide - aminated lignin nanoparticles	Aminated lignin	Methyl orange dye	98% degradation under UV light irradiation for 90 min	Feng et al. (2015)
4.	Zinc oxide – sodium lignosulfonate nanoparticles	Sodium lignosulfonate (SL)	Methylene blue dye	96% degradation under UV light irradiation for 30 min	Hao et al. (2015)

(continued)

Table 4.1 (continued)

S.No.	Nanocomposite material	Type of lignin	Targeted material	Efficiency	References
5.	Zinc oxide – sodium lignosulfonate nanoparticles	Sodium lignosulfonate (SL)	Methylene blue dye	93% in 1.5 h under UV light irradiation	Li et al. (2016a, b)
6.	Lignin-based carbon/Zinc oxide hybrid	Alkali lignin	Methyl orange and rhodamine B dyes	99.9% degradation of MO in 30 min and 79.2% degradation of RhB in 50 min	Wang et al. (2017b)
7.	Lignin-based carbon/zinc oxide Nanocomposite	Alkali lignin	Methyl orange dye	98.9% degradation in 30 min	Wang et al. (2017c)
8.	Mesoporous titanium dioxide nanoparticles	Alkali lignin	Phenol	97.9% degradation	Chen et al. (2016)
9.	Ball milled lignin-titanium dioxide nanoparticles	-	Lignin-titanium Titanium dioxide to phenolics	–	Nair et al. (2016)
10.	Copper oxide nanostructures	Aminated lignin (AL)	Methylene blue and methyl orange dyes	97.83% and 66.76% Respectively, for MB and MO	Wang et al. (2016)
11.	Copper oxide/zinc oxide nanocomposites hybrid	Sodium lignosulphonate (SLS)	Congo red and rhodamine B dyes	91.5% and 74.3% degradation respectively, for RhB and congo red under visible light irradiation for 4 h	Wu et al. (2017)
12.	Fe_3O_4/carbon/zinc oxide composite	Lignin amine	Methylene blue dye	97% degradation	Tian et al. (2018)
13.	Titanium dioxide/ lignin photocatalyst	Kraft lignin	Lignin	40.28% lignin conversion under UV irradiation of 5 h	Srisasiwimon et al. (2018)
14.	Carbon-modified titanium dioxide nanoparticles	-	Acetaminophen	70% conversion in 4 h	Gómez-Avilés et al. (2019)
15.	Titanium dioxide@ lignin-based carbon nanofibers	Reed based lignin	Methylene blue dye	100% degradation in 24 min	Dai et al. (2020)

4.6 Conclusion

From recent studies, it has been found that lignin has been successfully used as a matrix for the development of metal oxide nanoparticles. The reported lignin-based metal oxide nanoparticles were found to be biocompatible, low cost, and easy to synthesize. The photocatalytic applications of these nanoparticles were found to be the most explored area among all the applications and have great potential in the future for environmental remediation. Lignin-based metal oxide nanoparticles were successfully used as photocatalysts for dye, drug, or biomass removal via their degradation. These photocatalytic applications have great promise towards environmental clean-up via the removal of pollutants from both water and air. Moreover, these lignin-based metal oxide nanoparticles can be explored for developing supercapacitors, gas sensing, and adsorption/absorption of dyes and pollutants. These nanoparticles can also act as antimicrobial agents, but these studies are less explored to date. There has been a significant improvement in the ease of synthesis of these metal oxide nanoparticles in the last few years. As such, investigation of the practical applicability of these metal oxide nanoparticles in industrial processes is in the early stage of research. Great scope for improvements in the synthesis protocol and industrial applicability of lignin-derived metal oxide-based photocatalysts exists for the future.

Acknowledgments All authors acknowledge the Department of Biotechnology (DBT), Govt of India for funding support. J.B. thanks the Department of Science and Technology (DST) for financial support, R.K. thanks CSIR and S. C. thanks ICMR for their senior research fellowships. R.K. and S.C. acknowledge the Department of Microbial Biotechnology, Panjab University for their Ph.D. registration.

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Chapter 5
Valorization of Sitosterol from Agricultural Waste as Therapeutic Agent

Ruchika and Ankit Saneja

Abstract The agro-industry generates huge amount of waste, which leads to major economic loss and pollution. Yet this waste can be considered as a 'golden mine' of bioactive compounds such as flavonoids, carotenoids, tocopherols, phytosterols, tannins, polysaccharides and dietary fibers. This waste can be converted into biofuels, nutraceuticals, oils and fibers for various sectors including cosmetics, food industry, pharmaceuticals, paper and energy. In particular, β-sitosterol is a well-known nutraceutical which can be extracted from side stream biomass of agroindustries, e.g. fruits pomace, seeds, seed oils, nuts and rum factories. β-sitosterol has been well tested at preclinical levels but clinical application is limited by sitosterol low bioavailability and half-life. Here we review the extraction, chemistry, pharmacology, and delivery of β-sitosterol to enhance its therapeutic efficacy.

Keywords β-sitosterol · Agro-industrial waste · Phytosterol · Nutraceutical · Conventional methods · Non-conventional methods · Pharmacological activities · Nanocarriers · Delivery system · Polymeric nanoparticles · Lipid nanoparticles

5.1 Introduction

Agricultural sector is one of the fastest growing economically important sectors across the world. It consumes almost 11% (1.5 billion hectare) of the total land (13.4 billion hectare) on earth including that area also which is not even suitable for the agriculture purpose. Engagement of agriculture and industrial sector results in the elevation of economic aspect of both the parts but also results in the huge waste production which is an environmental challenge (Fierascu et al. 2019). According to

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_5

recent report of Food and Agriculture Organisation (FAO), around 1/3rd (total – 1.6 billion tons) of the total food produced annually goes into the account of waste food. Around 45% of fruits and vegetables and 30% of the cereals are wasted per year, globally. It is also estimated that around 14% of the food is get disoriented before reaching even at the market level. This huge amount of wastage is needed to be managed urgently, as FAO estimated that this much amount of waste results in the emission of 4.4 gigatons of CO_2 (>8% of the total anthropogenic greenhouse gas emission) (FAO report, 2020).

Agriculture sector alone generates five million metric tons of biomass annually and this much of wastage if not managed can turns out with the huge amount of pollution, economic and environmental loss. Damping/composite of this kind of waste results in the emission of harmful gases that have adverse effect on the eco-system (Ravindran et al. 2018). Sustainable methods are required to be developed for the proper exploitation of agro-industrial residue. In developed countries, conversion of waste to energy is become a regular practice but developing countries are lacking behind due to some economic issues.

The waste/ residues from the agro industries (fruit pomace, pulp, stems, seeds, husk, peel etc.) are not waste in the real sense. These can be utilized in various sectors such as cosmetics, biofuel, and bio-energy, bio-composite, animal feed, pharmaceutics, food industry and as functional food (Fierascu et al. 2019) in various forms after proper processing and treatment. Sustainable management of this agro-industrial residue/side streams can help in transforming it into main stream products (Beltrán-Ramírez et al. 2019). In order to by-pass the economic and environmental loss, various strategies have been applied and are still developing to bring out best from the worst. There are numbers of researches and review articles which gives the idea of sustainable management of bio-waste by using various techniques as it is filled with unique and diverse potential which can be exploited to develop valuable products and biofuels (Asl and Niazmand 2020; Beltrán-Ramírez et al. 2019; Fierascu et al. 2019).

Phytochemicals are the plants primary or secondary metabolites which exhibit wide range of biological activities and have the potential to fight against deadly diseases. The bio-waste/ biomass, result of agro industries, are the hub of potent therapeutic agents and can be a potential source for the extraction of biologically active phytochemicals with low inputs and higher output. They are rich in functional phytochemicals particularly antioxidants, phenolic compounds, carotenoids, tocopherols, tannins, polysaccharides, dietary fibres and phytosterols (Fierascu et al. 2019); In this regard, β-sitosterol, a natural dietary micronutrient belongs to the family of phytosterols and can be ubiquitously found in most of the plant species especially in seeds and nuts but not synthesized by animal body (Babu et al. 2020). It can be extracted from biowaste of agro-industries namely, fruits seeds (da Silva and Jorge 2017), strawberry calyx (Sallam et al.), watermelon waste (El-Attar et al. 2015) and spruce biomass (Kreps et al. 2017). Beta-sitosterol has several therapeutic properties such as anti-diabetic (Babu et al. 2020), anti-oxidant (Baskar et al. 2012), anti-inflammatory (Paniagua-Pérez et al. 2017), anti-cancer (Wang et al.

2020), hepatoprotective (Yin et al. 2018) and also used clinically to treat patients having high cholesterol health issue (Richard 2008).

This book chapter gives the overview of various techniques used for the extraction of β-sitosterol from agro-industrial waste, its therapeutic uses and finally the implications of delivery systems for enhancing its therapeutic efficacy.

5.2 Extraction of Beta-Sitosterol from Agro-Industrial Waste

Agro-industrial waste represents the waste generated from the various sectors related with agriculture and forestry such as livestock, dairy industry, food, fruit and beverage industry and from agriculture itself in the form of pomace, seeds, cakes, husk, fibres, stems and leaves. The centre of attraction of agro-industrial waste material is its enormous production and valuable products that can be generated through its proper and sustainable processing (Fig. 5.1) (Fierascu et al. 2019). In

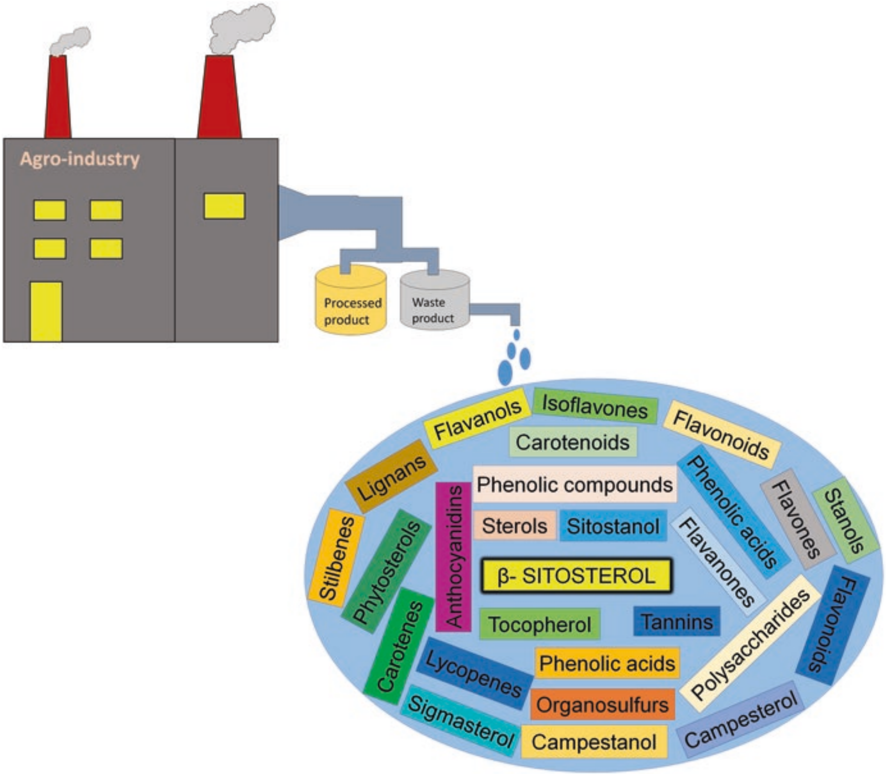

Fig. 5.1 Phytochemicals occurring in agro-industrial waste biomass. Bioactive agents mainly include phenolic compounds, tannins, anthocyanins, phytosterols, flavonoids, carotenoids, organosulfurs, polysaccharides and dietry fibers, which can act as natural therapeutic agents

India, around 350 million tonnes of waste is generated every year (Pappu et al. 2007). It is reported that around 673 million tonnes of waste is generated from rice agro forest industry in the form of rice straws, 709 million tonnes from wheat agro forestry (Fierascu et al. 2019) and around 209 million tonnes from olive industry (Nunes et al. 2016). Such a large amount of agro industrial waste if not used or managed properly than it can lead to major economic and environmental problems.

β-sitosterols is a phytosterol can also be extracted from the waste generated from fruit and oil industries (da Silva and Jorge 2017; Karaoglu et al. 2020). There are various studies which have been reported for the recovery of β-sitosterol from biowaste (Attard et al. 2015; Karaoglu et al. 2020; Rezende et al. 2018; Sallam et al.). For instance, in a recent study bioactive components extracted from agro-industrial waste of apple and guava seed oil contains highest amount of β-sitosterol which was 4.267 and 4.376 g/kg respectively. Besides β-sitosterol, these seed oils were also rich in EFA (linolenic acid) and phenolic compounds (da Silva and Jorge 2017). Likewise, β-sitosterol can also extracted from strawberry calyx (Sallam et al.), *Picea abies* waste biomass (Kreps et al. 2017), watermelon waste (El-Attar et al. 2015), sunflower oil waste (Karaoglu et al. 2020), sugarcane waste, sugarcane wax (Attard et al. 2015) and buckthorm pomace (Tsogtoo et al. 2020) (Table 5.1) by utilizing various extraction techniques.

5.2.1 Techniques for Extraction of Beta-sitosterol from Agro-Industrial Waste

There are various techniques which can be utilized for extraction of bioactive components from agro-industrial waste and choosing an appropriate technique in order to get maximum out of it is of crucial importance. These techniques can be broadly categorized in to conventional extraction methods (CEM) and modern extraction techniques (MET) (Fig. 5.2). Conventional extraction methods (CEM) include the exploitation of organic solvents on a large scale which have their own environmental and health hazards. Soxhlet extraction, hydro-distillation, percolation, reflux heating and maceration techniques comes under the area of conventional extraction method. Usage of large amount of organic hazardous solvents (hexane, ichloromethane, petroleum ether, ethanol, methanol and methyl chloride) and time consumption are the main disadvantages of onventional extraction techniques s (Fierascu et al. 2019; Sasidharan et al. 2018). In order to overcome these disadvantages, modern methods are introduced in the area of extraction. Non-conventional method includes extraction techniques namely, pulsed electric field assisted extraction (PEFA), enzyme-assisted extraction (EA), micro-wave assisted (MWA) extraction, ultrasound assisted (UA) extraction, supercritical fluid (SCF) extraction, pressurized liquid (PL) extraction and hydrotropic extraction (HT). All these extraction techniques incorporate the limited utilization of organic solvents and are also less time consuming (Easmin et al. 2015). Phytosterol extraction is mostly

Table 5.1 Recent representative studies conducted for the extraction of β-sitosterol from agro-industrial biomass

S. No.	Plant	Method of extraction/ detection	Quantity of β-Sitosterol obtained	References
1	Seed oils of Apple Orange Guava Papaya Strawberry Melon Mangaba Mango Citron Komquat Passion fruit Tomato Grape	Gas chromatography of previously saponified oil sample	4.267 g/kg 1.469 g/kg 4.376 g/kg 3.069 g/kg 2.986 g/kg 2.102 g/kg 3.471 g/kg 1.447 g/kg 1.325 g/kg 1.176 g/kg 1.386 g/kg 1.697 g/kg 2.508 g/kg	da Silva and Jorge (2017)
2.	Norway spruce (*Picea abies*) waste biomass	Hexane extraction and flash chromatography	3.9–6.8%in bark	Kreps et al. (2017)
3.	Watermelon waste	Methanolic extraction and chromatography	560 mg/3.3 g fraction	El-Attar et al. (2015)
4.	Sugarcane waste leaves bagasse	Super-critical fluid extraction quantified by gas chromatography	623.4 ± 144.9 μg/g 115 μg/g	Attard et al. (2015)
5.	Sea buckthorm pomace	Oil in water emulsion	36.5 mg/g	Tsogtoo et al. (2020)
6.	*Hippophae rhamnoides* L. seeds	Super critical fluid extraction	0.31 mg/g	Sajfrtová et al. (2010)
7.	*Pouteria lucuma* seed oil	Gas-chromatography-mass-spectrophotometry	851.49 ± 1.29 mg/100 g	Guerrero-Castillo et al. (2021)
8.	Olive pomace	Super-critical fluid extraction	198.9 ± 9.9 mg/100 g	Difonzo et al. (2021)

performed by the utilization of supercritical fluid, micro-wave assisted, enzyme-assistedand pulsed electric field assisted extraction methods (MS et al. 2018). Although various eco-friendly as well as economically friendly solvents (natural deep eutectic solvents, deep eutectic solvents (DES), ionic liquids, surfactants and terpenes) (Huguet-Casquero et al. 2020) and techniques (pressurized liquid, super-critical fluid, micro-wave assisted, ultrasound assisted and high voltage electric discharge (HVED)) (Galanakis 2015; Puértolas and Barba 2016) are developed but still there is a need to explore more about the eco-friendly, high yield and less expensive methods to be develop for the extraction of bioactive components from bio-waste.

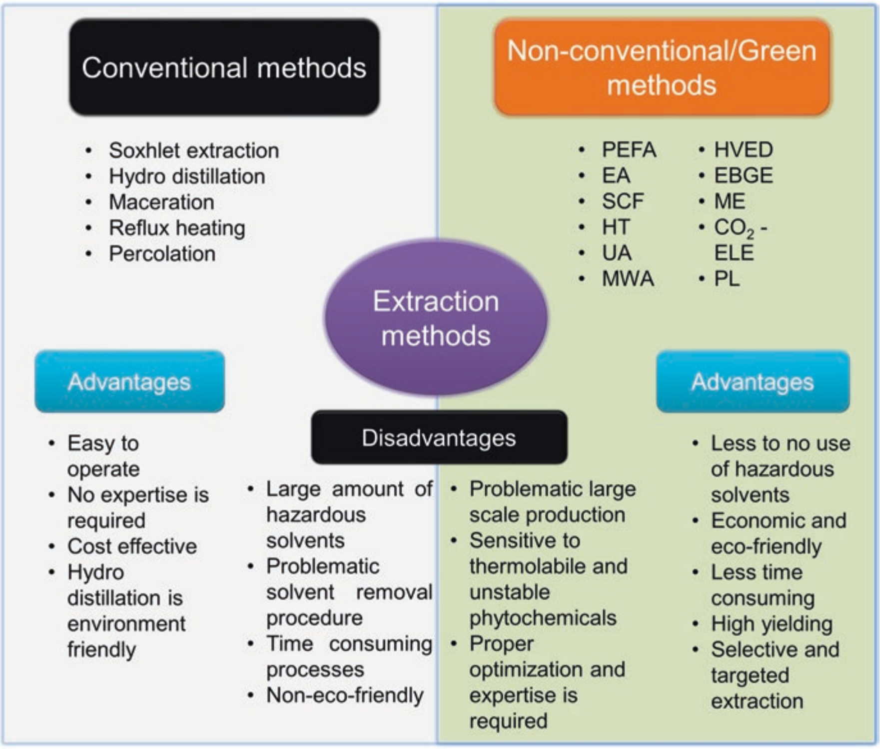

Fig. 5.2 Extraction methods, their costs and benefits. Natural organic molecule extraction methods can be categorized into conventional and non-conventional ones. Conventional methods provides an ease of operation, whereas, non-conventional methods includes utilization of modern techniques. *PEFA* Pulse electric field assisted extraction, *EA* Enzyme-assisted extraction, *SCF* Super critical fluid assisted extraction, *HT* Hydrotropic extraction, *UA* Ultra-sound assisted extraction, *MWA* Micro-wave assisted extraction, *HVED* High voltage electric discharge extraction, *EBGE* Emulsion based green extraction, *ME* Membrane extraction, CO_2*-ELE* Carbon-dioxide expanded liquid extraction, *PL* Pressurized liquid extraction

Recently, Tsogtoo and his colleagues reported the emulsion based green extraction (EBGE) of β-sitosterol and carotenoids from *Hippophae rhamnoides* (buckthorn) pomace (Tsogtoo et al. 2020). They also compared efficiency of emulsion based green extraction method with that of conventional extraction methods and concluded that emulsion based green extraction method is more advantageous in derivation of β-sitosterol and carotenoids. Extraction of fatty acids, phytosterols and terpenoids via supercritical fluid extraction method is evidenced to be high yielding as compared to conventional extraction method (soxhlet extraction using hexane).

Membrane filtration is another technique that can also be utilized in the extraction of bioactive phytochemicals from bio-waste. This technique involves the utilization of membrane filters of varying sizes (macro-filtration, ultra-filtration and nano-filtration) depending upon the average molecular weight of the targeted phytochemical. Filtration of particular type of bioactive component depend upon the nature (hydrophobic/hydrophilic) of membrane and extracting molecule, and also depends upon the interaction between the membrane material and phytochemical, molecular solubility, and polarity resistance. Most commonly used membranes are of polysulfone (MW 50–100 KDa and 10–25 KDa), composite fluoropolymer and polyether sulfone (both utilized for ultrafiltration of molecules having size range between 1–2 KDa) (Socaci et al. 2019). In comparison with conventional extraction method, membrane extraction (ME) approach possesses certain advantages, particularly cost effective, environment friendly, easily accessible to pilot scaling, versatility and moderate operating conditions which makes it a superior than conventional ones.

CO_2-expanded liquid extraction (CO_2-ELE) is a kind of new born extraction method which is not much explored in the area of extraction. This method involves the utilization of CO_2 pressurized and volumetrically expanded solvents, results in the more efficient solvent extraction method as compressed gas and expansion of solvents changes its physical and chemical attributes. This method also reduces the utilization level of toxic organic solvents up to 80%. Villaeneuva and co-workers demonstrated the extraction of phytosterols via CO_2-ELE method employing ethyl-acetate as green solvent (non-toxic, economically as well as environment friendly) (Vásquez-Villanueva et al. 2019).

As modern extraction methods solves the problem of low yield, long time consuming processes, non-selective extraction and organic solvent utilization but on pilot scale, these techniques somewhere becomes expensive, need optimization, maintenance and also become high energy consuming (Easmin et al. 2015). Moreover, like β-sitosterol, there are n numbers of phytochemicals that has the ability to fight against deadly diseases of mankind, but remained unexplored due to their scarcity and can be obtained from the sustainable utilization of agro-industrial waste. Therefore, it becomes the necessity of this era to develop new extraction techniques with fewer drawbacks.

5.3 Chemistry and Pharmacology of Beta-sitosterol

β-sitosterol is one of the most abundantly found phytosterol among rest of the plant sterols. It is more likely to present in lipid enriched plant foods such as in nuts, seeds, olive oil and legumes (Albuquerque et al. 2020; Bondioli et al. 2021; Karaoglu et al. 2020). Moreover, it is also present in various microalgal species such as haptophytes (in total amount of sterols, 23% to 73% is β-sitosterol in *Prymnesiophyceae*), *Bacillario phyceae*, diatome (*Asterionella glacialis* has 95% of β-sitosterol of total sterols) and chlorophyte (*Chlorophyceae, Prasinophyceae*) (Le Goff et al. 2019). Certain vegetables (beet root, cauliflower, brussels sprouts) and fruits (Banana, apple, and orange, strawberry, *Solanum xanthocarpum*) are also having good amount of β-sitosterol (Di Battista et al. 2018; Khanam and Sultana 2012). It is generally recognized as safe with fewer side effects and has very long history of being used as functional food and in pharmaceuticals, as β-sitosterol is used in numbers of herbal formulations, usually synthesized for the treatment and prevention of hypercholesterolemia, prostatic cancer (Prasad 2020), coronary diseases (Løvik et al. 2008) and prostatic hyperplasia like diseases, with an exception of 'phytosterolaemia' (Paniagua-Pérez et al. 2005). Phytosterolaemia, also known as sitosteroleamia, which is a sparse, inherited and recessive autosomal genetic disorder, characterised by deposition of sterols in all tissues of the body tuberous and tendon xanthomas, and premature atherosclerosis in arteries, except brain. But this condition can be managed by taking low cholesterol and low phytosterol diets (Llop-Talaveron et al. 2020). Incorporation of sitostanol in the diets also proved to be beneficial as it reduces the absorption of the cholesterol and phytosterols most probably due to the competitive inhibition in the absorption of sterols (Mantovani and Pugliese 2021).

5.3.1 Chemistry of Beta-sitosterol

β-sitosterol is a steroidal compound present in the cell membrane of almost all plants and provides structural flexibility, permeability and fluidity to the membrane. It is an optically active compound having similar structure with that of animal steroidal compound cholesterol ($C_{27}H_{46}O$) except an extra ethyl group attached at C-24 position. It has chemical formula of $C_{29}H_{50}O$ and IUPAC name 3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-ethyl-6- methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro1H-cyclopenta[a]phenanthren-3-ol (Gupta 2020). In comparison with other phytosterols (stigmasterol, campesterol and sitostanol) present in the plants, it is the saturated form of stigmasterol, as stigmasterol ($C_{29}H_{48}O$) has double bond at C-22 position, whereas, campesterol possess a methyl substituent at C-24 position unlike ethyl substituent in β-sitosterol chemical structure (Fig. 5.3). In case of stanols, sitostanol is the saturated form of β-sitosterol, there is no double bond. β-sitosterol is a white colored powdered compound having waxy texture with a characteristic aroma. It may found in three different forms depending upon the water molecules attached with it as, monohydrated, hemihydrated and anhydrous form (Babu and Jayaraman 2020; Saeidnia et al. 2014). β-sitosterol monohydrated crystals has needle shaped structure whereas, anhydrous crystals has platy-like shape (Christiansen et al. 2002). β-sitosterol is also known by many other names such as sitosterin, cinchol, (3β)-stigmast-5-en-3-ol, α-dihydrofucosterol, cupreol, quebracol, rhamnol and 22:23-dihydro stigmasterol (Babu and Jayaraman 2020).

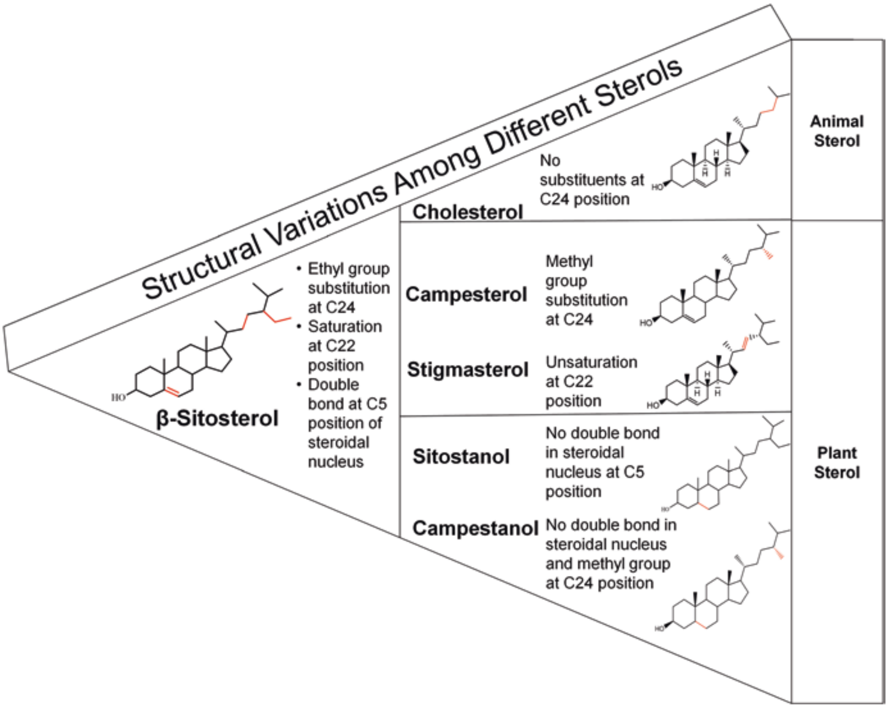

Fig. 5.3 Diagramatic illustration of structural variations among different animal and plant sterols. β-sitosterol, campesterol, stigmasterol, sitostanol and campestanols are susbstantial type of phytosterols, whereas, cholesterol is found only in animals. These sterols have a common cyclopentanoperhydrophenanthrene ring skeleton and differ only in the side aliphatic chain attached at C17 position of the ring

5.3.2 Pharmacological Activities of Beta-sitosterol

β-sitosterol is a natural dietary micronutrient which possess number of health nurturing properties, e.g. anti-cancer, anti-diabetic, anti-hyper lipidemic, anti-inflammatory, antioxidant, anti-bacterial immunomodulatory, antinociceptive, and anxiolytic, One factor which bring it in the glare is its antagonist activity against hypercholesterolemia/hyperlipidemia which in results leads to the prevention of coronary heart diseases, angiogenic, diabetes and non-alchohalic fatty acid disease (Abbas et al. 2019; Gumede et al. 2020; Ododo et al. 2016; Park et al. 2019). Several research studies demonstrate its blood cholesterol lowing effect in *in-vivo* models. Most possible mechanism behind β-sitosterol hypolipidemic effect is its resemblance with the cholesterol structure which creates a competition between these two (cholesterol and β-sitosterol) both at binding sites and in absorption mechanism (Olaiya et al. 2015; Racette et al. 2010) Moreover, the decrease in the blood cholesterol profile is dependent upon the dose of the phytosterol incorporated in the diets of the test organism (Olaiya et al. 2015). USFDA also assigned β-sitosterol as a

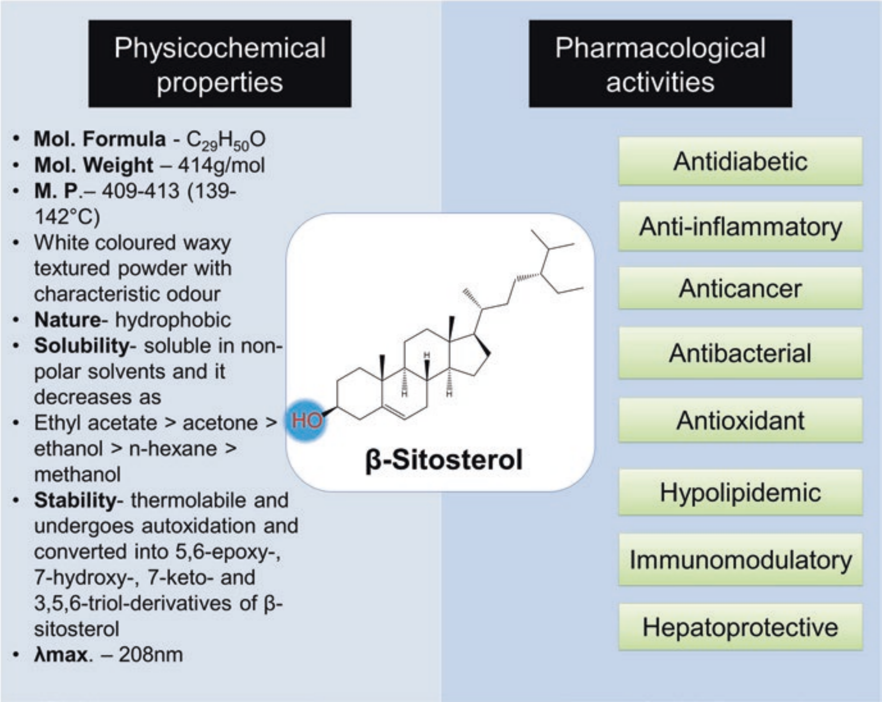

Fig. 5.4 Physicochemical properties and pharmacological activities of β-sitosterol. It is a hydrophobic phytosteroid having hydroxyl group (-OH) at 3C position in the steroidal nucleus, where, it provides an ease of modification, moreover, its steroidal nucleus imparts the capability of showing competitive inhibition in cholesterol absorption

treatment drug for the prevention of heart diseases targeted through hypercholesterolemic or hyperlipidemic effects (Retelny et al. 2008). Some of the prominent biological activities are reviewed below (Fig. 5.4).

5.3.2.1 Antioxidant

Imbalance between free radical generation (reactive oxygen and nitrogen species) and free radical scavengers inside the body usually associated with the many health challenging diseases such as diabetes, cancer, immune and neurodegenerative disorders and were not. Therefore, targeting this pathway may conclude in the prevention of life threatening diseases (Liguori et al. 2018; Oguntibeju 2019). β-sitosterol also acts as an mild anti-oxidant and helps in the prevention of diabetes and cancer like deadly diseases. There are many studies which are in the favour of β-sitosterol anti-oxidant nature and reported it’s mild to moderate effects in lowering lipid peroxidation in colonic and hepatic tissues. This also helps in elevation of endogenous anti-oxidants particularly superoxide dismutase (SOD), glutathione reductase, glutathione peroxidase and glutathione S-transferase and refurbishing of non-enzymatic anti-oxidants namely, vitamin C and E (Baskar et al. 2012). In another study of Yin et al. β-sitosterol exorbitantly elevates the level of enzymatic anti-oxidants (SOD, CAT and GSH) and helps in the suppression of lipopolysaccharide induced hepatic injury in mice model (Yin et al. 2018).

5.3.2.2 Antidiabetic

Diabetes mellitus (type 2 diabetes) is metabolic disarray which is conventionally identified by hyperglycaemic condition. It is the most frequent type of diabetes as it represents about 90% cases among all types of diabetes suspects (Inzucchi et al. 2012). Recently, International Diabetes Federation, Diabetes atlas in its ninth edition 2019 reported that almost 463 million adults are living with diabetes and it will rise to 700 million by the year 2045 which is a huge number. β-sitosterol is a natural compound which has well documented evidence of being anti-diabetic. There are several previous and recent studies which demonstrated the antidiabetic effect of β-sitosterol along with possible mechanisms. There are many pathways that can be targeted in order to prevent or treat patients suffering from diabetes mellitus (Babu et al. 2020; Ramalingam et al. 2020; Saravanan et al. 2020). One such approach is by targeting carbohydrate metabolism. Saravanan et al. reported that, there is a significant increase in the carbohydrate metabolic enzyme (glucose-6-phosphate, PEPCK and glycogen phosphorylase) activity in high fat diet and sucrose induced diabetic wistar rats after treating with 20 mg/kg body weight of β-sitosterol (Saravanan et al. 2020). Another approach is to increase the insulin sensitization, for instance, in a recent study, it is demonstrated that in high fat diet (HFD) and streptozotocin induced diabetic rats, there is a significant decrease in the blood glucose levels, increment in the insulin levels, normalization of body weight, Hb and glycated Hb levels, amelioration of expression levels of PPARγ and GLUT4 proteins on oral administration of 15 mg/kg body weight of β-sitosterol for 30 days. Moreover, histopathology of this study also revealed the anti-oxidant nature of β-Sitosterol (Ramalingam et al. 2020). Further Babu *et al*, reported the regulation of post- receptor insulin signal transduction through β-sitosterol in diabetic rats and concluded that β-sitosterol can acts as potential phyto-medicine in order to manage type 2 diabetes with the dose efficiency of 20 mg/kg body weight for 30 days (Babu et al. 2020). As, it regulates the IRS-1/Akt pathway by attenuating the phosphorylation of serine in IRS-1, upregulation of m-RNA expression of IR, IRS-1, Akt, β-arrestin-2, GLUT-4 and AS160.

5.3.2.3 Anti-cancer

Cancer is a non-communicable, death dealing disease which becomes the foremost cause of mortality world-wide. World Health Organisation (WHO) estimated and reported that in 2018, cancer is the mainspring before 9.6 million deaths worldwide, in which, lung cancer contributes around 1.96 million deaths, colorectal cancer 86,200 deaths, stomach cancer 7,83,000 deaths, liver cancer estimated about 7,82,000 and breast cancer contributes 6,27,000 deaths around the world. Numerous strategies such as chemotherapy, radiotherapy or surgery can be utilized for its treatment. However, one of the major limitations of chemotherapy isis multi drug resistance, reoccurrence and side effects with treated therapeutic drugs. Therefore, the exploitation of novel methods (plant derived natural compounds) which has lesser side effects, multiple pathways targeting efficacy, safe and non-toxic are comes into the limelight (Rajavel et al. 2017). Various small molecules of natural origin are already identified and are utilized as a better treatment for cancer in particular; vinblastin, pactilaxel, etoposide, curcumin, docetaxel, sulforaphone, camptothecin, teniposides (Rajavel et al. 2017). There are several studies which gives the evidence of β-Sitosterol anti-oncogenic activity. β-Sitosterol exhibits anti-cancer activity by targeting various cell regulatory pathways in variant cancer cell lines such as Dalton's Lymphoma Ascites (DLA) tumour cell line (Lekshmi and Swapna 2020), AGS adenocarcinoma cells, non-small cell lung cancer cell line (A549) (Rajavel et al. 2017), Human breast adenocarcinoma cells (MCF-7) (Pradhan et al. 2018), hepatoma cell lines (Huh7 and HepG2) (Vo et al. 2020), HCT116 human colorectal cancer cell line and also in *in-vivo* models (Wang et al. 2020). Numerous scientific reports suggested the mechanism behind β-sitosterol anti-oncogenic activity is inhibition of cell proliferation and induces cell death through cell cycle arrest (Awad et al. 2005; Awad et al. 2001; Vo et al. 2020), induction of apoptosis by elevating caspase-8 activity, FAS ligand levels (Awad et al. 2007), inhibition of breast cancer resistence protein (BCRP) expression, by interfering in p53-MDM 2 interaction (Wang et al. 2020), increased expression of AMPK, PTEN, caspase3/7 activity, G2/M phase cell cycle arrest (Rajavel et al. 2017), activation of caspase 3, 9 activity and disruption of β-tubulin (Pradhan et al. 2018). β-sitosterol has the potential to reverse the effect of multi drug resistance in colorectal cancer which is the main reason behind the failure of all cancer therapies (either chemo, radio or natural molecule based). Wang *et al* reported the re-establishment of oxaliplatin drug sensitivity utilizing beta-sitosterol against human colorectal cell lines and also in *in vivo* model (BALB/c mice) through the inhibition of BCRP expression, interfering in p53-MDM2 complex formation which leads to the translocation of p53 to the nucleus and ultimately leads to the suppression of NF-κB pathway. Initiation of this pathway is necessary for the expression of BCRP protein. This study also reported the synergistic anti-cancer effect of oxaliplatin- β-sitosterol combination in xenografted animal model (Wang et al. 2020). Further, Pradhan *et al* demonstrated the β-sitosterol binding efficiency with tubulin (β_{II} and β_{III}) via *in vitro* and *in silico* both, which results in the disruption of cytoskeleton of the cells and also chromosomal organisation. Tubulin is a protein that associates together in the form of cylinders to form cytoskeletal of the cell, named as microtubulin. It has two subunits, alpha and beta, beta subunit possesses almost 8 isotypes which are tissue specific and many of them are mostly associated with the cancer drug resistance (Pradhan et al. 2018). This study also concluded the anti-metastatic nature of β-sitosterol in breast cancer cell line (MCF-7).

β-sitosterol also reduces the cancer cell proliferation by targeting apoptosis inducing pathways such as AMPK and PTEN. AMPK (AMP-activated protein kinase) and PTEN (phosphatase and tensin homolog) upon activation regulated apoptosis and inhibit cancer cell proliferation via various signalling pathways such as mTOR, Akt, COX2 which finally leads to the activation of p53 and p21 proteins and pro-apoptotic protein. Moreover, this can also supresses the expression of Hsp90 protein. This phytosterol demonstrated to inhibit gastric tumours in *in vitro* as well *in-vivo* (xenograft mouse model) models without any toxic effect via apoptosis by mediated AMPK and PTEN signalling pathways (Shin et al. 2018). β-sitosterol present in the leaf extract of plant *Grewia tiliaefolia* inhibits the proliferation of lung cancer cell line (A549) via cell cycle arrest at G2/M phase and also shows non-toxic effect on normal lung cell lines (L132 and PBMC) (Rajavel et al. 2017).

Along with anti-oxidant, hypolipidemic effect, anti-oncogenic and anti-diabetic like biological activities, β-sitosterol also exhibits anti-inflammatory, immunomodulatory, cardiac, renal, osteo-protective, anti-pyretic and anti-bacterial properties (Table 5.2). Despite having vast functional attributes, β-Sitosterol is still considered as an orphan micronutrient and has mild to moderate clinical efficacy. So, further critical investigations are needed at both pre-clinical and clinical levels.

5.4 Beta-Sitosterol Delivery Systems

Beta-sitosterol is accredited as an approved agent for treatment for hypercholesterolemia by USFDA and considered as a generally recognized as safe (GRAS). Commercially, β-sitosterol can be synthesized or derived from vegetable oil distillates, wood pulp and tall oil. There are also certain commercial suppliers of β-sitosterol in the form of mixture of phytosterols, stenols, esterified sterols and stenols under various brand names such as Phytopin®, Benecol®, Vegapure®, Multibene®, Beta-sitosterol, Cardio Aid™, Prolocol™, Corowise™, Riducol™, CardiaBeat™ (Richard 2008). There is no doubt in designating β-sitosterol as functional food but still it is treated as an orphan nutraceutical with limited clinical efficacy. The main hurdle in the therapeutic efficacy of β-sitosterol is its hydrophobic nature, poor stability, solubility, absorption and fast degradation (Bilia et al. 2017).

Metabolism of β-sitosterol was described very earlier, further its pharmacokinetics, bioavailability and metabolic turnover studies has been conducted on both *in-vivo* (rats and beagel dogs) as well as on health human suspects by various research groups. All these studies ended up with the conclusion of its poor absorption and lesser bioavailability (Duchateau et al. 2012; Ikeda and Sugano 1978; Ritschel et al. 1990; Salen et al. 1970). Slower rate of esterification of β-sitosterol in comparison with that of cholesterol may be one of the possible reason of its poor absorption moreover it also has shorter half-life and fast excretion rate. Another reason of its

Table 5.2 Experimental studies demonstrating pharmacological potential of Beta-sitosterol

Biological activity	Study type	Model used	Mechanism	References
Antidiabetic (type 2)	*In-vivo*	Wistar strain adult male albino rats	Regulates IRS-1/Akt pathway of insulin signaling	Babu et al. (2020)
Carbohydrate metabolism	*In-vivo*	Adult male wistar rats	Upregulated glycogen metabolism and downregulation of glycogen synthase	Saravanan et al. (2020)
Colorectal cancer	*In-vitro*	Human colorectal cancer cells	Inhibits p53-MDM2 interaction and suppresses the expression of breast cancer resistance protein	Wang et al. (2020).
Prostatic cancer	*In-vivo*	Adult male wistar rats	Induces apoptosis by suppressing anti-apoptotic protein expression and elevating pro-apoptotic protein expression	Prasad (2020)
Against non-alcoholic fatty liver disease	*In-vivo*	Male Sprague-Dawley rats	Suppression of lipogenic gene expression	Gumede et al. (2020)
Glucose homeostasis	*In-vivo*	Male albino wistar rats	Increased expression of PPARγ and GLUT4 proteins	Ramalingam et al. (2020)
Antioxidant	*In-vivo*	Male albino wistar rats	Scavenging of body free radicals and decrement in lipid peroxidation	Baskar et al. (2012)
Immunomodulatory effect	*In-vivo*	10 week old male pigs	Ameriolate immune response by activating dendritic cells and up regulation of IFN-α	Fraile et al. (2012)
Wound healing capability	*In-vitro*	Human fibroblast cells	Alleviate super oxide dismutase activity and decrement in IL-1β levels	Abbas et al. (2020)
Hepatoprotective	*In-vivo*	Mice	Increased levels of antioxidant enzymes, Nrf2 and HO-1 and decreased levels of AST,ALT, TNF-α, IL-1β, IL-6, TLR4 and NF-κB	Yin et al. (2018)
Renal, Cardiac and Osteo protective effect	*In-vivo*	Wistar albino rats	Decreases the levels of renal damage markers, bone demineralization markers and markers of atheroseclerosis	Olaiya et al. (2015)

Abbreviations: *IRS-1/Akt* Insulin receptor substrate-1/ Protein kinase B, *HCT116* Human colorectal carcinoma-116, *p^{53}-MDM2* Tumour suppressor protein 53-Murine double minute 2, *PPARγ* Peroxisome proliferator-activated receptor gamma, *GLUT4* Glucose Transporter type4, *IFN-α* Interferon alpha, ATCC-American type cell culture collection, *SOD* Super oxide dismutases, *IL-1β* Interleukin-1, *DPPH* 2,2-diphenyl-1-picrylhydrazyl, *Nrf-2* Nuclear factor erythroid 2–related factor 2, *HO-1* Heme oxygenase-1, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *TNF-α* Tumour necrosis factor alpha, *TLR-6* Toll-like receptor-6, *NF-κB* Nuclear factor kappa light chain enhancer of activated B cells poor absorption is rapid efflux of β-sitosterol from enterocyte into the gastrointestinal tract via ABC transporter proteins (ABC G5 and G8). These ATP-binding cassette transporters are present on the apical surface of enterocytes and responsible for the efflux of sterols (both animal and plant based) (Berge et al. 2000). The absorption percentage of β-sitosterol is ≤5%, whereas it is 45–54% for the cholesterol from the daily intake diet. Upon action of bile, β-sitosterol majorly metabolised into two compounds namely cholic and chenodeoxycholic acid and about 20% of absorbed β-sitosterol breakdown into these components and rest all is excreted as free sterols (Field and Mathur 1983). Micro gut flora also interact with the β-Sitosterol and metabolize it into 24-ethyl-coprostanol (mainly), coprostanol and 24-ethyl-coprostanone (Salen et al. 1970; Shahzad et al. 2017). In a comparative view with cholesterol, absorption of β-sitosterol, compesterol, sitostanol, compestanol and cholesterol is 0.5%, 1.9%, 0.04%, 0.16% and 56% respectively (Salen et al. 1970; Shahzad et al. 2017). The level of β-sitosterol in plasma up-to a threshold limit can only be maintained by incorporating β-sitosterol in our daily diet as it is not synthesized endogenously and plasma become β-sitosterol free as soon as there is no β-sitosterol in our diet (Duchateau et al. 2012). The absolute oral bioavailability (AOB) of β-sitosterol in a healthy subject is around 0.41%, so in order to get the turnover of 5.8 mg/day in the plasma, our diet should contains around 1400 mg of β-sitosterol by weight, regularly (Fig. 5.5).

Nano drug delivery (NDD) is the emerging drug delivery system and proved to be a revolutionary approach in ameliorating the therapeutic efficacy of natural bioactive components by solving their problem of being insoluble/ highly soluble, poor absorption and stability, fast degradation, short circulating period (half-life) and poor targeting efficiency (Díaz and Vivas-Mejia 2013). Several experiments has been conducted on different bioactive compounds paclitaxel (Liu et al. 2021), resveratrol (Ha et al. 2021), vincristine (Mehrabi et al. 2020), curcumin (Kumar et al. 2020), doxorubicin (Ghosh et al. 2020), catechins (Ahmad et al. 2020), 3, 3′-diindolylmethane (Bhowmik et al. 2017), ellagic acid (Pirzadeh-Naeeni et al. 2020), papaverine (Berkó et al. 2018), thymoquinone (Alshehri et al. 2021) and camptothecin (Al-Musawi et al. 2020)) and concluded on this aspect that nano-formulations effectively and significantly enhances the therapeutic/clinical efficacy of these nutraceuticals (Bilia et al. 2017). Many of these natural product based nanomedicines are already in the market after getting final approval from FDA. Ventola in his review on nanomedicines enumerated that in total approved nanomedicines, 34% commercial nanomedicines are polymer based, 30% nanocrystal, 20% liposome, 10% are organic, 4% protein based and 2% are in the form of micelles but nanomedicines which are under investigation or trial are mostly liposome based (Ventola 2017). The stone of nanoformulation based commercial drugs was laid in 1995 when FDA approves first nanomedicine under the trade name Doxil®, encapsulating doxorubicin drug in the form of liposomes for the treatment of ovarian cancer (Barenholz 2012; Bhardwaj et al. 2019). In a recent review performed by Bhardwaj and colleagues reported that approximately 80% of commercially and FDA approved nanomedicines for the treatment of cancer is lipid (liposomes) and polymer based (Bhardwaj et al. 2019). For the treatment of oncology and neurological

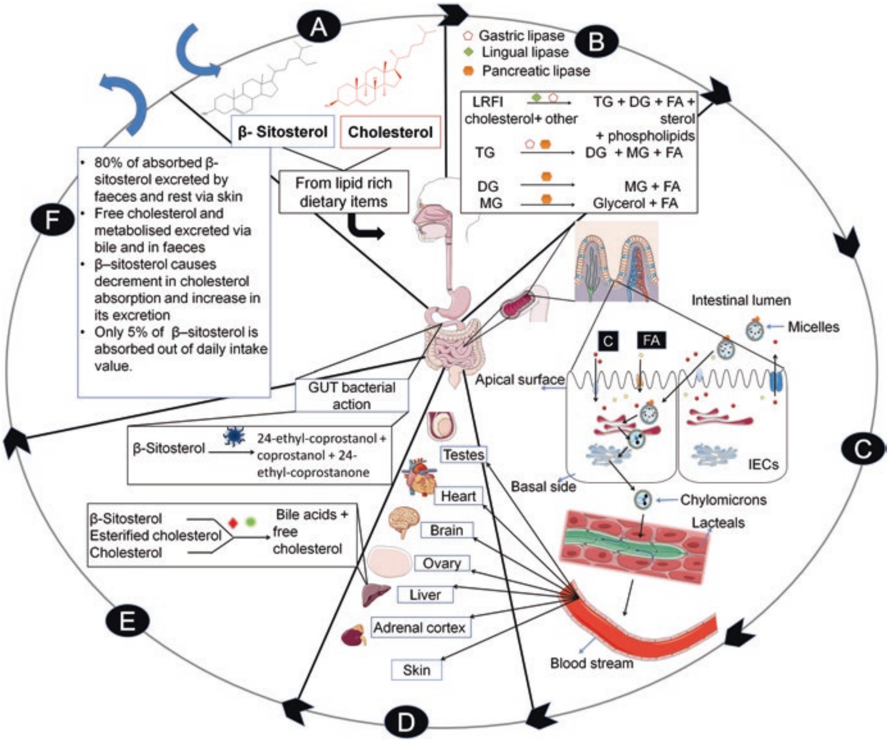

Fig. 5.5 Pharmacokinetics of β-sitosterol and cholesterol
A- Ingestion of β-sitosterol and cholesterol through diet
B- Digestion (partial) of lipids in buccal cavity and stomach, no digestion of β-sitosterol and cholesterol takes place here
C- Absorption of cholesterol and β-sitosterol through intestinal epithelium in the form of micelles and changes to chylomicron after esterification of cholesterol and modification by the action of enzymes present in intestinal cells, chylomicron moves from cells to the lacteals and then to the blood and from here it takes the structure of low and high density lipoproteins
D- Distribution: β-sitosterol distributed via blood to different parts of body such as brain, heart, liver, adrenal gland, ovary, testes and skin, whereas, cholesterol goes to the liver for further processing
E- Metabolism of β-sitosterol and esterified cholesterol takes place inside liver where by the action of bile and other enzymes it is converted into bile acids and free cholesterol
F- Excretion of β-sitosterol and cholesterol
Abbreviations: *GUT* Gastrointestinal tract, *IECs* Intestinal epithelial cells, *LRFI* Lipid rich food intake, *TG* Triglycerides, *DG* Diglycerides, *MG* Mono-glycerides, *FA* Fatty acids, *C* Cholesterol

disorders, USFDA approves more than 20 clinical drugs based on nano-formulations.

Depending upon the atomic nature of excipients used for the synthesis of nanoformulation, on the whole, nanocarrier (NCs) can be classified into two categories: organic and inorganic nanocarriers. Organic nanocarrier can be further subdivided into lipid based and polymer based NCs (Arora and Jaglan 2016). Amalgamation of

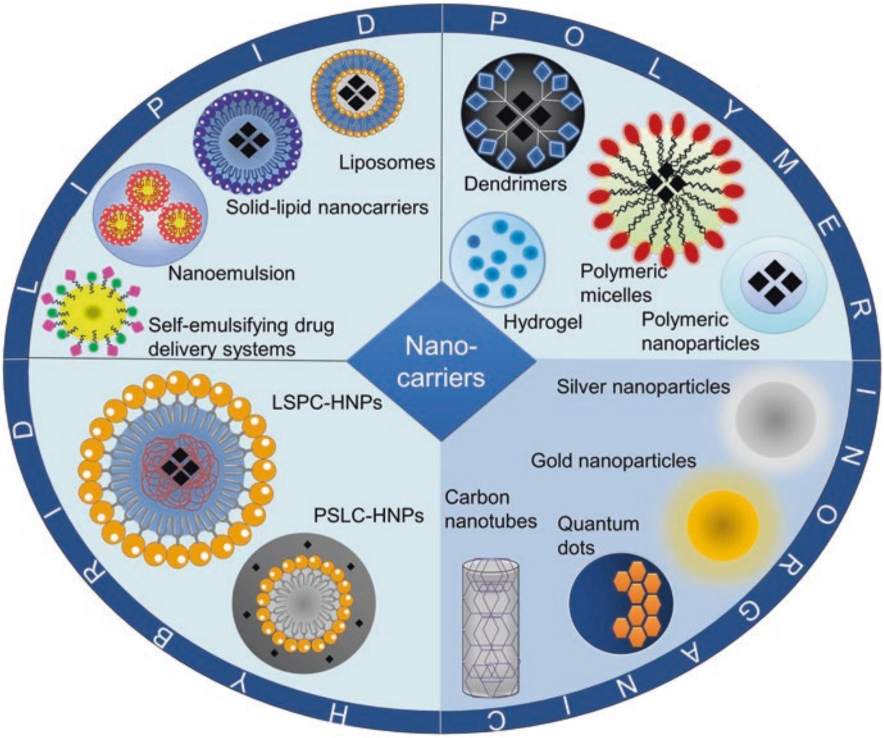

Fig. 5.6 Nanocarriers differentiated on the basis of main excipient used in their formulations employed for the enhancement of therapeutic efficacy of beta-sitosterol. Abbreviations: *LSPC-HNPs* Lipid shell polymeric core-hybrid nanoparticles, *PSLC-HNPs* Polymeric shell lipid core-hybrid nanoparticles

nanotechnology with the drug delivery system for the elevation of therapeutic effect of β-sitosterol is proved to be an excellent approach (Fig. 5.6). Polymer (poly-lactic co glycolic acid and polyethylene) based nanocarriers of β-sitosterol enhances its solubility by providing it amphiphilic nature of PLGA and PLGA-PEG shell, increases its half-life and dissolution time, and imparts stability in proteinous environment. Moreover, these nanocarriers also elevate the anti-oncogenic efficacy of β-sitosterol for many times via enhancing its cellular uptake in human breast cancer cell lines (MDA-MB-231 and MCF-7) and exerting anti-proliferating activity (Andima et al. 2018). Chitosan nanofibers encapsulating β-sitosterol enhances its solubility in the aqueous medium by converting crystalline β-sitosterol in amorphous halo and hence improve dissolution of β-sitosterol. This study also projected that polymer based nanofibers (using electro-spun technique) of β-sitosterol can have better cholesterol lowering effect than β-sitosterol alone via oral route (Paaver et al. 2016). Nanogel drug delivery system is used for the topical prolonged and specific site effects. It involves the utilization of water soluble polymer which provides versatility, biocompatibility, imbibition and higher hydrophilicity like advantages to this delivery system (Inamdar et al. 2018). β-sitosterol nanogel, provides its sustained release, higher stability, bioavailability, solubility in aqueous medium and also elevated antibacterial activity against *P. vulgaris* and *S. aureus*.

Lipid based nanocarriers namely liposomes, micelles, solid lipid nanoparticles, nano-emulsions are well proved in pushing up the therapeutic efficacy of various nutraceuticals. Likewise, lipid nanocarriers encapsulating β-sitosterol prepared by using grape seed oil enhances the overall bioavailability of β-sitosterol via sustained release, higher stability and also potentiate antioxidant activity of β-sitosterol such that it can able to block higher chain reactions, scavenging of almost 92% of free radicals which is much higher than β-sitosterol alone (36.5%) (Lacatusu et al. 2012). Solid lipid nanocarrier enhances the solubility, stability (extra stable at lower temperature), bio-accessibility and *in-vivo* hypo-cholesterolemic effect of β-sitosterol (Soleimanian et al. 2020). Solid lipid nano-carriers s encapsulating β-sitosterol brush up the total cholesterol and low density lipoproteins lowering ability of β-sitosterol nutraceutical.

Self-emulsifying drug delivery system (SEDDS) is the lipid based nano-formulation approach which furnishes the nutraceuticals with many advantages; in particular, this method improves the solubility and stability of hydrophobic drug, forms nano-size emulsion droplets, enhanced penetration efficacy of drug through gut epithelia, which ultimately increases the absorption, bioavailability and hence therapeutic aspect of nutraceuticals. Moreover, this method is also easy to administer via any oral, intravenous or topical route. Lipids, surfactant and co-surfactants are raw and the backbone in the SEDDS as they provide the main body to the nanocarriers (Mishra et al. 2020). Here, lipids acts as hydrophobic sink and core for the hydrophobic drug, surfactants for the solubilisation or emulsification purpose and solvation is assisted by co-surfactants (Kumar et al. 2013). Recently, Yuan with his co-workers demonstrated refined hypo-lipidemic effect of β-sitosterol self-micro-emulsion than β-sitosterol-linolenic acid ester and β-sitosterol health tablets (Yuan et al. 2019). Enhancement in cholesterol excretion and its reduced absorption is because of competitive association of β-sitosterol in micelle formation and increased solubility of it due to self-emulsifying nanocarriers.

Polymeric nanocarriers (encapsulate both hydrophilic and lipophilic drugs, sustained release and stability) and lipid nano-carriers (modified surface provide prolong half-life and elevated pharmacokinetic) have many advantages individually but still they possess some pitfalls such as utilization of hazardous organic solvents, cytotoxicity and deterioration of polymers; and poor encapsulation, physical and chemical instability and fast release respectively. Therefore, amalgamation of polymeric and lipid approach has been developed in the form of hybrid nanocarriers, having both the advantages (Raman et al. 2020). In hybrid nanocarriers, polymer forms the core and lipid forms the shell of nanocarriers or vice-versa (Abdou et al. 2019). Hybrid nano carriers of β-sitosterol formulated by using PLGA polymer and DSPE-PEG-2000 as lipid, demonstrated to be a better choice for hepato-protective efficacy and can be treated as a potentiate drug because high encapsulation efficiency (94%), dissolution time of an hour, elevated restoration of liver enzymes

(ALT and AST), normalization of bilirubin, albumin, CAT and MDA levels with decreased activity of executioner caspase (caspase 3).

Inorganic nanocarriers are the most commonly used nanostructure in the field of nanotechnology due to its lone physical (size, shape and surface to volume ratio), chemical (chemical composition) and optical (Surface Plasmon resonance especially in silver nanoparticles) properties (Ijaz et al. 2020). This approach of delivery system includes gold, silver, magnetic, silica nano particles, quantum dots and carbon tubes, Out of which Gold (Au) and silver (Ag) NPs are the extensively utilized nanostructures in the field of nutraceuticals due to their biocompatibility, inert nature and easy synthesis. Recently, silver nanoparticles of β-sitosterol were evaluated on the parameter of cytotoxic effect on human colon cancer cell line (HT-29) and concluded that β-sitosterol AgNPs (IC_{50}–7 ng/ml) has the ability to induce apoptosis in cancer cell lines via the upregulation of p53 expression (Chithambara Shathviha et al. 2020).

Table 5.3 demonstrates delivery approach of β-sitosterol for augmenting its therapeutic efficacy.

5.5 Conclusion

With the increase in population, demand of food and agricultural practices is also elevated and this will lead to the necessity of fast food production with higher functionality and longer shelf-life. Agro-industries solves the problem with mass production of food but also has a drawback of discarding non-essential mass residues of food (seeds, peel, stem, leaves, petals, husk and pomace) as waste and disposal of this into the pits and water bodies, results in environmental pollution. In the approach of dealing with increased food demand and waste production, 3R principle (Reduce, Reuse and Recycle) is becoming an excellent idea. This bio-waste is the treasure of bioactive compounds which possess wide range of biological activities and may prove better as a treatment of major health challenging disorders. So, in order to avoid the wastage of these active ingredients, sustainable methods were developed and researches are still going on for the extraction of therapeutic agents.

Majorly conventional and non-conventional methods are applied for the extraction of phytochemicals from the biowaste. As described earlier conventional method is economically friendly but not environmentally, moreover residues of organic solvents in the extracted phytochemical hinder its activity and may become unfit for the human consumption. Non-conventional methods solve these problems but it also has its own cons. So there is a need for the development of such a method which is

- Economically and environmentally suitable.
- Involves minimized utilization of organic solvents.
- Can be employed for the pilot scale production.
- Easy to learn and operate so that a layman can easily grasp the technique.
- High yielding and consume less time for the extraction.

Table 5.3 Studies conducted for the enhancement of therapeutic efficacy of β-sitosterol utilizing nano-drug delivery system

Nano-structure	Method	Excipient used	Biological activity	Size (nm)	Conclusion	References
Nano fiber	Electrospinning	Chitosan	NA	150–218	Increased solubility and dissolution time/half-life	Paaver et al. (2016)
Polymeric nanocarriers	Emulsion solvent evaporation	Poly(lactide-co-glycolic acid) poly(ethylene glycol)-block-poly(lactic acid)	Anti-tumor activity (breast cancer)	~ 215 ~ 240	Resultant nanoparticles exhibited better cytotoxicity in comparison to lone β-sitosterol	Andima et al. (2018)
Nanogel	Nanoprecipitation	Eudragit RL100, Carbopol 934	Anti-bacterial	ND	Synthesized nanocarriers exhibited enhanced anti-bacterial activity in comparison to alone therapeutic agent	Inamdar et al. (2018)
Solid lipid nanoparticles	DESD	Compritol 888	Arthritis	ND	Increased anti-arthritis effect by activation of HO-1/Nrf2 pathway and suppression of NF-κB expression	Zhang et al. (2020)
SMEDDS	Self emulsifying method	Polyethylene glycol 400, polyoxyethylene hydrocastor oil	Hypolipidemic effect	48	Increased blood lipid lowering effect	Yuan et al. (2019)
PEGylated niosomes	Film hydration	Polyethylene glycol 2000	Antineoplastic	219.6	Enhanced dissolution, encapsulation, cellular uptake and cytotoxicity on HepG2 cells than alone β-Sitosterol	Nisha et al. (2020)
Inorganic silver nanoparticles	Reduction	Silver nitrate	Anticancer	ND	Ameliorated cytotoxic activity and induce apoptosis in cancer cell lines	Chithambara Shathviha et al. (2020)
LPHNPs	Nanoprecipitation	Poly(lactide-co-glycolic acid) DSPE-PEG-2000	Hepatotoxicity	181.5	Restoration of ALT, AST, malondialdehyde, catalase like enzymes and decreased expression of cleaved caspase 3	(Abdou et al. 2019)

Nano lipid carriers	Melt emulsification	Propolis wax Propolis wax + glyceryl behenate	Hypo- cholesterolemic	96.5 105.5	Increased solubility and decreased blood cholesterol level	Soleimanian et al. (2020)
Polymeric nanoparticles	Emulsion-solvent-evaporation	Poly(lactide-co-glycolic acid) poly(ethylene glycol)-block-poly(lactic acid)	Anticancer	215 240.6	Enhanced anti-proliferating activity of β-sitosterol and poly(lactide-co-glycolic acid) is better nano-drug delivery system	Andima (2020)
HBCM	Esterification reaction	Thiolated heparin	Anti-metastatic	145	Enhanced stability, hemo-compatibility, drug loading and anti-metastatic activity	Debele et al. (2017)
Liposomes	Film hydration high pressure homogenization	Lecithin	Anti-hypercholesterolemic	194–197	Improved stability, bioavailability,controlled release of curcumin	Tai et al. (2019)
Lipid nanoparticles	MECH	Tween 20/80	Antioxidant	<200	Ameliorated antioxidant activity and sustained released	Lacatusu et al. (2012)

Abbreviation: *NA* Not Applicable, *DESD* Double emulsion solvent displacement method, *SMEDDS*, Self-microemulsion drug delivery system, *POE-HC* Polyoxyethylene hydrocastor oi, *LPHNPs* Lipid polymer hybrid nanoparticles, *DSPE-PEG* (1,2-distearoyl-sn-glycero-3-phosphoethanolamine- N-carboxy (polyethylene glycol), *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *MCF* Human breast cancer cell lines, *HBCM* Haparin beta-sitosterol conjugated micelle, *MECH* Melt emulsification coupled with high shear homogenization β-sitosterol is an bioactive molecule present in most of the plant species having hypocholesterolemic activities along with anti-oncology, anti-inflammatory, anti-oxidant, anti-diabetic, hypolipidemic properties. It can be extracted from the biomass generated from the agro-industries of watermelon, sugarcane, rumfactory and fruits. As discussed in this chapter that different extraction methods can be used for the extraction of β-sitosterol and can be utilized further for preventing and even curing many health ailments.

β-sitosterol is well explored at *in-vitro* and preclinical levels but has very few studies demonstrating its clinical efficacy. Short half life (3 h) and poor pharmacokinetic properties limit its therapeutic capabilities and gives it a designation of orphan molecule. Therefore to overcome this limitations various delivery system have been explored to improve its therapeutic efficiacy. Despite of its enormous reported nanoformulations, none of them has been reached upto clinical trials and therefore, further pre-clinical and clinical investigations are required.

Acknowledgements The authors are greatful to Director, CSIR- Institite of Himalayan Bioresource Technology, Palampur for his constent support and encouragement. AS acknowledges financial assitance from Council of Scientific and Industrial Research (CSIR), New Delhi for major laboratory project (MLP-0204). R acknowledges Council of Scientific and Industrial Research (CSIR), New Delhi for providing fellowship (File number: 31/054(0163)/2020-EMR-I). Some figures are drawn from the material provided by Servier Medical Art under the Creative Common Attribution 3.0 Unported License. The book chapter is institutional commuication number: 4803.

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Chapter 6
Exploration of Bioactive Constituents from Abandoned Parts of the Tea Plant

Ranjana Sharma, Ajay Rana, Dinesh Kumar, and Sanjay Kumar

Abstract The agroprocessing industries are producing a large volumes of waste biomass that contains valuable nutrients which if recycled properly could save millions of dollars. This is the case for the tea industry which produces large amounts of biomass from the tea plant, *Camellia sinensis*. Here, we review bioactive compounds from tea leaves, flowers and fruits, and their applications in medicine. Compounds include vitamins, aromatic compounds, spermidine derivatives, polysaccharides, saponins, polysaccharides, fatty acids, flavanols, phenolic acids and methylxanthenes. Pharmacological properties include antioxidant, antimicrobial, anti-COVID, antiobesity, antidiabetic, antihypertensive and anticancer.

Keywords *Camellia sinensis* · Polyphenols · Spermidine · Functional molecules

6.1 Introduction

The tea plant *Camellia sinensis* is an angiosperm plant belongs to the Theaceae family. Its origin was reported in South Asia. It was discovered by Emperor Shen Nong in 2700 B.C. Tea beverage came into existence by serendipity when some tea leaves blew into the kettle of boiling water, resulted in pleasant fragrance (Bonheure et al. 1992) This beverage is popular worldwide and consumed by almost all age groups (Katiyar and Mukhtar 1996). Presently tea is cultivated in around 30 countries of the world, and India is the second-largest tea-producer (21%) after China,

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_6

which accounts for approximately 30–40% global tea produce. Europe, America and various other nations meet the demand of tea by importing from India, China, Kenya, and Sri Lanka (Zhang et al. 2019). *C. sinenis* is an evergreen shrub that consists of green leaves, fruits, seeds and flowers. The flowers consist of white petals with yellow stamens in solitary or a bunch forms, while fruits are in the form of capsules with enclosed seeds. The young tea shoots are green, soft while mature leaves are dark-green glossy, elongated, and ovate.

Tea extract has been widely used as a traditional medicine in China and India (Katiyar and Mukhtar 1996). Fresh tea shoots are processed into different types of teas having unique flavour and taste as follows green tea, oolong tea, white tea, black tea (orthodox tea and crush tear curl tea) and Pu'erh tea. The most noteworthy effects of its consumption might be emerged from its chemotherapeutic and preventive properties, which may be belongs to its diversified metabolites (Lee et al. 2000). The major chemical constituent's in *C. sinensis* are polyphenols (Phenolic acids, catechins and flavonols), methylxanthines (caffeine theobromine, theophylline), saponins, polysaccharides, amino acids, organic acids, chlorophylls, and proteins (Koch et al. 2018). These metabolites are distributed throughout the plant as per their requirement. Reserachers have studied the distribution of polyphenols and observed variability of content in the different tea plant parts (Forrest and Bendall 1969; Rana et al. 2016; Sharma et al. 2020). *C. sinensis* metabolites have sound health effects and reported for the aid and interruption of several metabolic conditions (Xue et al. 2007). The regressive studies have been published for chemical and bioactive studies of tea leaves. Polyphenols from tea leaves have been extensively studied against various metabolic syndromes like obesity, diabetes, cardiovascular diseases, cancer, etc. The findings of the authors have revealed a significant role of tea leaves metabolites against fatal disorders. Further, diversified tea plant metabolites and their bio-functional effects are highlighted in Table 6.1. However, tea flowers and fruits have received less consideration while seeds of mature fruits are only targeted occasionaly for the extraction of oil. Therefore, a comprehensive review was focused to explore its utilization, importance and future research directions.

6.2 Methodology

This review chapter is focussed on english language literature. The literature search was conducted in pub med, sci-hub, and science direct data basis. The selected keywords were of following terms phytochemicals, bioactivities, biofunctional, *in vitro* studies, pharmacology, and toxicology. Total numbers of 205 articles were peer-reviewed in english to conclude the whole manuscript. Each section was critically examined and carefully discussed and summarized.

Table 6.1 Products from tea and their health beneficial effects

Tea products	Effects	Countries of origin	References
Polyphenon, Sunphenon, Thea-Flan	Health maintenance and prevention of illness	Tokyo, Japan,Taiyo Kagaku Co., Yokkaichi, Japan, Mitsui Norin Co., Ltd.	Ghosh (2006)
Tea catechin capsules	Antioxidant	U.S.	Ghosh (2006)
Catechin + vitamin (A, C, E) tablets	Maintain body wellness	Japan	Tea (2005)
Catechin + oligosaccharides	Maintain intestinal floral health, improve bowel modulation action	USA	Tea (2005)
Green Tea Tablet	Prevent cold, antioxidant, refreshing effect	Japan, China, Korea, India	Ghosh (2006) and Tea (2005)
100 mg catechins/capsule	Antiviral, antibacterial effect, cure cold	Japan and US	Ghosh (2006)
Catechin 100 Plus Oligo	Inhibits the growth of putrefactive bacteria	Japan	Ghosh (2006) and Hara (2001)
Catechin 50	Reduce unpleasant faecalodours	Japan,	Ghosh (2006)
Catechin ACE	Antioxidant property	Japan	Hara (2001)
Catechin Car-Air-Filter and Air Cleaning System	Reduce odorous volatiles inside the car	Matsushita Electric (Panasonic), Suzuki Motor Corporation, Japan	Ghosh (2006)
Antiflu Mask	Protect from influenza virus and hay-fever	Japan	Ghosh (2006)
Catechin Miramat	Absorb formaldehyde,antibacterial and deodorizing properties	Japan	Ghosh (2006) and Hara (2001)
Catechin Cosmetics(shampoos and conditioners,ultraviolet screens and colourprotectants,soap, moisturizer's perfumes, sunscreens and foundations)	Retain healthy and radiant skin, UV protecting function,prevent pigment colouration	Japan and South Korea, European and Asian market	Ghosh (2006) and Sandeep and Nisha (2012)

(continued)

Table 6.1 (continued)

Tea products	Effects	Countries of origin	References
Catechin Jell,toothpaste or gum,Catechin Candy, tea toffee	Prevent dental caries, periodontal diseases and candidiasis	Japan, China India	Tamura and Ochiai (2012), Sakanaka et al. (1996), and Kakuda et al. (1994)
Catechin pet foods	Reduce faecalodour and caries in cats and other pets	Japan.	Ghosh (2006)
Kitchen Spray	Hand spray,absorb amines (fishy smell)	Japan	Kakuda et al. (1994)
Catechin feed	Reduce fat and peroxide contents of eggs	Mitsui Norin Co., Ltd., Japan	Ghosh (2006) and Chen et al. (2001)
Catechin Tea Bar	Great source of fibre, natural cellulose, vitamin B and essential amino acids		Ghosh (2006)
Bottle Catechin Drinks	Strong scavenging action on active oxygen	Japan,Taiwan and US, Korea	Chen and Lin (2015)
Green tea Ice Cream	Inherent health benefits	Japan, East and West Asia	Hara (2001)
Tea Saponin formulations	Pesticide, natural surfactants, dispelling insects, prevent prawn black gill disease	China	Ghosh (2006)
Edible tea Seed Oil	High content of unsaturated fatty acids	China	Hara (2001)
Tea wine, apple tea	Refreshing, antioxidant enriched	India	Ghosh (2006)

6.3 Scope and Potential

Notably, for the manufacture of different types of teas, only tender tea shoots are used (Zhang et al. 2019). However, other parts of the tea plant such as coarse leaves, fruits, and flowers remain unutilized. These economically underutilized parts produce colossal biomass and seems to be a good source for the value addition and reduction on bioload. As per the earlier published reports, one hectare of tea plantation serves around 3000–12,000 kg flowers (Chen et al. 2018). In concern with biomass production from the tea plant, valuable phytochemical exploration can prevail their exact utilization. Further, the explored metabolites from tea flowers and fruits are reported to exert beneficial health effects. Catechin, polysaccharides, and saponins from tea flowers reported for their antioxidant, antitumor, immune stimulating, antidiabetic, antiobesity, antihyperlipidemic, and antihyperglycemic abilities (Chen et al. 2018). Limited studies on tea fruits revealed the presence of flavonoids and phenolics (Rana et al. 2015). Hence, it is necessary to harness the functional molecules from less utilized parts of *C. sinensis* (Fig. 6.1). The demand for

Fig. 6.1 Tea plantation with *Camellia sinensis* and *Camellia assamica* variety of teas and major plant parts (fruits, leaves and flowers)

bioactive metabolites is increasing day by day and harnessing of valuable products from underutilized parts is the key stumili to enhance the livelihood of farmers. Hence deliberation on phytochemicals from waste biomass seeks attention.

6.4 Current Use of Tea Plant in Natural Health Products

Tea as a beverage is consumed in every part of the world, and India is the second largest producer. The diversified products from tea plant have taken the edge to enhance its market value. Countries like Unite States, China and Japan have numerous industries for diversified tea-based cosmetics, nutraceuticals, functional drinks, and pharmaceutical formulations (Table 6.1). Catechin enriched drinks, chocolate bars, toothpaste, capsules, antiviral masks, cosmetics, pet feed, tablets and saponin enriched pesticide, natural surfactants, soap formulatitions are all tea plant based products that are gaining attention (Table 6.1). This indicates the upcoming demand of tea metabolites in near future. To date mainly catechins have been targeted to exploit their activities and respective product formulations. However, the further need is to utilize other metabolites present in different parts of *C. sinensis* (Fig. 6.1) for product formulations so that flowers and fruits can be used in diversified product formulations.

A wide range of tea-based products available in global markets that are gaining popularity day by day are presented in Table 6.1 (Ghosh 2006; Tea 2005; Hara 2001; Sandeep and Nisha 2012; Kuroda and Hara 2004; Tamura and Ochiai 2012; Sakanaka et al. 1996; Kakuda et al. 1994; Tanaka et al. 2013; Chen et al. 2001; Chen and Lin 2015). In the past few years, researchers have identified potential secondary metabolites from industrial waste like peel, husk, pomace, seeds, etc. Compounds obtained from these neglected parts exhibited useful properties that can be utilized in the food and pharmaceutical industries (Goli et al. 2005; Makris et al. 2007). Concerning with tea chemistry, efforts are made for the comparison of phytochemical variation among economically underutilized parts (flower, fruits) of tea plant with its shoots. In recent times isolation and identification of metabolites from tea flowers and fruits have focussed.

However, the comparative evaluation of these molecules, along with tea shoots, has not been done. Present review highlights the competence of neglected parts of *C. sinensis* with tender tea shoots. Furthermore, biofunctional effects of metabolites are discussed to present their scope for potential utilization. This study will further help to highlight the unmet research among neglected parts of *C. sinensis*.

6.5 Chemical Components of Tea Leaves, Flowers, and Fruits

6.5.1 Volatiles and Fatty Acids

Volatile compounds are essential constituents responsible for distinct aroma and flavor of the tea. Around 600 volatile compounds are reported from tea to date. These are further classified into 11 main categories. These volatile compounds are spawned from carotenoids, lipids, and glycosides. Studies reported cis-2-pentenol, hexanol, cis-3-hexenol, trans-2-hexenol, linalool, linalool oxide, nerol, geraniol, phenylmethanol, 2-phenylethanol, nerolidol molecules in tea leaves. The increase in the content of free forms of aroma molecules is observed during the black tea oxidation process and decrease inbound forms during tea manufacturing (Saijo and Takeo 1973). Glycolipids are abundant lipids reported in fresh tea shoots. These lipids contribute significantly to the aroma and volatile flavours. Neutral lipids reported from tea are rich in linoleic, oleic, lauric, stearic, myristic, and palmitic acids (Ravichandran 2002). The hydrolytic or oxidative action of enzymes results in flavor production from lipids. This process generally happens during tea manufacturing hence reported in manufactured teas. Fatty acid derivatives such as alcohol, aldehyde, and lactones in fresh shoots impart fragrance to leaves (Winterhalter and Rouseff 2001). The aldehydes are produced by di-oxygenation of unsaturated fatty acids that are catalyzed by an enzyme called lipoxygenase. These aldehydes get transformed into alcohol by an enzyme called alcohol dehydrogenase.

Major terpene derivatives present in tea are geraniol, linalool, linalool oxide etc. (Chen et al. 2018). Methylerythritol phosphate pathway results in the production of geranyl pyrophosphate, while geranyl phosphate is the precursor of terpenoid derivatives. The less volatile compounds are also present in glycosidically bound forms and are water-soluble as compared to aglycone counterparts. It was observed that primeverosides and glucosides are reported to be major glycosides in fresh leaves of *C. sinensis,* and they disappeared at the last stage of processed tea (Ma et al. 2014). Moreover, 1-ethyl-3, 4-dehydropyrrolidone, pyrazines, pyrroles, pyrans, and furans are resultant of Maillard reaction (reaction between reducing sugars and amino acids at high temperature) during tea manufacturing.

Phenylpropanoid/benzenoid derivatives are vital flavor contributors in tea and produced from the shikimic acid pathway (Fig. 6.2). Phenylpropanoids have fruity and floral fragrance. The 2-phenyl ethanol is a major benzenoid reported in leaves and flowers of *C. sinensis.* However, the quantity reported in leaves is low (Dong et al. 2016). Flowers also reported to contain linalool, linalool oxide, geraniol, nerolidol, beta-ionone, 2, 4-di-tert-butylphenol, methyl palmitate, methyl linoleate, methyl salicylate, terpineol compounds along with some minor volatiles (Dong et al. 2016). However, the volatile flavor from tea fruits is not reported. Tea seeds

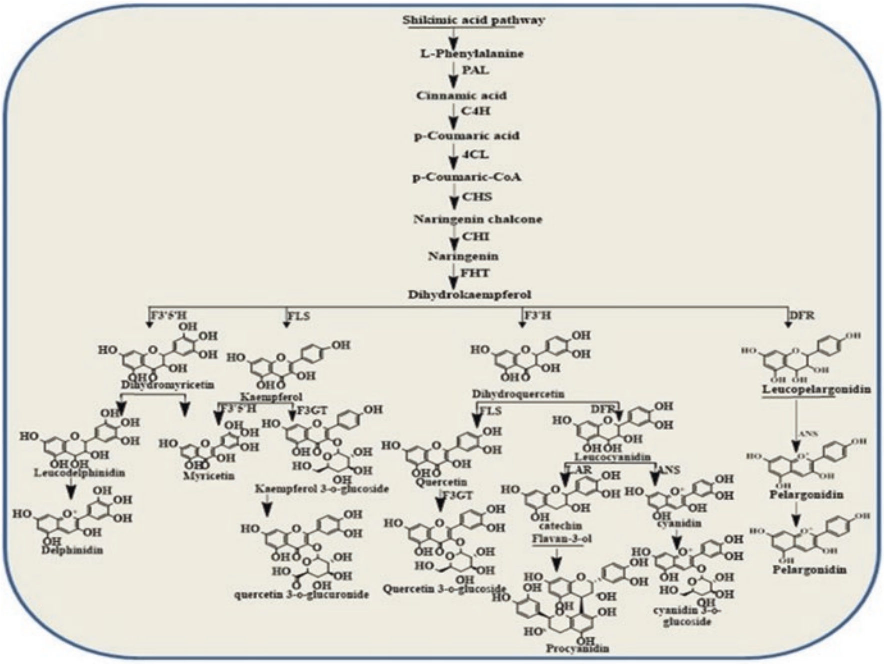


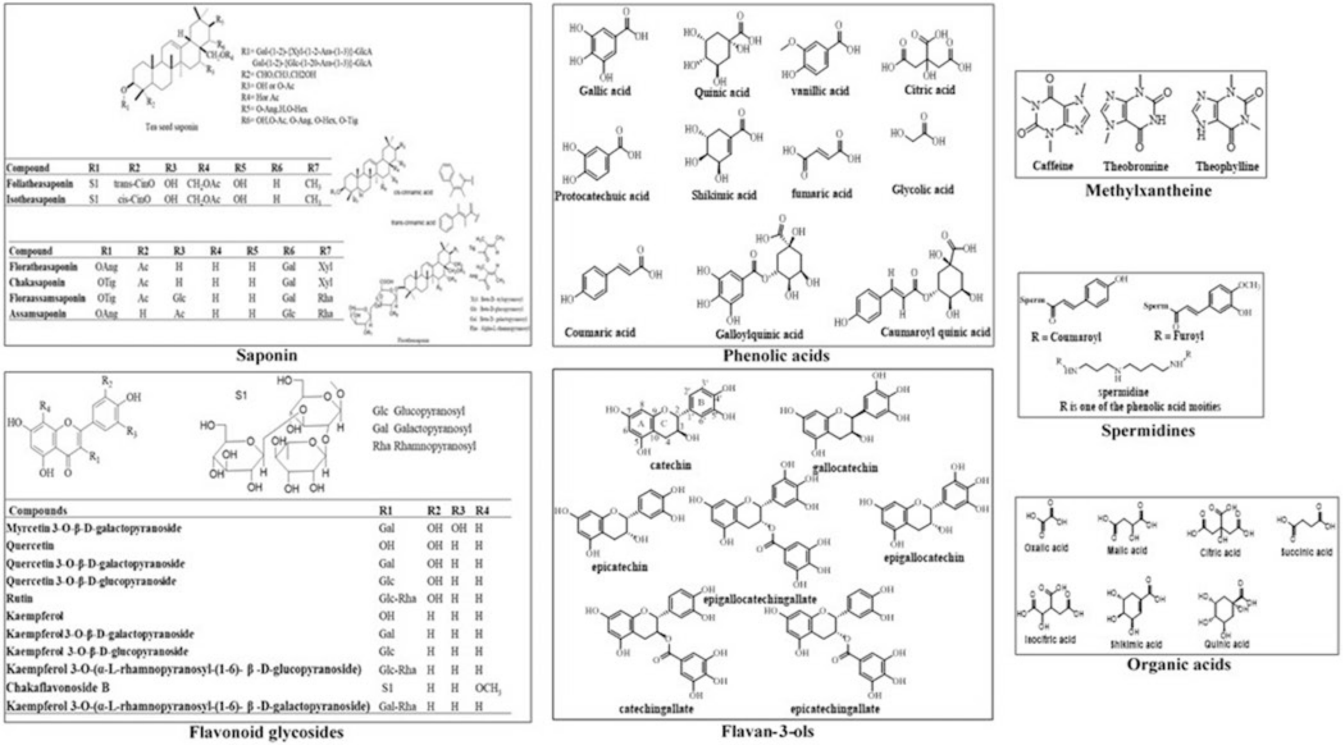
Fig. 6.2 Biopsynthesis of phenolics, *PAL* phenylalanine ammonia lyase, *C4H* cinamate 4- hydroxylase, *4Cl* 4-coumaroyl CoA ligase, *CHS* chalcone synthase, *CHI* chalcone isomerase, *DFR* dihydroflavonol reductase, *FLS* flavanol synthase, *F3H* flavanone 3-hydroxylase, *ANS* anthocyanidin synthase, *LAR* leucoanthocyanidin reductase

contain monounsaturated and polyunsaturated fatty acids. Tea seeds contribute around 29% oil. Oleic acid, linoleic acid, palmitic acid, and stearic acid are the major fatty acids (Wang et al. 2011). Around 80% of the fatty acids in tea seed oil are unsaturated fatty acids and stable with antioxidant potential. Total free fatty acids are reported <1.5%, iodine value, peroxide value and saponification values of tea seeds are 86 to 91 g I_2/100 g, < 3.5 meq O2/kg, 182 to 187 mg KOH/g respectively (George et al. 2013).

Polycosanols are long chain primary alcohols that are important constituents of tea. These are extracted from plant origin waxes because of their health beneficial effects (Narayan et al.1988). Policosanols are not focussed much although tea leaves are rich source. Triacontanol is major polycosanol reported in tea leaves. Triacontinol is a long chain fatty alcohol having molecular formulae $CH_3(CH_2)_{28}CH_2OH$ (Rao et al. 1987). It has been reported in black tea, green tea and even in spent waste of tea. It has been recognised as an significant constituent of plant waxes (Narayan et al.1988). Triacontinol is a secondary plant growth constituent and synthesised synthetically also. The activities reported for natural and synthetic triacontinol are equivalent. Other polycosanols reported in tea leaves are Octacosanol (C_{28}-OH), Eicosanol (C_{20}-OH), Heneicosanol (C_{22}-OH), Tricosanol (C_{23}-OH), Tetracosanol (C_{24}-OH), Pentacosanol (C_{25}-OH), Heptacosanol (C_{27}-OH), Nonacosanol (C_{29}-OH, Hentriacontanol (C_{31}-OH), Dotriacontanol (C_{32}-OH), Tetratriacontanol (C_{34}-OH). Total polycosanols estimated in tea leaves are 726.2–1363.6 mg/kg while green tea infusion contain upto 1629.4 mg/kg (Choi et al. 2016).

6.5.2 *Flavonoids*

Flavonols are a major class of polyphenols present in *C. sinensis* (Fig. 6.3). These functional molecules exhibit extraordinary health benefits. Predominantly flavonols occur in the glycosidic form in tea plant. Quercetin, myricetin, and kaempferol are the main flavones that occur in tea plant in their glycon as well as aglycone forms (Zhang et al. 2019). The sugar units attached to these flavonols are glucose, fructose, galactose, arabinose, rhamnose. Tea leaves account for around 2–3% of flavonols in dry weight matter. The content of flavonol glycosides in different tea infusions is reported around 127.3–578.3µg/ml (Monobe et al. 2015). Quercetin, myricetin, and kaempferol glycosides are chief glycosides in tea. Quercetin-3-*O*-glucosyl-(1–3)-rhamnosyl-(1–6)-glucoside is a major flavonoid glycoside in leaves. The seasonal variation studies showed the maximum content of kaempferol glycoside during the month of April while myricetin glycosides during June and August season (Forrest and Bendall 1969). Whereas, Kaempferol glycosides are present in young leaves while quercetin and myricetin glycosides are reported in third and fourth leaf (Chen et al. 2018). The isolated flavonoid glycosides from leaves are camellia-quercetisides A–D, quercetin 3-O-[alpha-L-arabinopyranosyl (1–3)] [2-O″-(E)-p-coumaroyl][b-D-glucopyranosyl(1–3)-alpha-L-rhamnopyranosyl(1–6)]-beta-D-glucoside, quercetin3-O-[2-O″-(E)-p-coumaroyl]



Compound	R1	R2	R3	R4	R5	R6	R7
Foliatheasaponin	S1	trans-CinO	OH	CH_2OAc	OH	H	CH_3
Isotheasaponin	S1	cis-CinO	OH	CH_2OAc	OH	H	CH_3

Compound	R1	R2	R3	R4	R5	R6	R7
Floratheasaponin	OAng	Ac	H	H	H	Gal	Xyl
Chakasaponin	OTig	Ac	H	H	H	Gal	Xyl
Floraassamsaponin	OTig	Ac	Glc	H	H	Gal	Rha
Assamsaponin	OAng	H	Ac	H	H	Glc	Rha

Compounds	R1	R2	R3	R4
Myrcetin 3-O-β-D-galactopyranoside	Gal	OH	OH	H
Quercetin	OH	OH	H	H
Quercetin 3-O-β-D-galactopyranoside	Gal	OH	H	H
Quercetin 3-O-β-D-glucopyranoside	Glc	OH	H	H
Rutin	Glc-Rha	OH	H	H
Kaempferol	OH	H	H	H
Kaempferol 3-O-β-D-galactopyranoside	Gal	H	H	H
Kaempferol 3-O-β-D-glucopyranoside	Glc	H	H	H
Kaempferol 3-O-(α-L-rhamnopyranosyl-(1-6)- β -D-glucopyranoside)	Glc-Rha	H	H	H
Chakaflavonoside B	S1	H	H	OCH_3
Kaempferol 3-O-(α-L-rhamnopyranosyl-(1-6)- β -D-galactopyranoside)	Gal-Rha	H	H	H

Fig. 6.3 Secondary metabolites of *Camellia sinensis*. Different classes of metabolites such as saponins, flavonoid glycosides, phenolic acids, flavan-3-ols, methylxantheine, spermidines and organic acids

[beta-D-glucopyranosyl(1–3)-alpha-L rhamnopyranosyl (1–6)]-betaD-glucoside, quercetin3-O-[a-L-arabinopyranosyl(1–3)][2-O″-(E)-p-coumaroyl][a-L-rhamnopyranosyl (1–6)]-beta-D-glucoside, and quercetin 3-O-[2-O″-(E)-*p*-coumaroyl][a-L-rhamnopyranosyl(1–6)]-beta-D-glucoside (Manir et al. 2012). Similarly, tea flowers also contain flavonols in glycosidic form. Earlier flavanol, mono, and diglycosides have been reported from tea flowers (Yang et al. 2009). Flavonol glycosides reported from ethanolic extract of tea flowers are myricetin 3-O-β-D-galactopyranoside, quercetin 3-O-β-D-galactopyranoside, quercetin 3-O-β-D-glucopyranoside, kaempferol 3-O-β-D-galactopyranoside, kaempferol 3-O-β-D-glucopyranoside, kaempferol 3-O-(α-L-rhamnopyranosyl-(1–6)-β-D-glactopyranoside, and kaempferol 3-O-(α-L-rhamnopyranosyl-(1–6)-β-D-glucopyranoside)). Along with these flavonoids, kaempferol, kaempferol 3-O-rutinoside, quercetin, rutin, chakaflavonoside are also reported in tea flower buds (Chen et al. 2018). Flavonoid glycosides from tea fruits are not directed much.

6.5.3 Catechins

Catechins are synthesized by shikimic acid (Fig. 6.2) and mevalonic acid pathway. An enzyme named as chalcone synthase is vital for their synthesis (Forrest and Bendall 1969). This enzyme, along with flavonone-3-hydrolase catalyzes the caffeoyl-CoA and coumaroyl-CoA to an intermediate dihydro-flavonol. Dihydroflavonol is a further precursor of flavanol molecules in the tea plant. Tea leaves account for around 12–15% catechins on a dry weight basis. Different types of polyphenols have been identified in leaves, and their structures vary with the substitution and position of the hydroxyl group (Zhang et al. 2019). Monomeric catechins, dimers, condensed tannins, methyl derivatives, and glycosides type catechins are its different forms. Chemical structure of catechins contains three hydroxyl groups at position 3′, 4′ and 5′ at ring "B" and resultant molecules are called gallocatechin. Whereas, the substitution of gallic acid at position 3 of ring "B" is characterized as catechin gallate. Catechin, epigallocatechin, epicatechin, epicatechin gallate, epigallocatechin gallate, are the main monomeric catechins reported in tea coarse leaves and flowers (Chen et al. 2018). Around 70–80% of polyphenols are catechins in flowers of *C. sinensis*. Monomeric catechins reported in tea leaves are also quantified in flower and fruit of tea (Lin et al. 2003). The content of catechins in tea flowers is less as compared to its leaves. The maximum content of catechins in flowers is reported in the early stage when petals start to split. Among different floral organs, calyx contains the highest content of epigallocatechin gallate (Forrest and Bendall 1969; Joshi and Gulati 2011; Rana et al. 2016). The total content of catechins reported in flowers of *C. sinensis* is around 3–4% on a dry weight basis (Lin et al. 2003). These molecules are distributed in the whole plant of *C. sinensis*. Previous studies revealed good content of catechins in immature fruits after leaves and flowers. Mature seeds, along with its different parts such as seed coat, cotyledon and embryo have been reported for the presence of two significant catechins (catechin, epicatechin) (Rana et al. 2016). The polymeric form of catechin is tannins and contributes a large portion of polyphenols and well distributed in the whole tea plant (Zhang et al. 2019). Tannins provide taste and well known to bind with protein molecules. These are complex metabolites that contain polyhydroxy groups.

6.5.4 Polysaccharides

Polysaccharides are water-soluble high molecular weight compounds and contain more than ten monomeric units linked together with a glycosidic bond (Chen et al. 2018). This glycoside bond is formed by joining of glycosyl unit of either hemiketal or hemiacetal with a hydroxyl unit of another sugar moiety. Tea polysaccharides contain 44.2% of neutral sugar, 43.1% of uronic acid, and 3.5% of the protein part (Du et al. 2016). Different methods used for their extraction are hot water extraction, enzymatic extraction, and boiling water extraction (Wang et al. 2010). Sugars identified from tea leaves are rhamnose, L-arabinose,D-(+)-galacturonic acid, galactose, glucose and glucuronic acid, D-(+)-xylose and mannose. However, the molecular weight of *C. sinensis* leaves polysaccharides is less than flower polysaccharides. Tea polysaccharides are mainly composed of rhamnose, L-arabinose, D -(+)-galacturonic acid, galactose, glucose units, and molecular distribution of tea leaves polysaccharides is between 3.67 × 103 to7.58 × 105 Da (Wang et al. 2012). From the past few years, interestingly, tea flowers are being explored, and higher molecular weight polysaccharides are reported. Tea flowers contain a large proportion of saccharides that accounts for around 20–25% polysaccharides (Wei et al. 2010). Acidic polysaccharides that are made up of arabinose, rhamnose, xylose, mannose, glucose, glucuronic acid, and glacturonic acid are constituents of tea flowers. Tea plant bear capsule-like fruits that form seeds after maturation. Seeds contain polysaccharides, and the total content of polysaccharides reported in tea seeds is 47.58%. Glucose is an important monosaccharide and seeds account glucose, galactose, xylose, rhamnose, and arabinose sugar units (Quan et al. 2011). Polysaccharides identified from tea seeds with different molecular weights are 500 kDa, 130 kDa, and 5 kDa. These are reported for a wide range of activities as presented in the Table 6.2.

6.5.5 Methylxanthines

Tea plant contains methylxanthines such as caffeine, theobromine, and theophylline. Caffeine is a chief alkaloid present in the tea plant (Fig. 6.3). It is a non-nutritive ingredient but has potential utilization. In tea plants, caffeine is distributed in all parts, and maximum content is reported in leaves (Zhang et al. 2019). Leaves contribute 2–3% caffeine on a dry weight basis. Caffeine synthase is the key enzyme involved in the synthesis of caffeine. This enzyme catalyzed reaction of

Table 6.2 Phytochemicals of *Camellia sinensis* and their characteristic functions

Compounds	Molecular formulae	Part	Characteristic functions	Reference
Volatiles	–	Flower, leaves	Protection against biotic stress, deterrents to herbivores, antimicrobial activity	Zhao et al. (2020) and Kubo et al. (1992)
Phenylpropanoid derivative	–	Flowers	Antimicrobial, antioxidant, anti-inflammatory, antidiabetic, anticancer activity, neuroprotective, cardioprotective, renoprotective and hepatoprotective effect	Neelam and Sharma (2020), Commisso et al. (2016), and Hemaiswarya et al. (2011)
Fatty acids	–	Flower, leaves, seeds	Anticancer activity, antibacterial activity, antioxidant activity	Mandal et al. (2019) and Karimi et al. (2015)
Terpenes	$(C_5H_8)n$	Flower, leaves	Antibacterial activity,cytotoxic activity, immunomodulatory activity,chemotherapeutic agent, radical scavenging activity	Guimarães et al. (2019) and Paduch et al. (2016)
Quercetin	$C_{16}H_{10}O_7$	Flower, fruit, leaves	Antioxidant and pro-oxidant effects, reduce inflammation by scavengingfree radicals, decreasing leukocyte immobilization, antibacterial activity, reduce cisplatin induced nephrotoxicity, anti-angiogenic effect, inhibitor of platelets aggregation, inhibitor of the enzyme aldose reductase hence cause antidiabetic effect, treat peptic ulcer, antiviral effect	Alrawaiq and Abdullah (2014)

(continued)

Table 6.2 (continued)

Compounds	Molecular formulae	Part	Characteristic functions	Reference
Myrcetin	$C_{16}H_{10}O_8$	Flower, fruit, leaves	Anti-Oxidant, antiphotoaging activity, anticancer activity, anti-platelet aggregation activity, antihypertensive activity, immunomodulatory activity, anti-Inflammatory activity, anti-allergic activity, analgesic activity, activity against aone-aelated disorders, activity against CNS disorders, antidiabetic and anti-obesity activities, antimicrobial activity	Semwal et al. (2016)
Kaempferol	$C_{16}H_{10}O_6$	Flower, fruit, leaves	Anticarcinogenic effects, antioxidant, modulates apoptosis, angiogenesis, inflammation, and metastasis	Chen and Chen (2013)
Flavonol glycosides	–	Flower, fruit, leaves	Antioxidant	Chen and Chen (2013)
Kaemferol glycoside	$C_{21}H_{20}O_{11}$	Flower,leaves	Antioxidant and anticancer properties, hypoglycaemic properties	Kumar and Pandey (2013)
Quercetin glycoside	$C_{21}H_{20}O_{12}$		Immunomodulatory effect, cardiovascular protection activity, anticancer activity, antitumor activity, anti-ulcer, anti-allergy, anti-viral, anti-inflammatory potential, anti-diabetic effect, gastro protective effects and antihypertensive effect.	Alrawaiq and Abdullah (2014)
Myrcetin glycoside	$C_{21}H_{20}O_{13}$	Flower, leaves	*in vitro* anti-HIV-1 activity, antioxidant activity	Chen and Chen (2013)
Rutin	$C_{27}H_{30}O_{16}$	Flower, leaves	Antiviral activity against (Parainfluenza virus, influenza virus, and potato virus)	Kumar and Pandey (2013)
Apigenin	$C_{15}H_{10}O_5$	Flower, leaves	Herpes simplex virus type, and Auzesky virus, Cancer Prevention	Kumar and Pandey (2013)

(continued)

Table 6.2 (continued)

Compounds	Molecular formulae	Part	Characteristic functions	Reference
Catechins	$C_{15}H_{14}O_6$	Flower, fruit, leaves	Anti-oxidant, anti-parkinson activity, anti-stroke activity, cardiovascular disease, anti-cancer activity, anti-diabetic activity, anti-obesity activity, anti-ageing activity, anti-bacterial, anti-allergic, anti-inflammatory	Agarwal et al. (2017)
Polysaccharides	$(C_6H_{10}O_5)_n$	Flower, leaves, fruit	Antioxidant activity, immunostimulating activity, antidiabetic activity, antitumor activity, hepatoprotective activities, immunostimulating activity anti-obesity activity, anti-fatigue activity α-glycosidase inhibitory property	Nie and Xie (2011) and Huang et al. (2013)
Caffeine	$C_8H_{10}N_4O_2$	Flower, leaves, fruit	Antimicrobial activity, increase alertness	Fredholm (1985)
Theobromine	$C_7H_8N_4O_2$	Flower, leaves, fruit	Antimicrobial activity, useful in respiratory tract problems, antitumor property, anti-inflammatory or cardiovascular protector	Martínez-Pinilla et al. (2015)
Theophylline	$C_7H_8N_4O_2$	Flower, leaves, fruit	Antibacterial activity	Martínez-Pinilla et al. (2015)
Saponin	$C_{58}H_{94}O_{27}$	Flower, leaves, fruit	Immunomodulatory effect, anti-inflammatory activity,hepatoprotective activity, antidiabetic effect, hypolypidemic effect, antio steoporosiseffect,antiviral effect, antifungal and antimicrobial effect, anthelmintic activities, cytotoxic activity, antifungal, anticancer	Abdou et al. (2013)
Phenolic acid	–	Flower, leaves, fruit	Antioxidant, antitumor, antimicrobial, apoptosis and necrosis in HeLa cervical cancer cells,	Heleno et al. (2015)

(continued)

Table 6.2 (continued)

Compounds	Molecular formulae	Part	Characteristic functions	Reference
p-Hydroxybenzoic acid	$C_7H_6O_3$	Flower, leaves	Antioxidant activity, antimicrobial activity, Oestrogenic activity	Rice-Evans et al. (1996)
Gallic acid	$C_7H_6O_6$	Flower, leaves, fruit	Antioxidant properties, antineoplastic, bacteriostatic, antimelanogenic, anticancer properties antimutagenic activity	Heleno et al. (2015)
Vanillic acid	$C_8H_8O_4$	Flower, leaves	Snake venom 5′-nucleotidase, antisicking and anthelmintic activities, suppress hepatic fibrosis	Dhananjaya et al. (2009)
Protocatechuic acid	$C_7H_6O_4$	Flower, leaves	Antioxidant, antimicrobial, cytotoxic, chemopreventive, apoptotic, and neuroprotective, LDL oxidation inhibitor	Yin et al. (2009)
Fumaric acid	$C_4H_4O_4$	Flower, leaves	Antioxidant activities, antimicrobial agents against pathogenic bacteria and fungi	Heleno et al. (2014)
p-coumaric acid	$C_9H_8O_3$	Flower, leaves	Antioxidant activity against free radicals, antitumor activity against breast, antimicrobial activity	Heleno et al. (2014)
Syringic acid	$C_9H_{10}O_5$	Flower, leaves	Antioxidant, antibacterial and hepatoprotective activities	Heleno et al. (2015)
Organic acids	–	Flower, leaves, fruits	Antioxidant activity, Antibacterial activity Preservative property improved nutrient digestibility	Sharma et al. (2018a, b)
Chlorophyll and Carotenoids	$C_{55}H_{72}MgN_4O_5$ and $C_{40}H_{56}$	Flower, leaves, fruits	Antioxidant Activity, skin protection, modulation of apoptotic signallingin cancer cells, anticarcinogenic agents coronary heart disease prevention, enhance immune functions Skin Protection	Stahl and Sies (2005)
Amino acids	–	Flower, leaves	Cognitive functioning and cognitive decline	Van et al. (2013)

(continued)

Table 6.2 (continued)

Compounds	Molecular formulae	Part	Characteristic functions	Reference
Theanine	$C_7H_{14}N_2O_3$	Flower, leaves, fruits	Regulate CNS disorders, anti-stress and neuroprotective role, modulate anti-neoplastic agents, influential effects ondiabetes, cardiovascular disorders, hypertension, tumor suppression	Sharma et al. (2018a, b)
Vitamin A	$C_{20}H_{30}O$	Flower, leaves	Support vision, immune system, inflammatory systems, cell growth and development, antioxidant activity	Maqbool et al. (2018)
Vitamin E	$C_{29}H_{50}O_2$	Flower, leaves	Antioxidant, Protect oxidative damage of low-density lipoproteincholesterol, membrane fats, maintain cellular function	Maqbool et al. (2018)
Vitamin K	$C_{31}H_{46}O_2$	Flower, leaves	Antioxidant, generate energy by electron movement, helps in blood clotting, maintain bone health	Maqbool et al. (2018)
Vitamin C	$C_6H_8O_6$	Leaves, flowers	Antioxidant, help in iron absorption, protect eye lens, help in collagen production, involved in neurotransmitter synthesis.	Maqbool et al. (2018)
Vitamin B2	$C_{17}H_{18}N_4O_7$	Leaves	Antioxidant, promotes iron metabolism	Maqbool et al. (2018)
Vitamin B1	$C_{12}H_{17}ClN_4OS$	Leaves	Central in energymetabolism	Maqbool et al. (2018)
Vitamin B3	$C_9H_{17}NO_5$	Leaves	Energy production, antioxidative defense	Maqbool et al. (2018)

S-adenosyl-L-methionine-dependent N-1- and N-3-methylation to form final product called as caffeine (Kato et al. 2009). Caffeine is a well-known component that enhances body alertness and helps to rejuvenate (Chen et al. 2018). Theobromine and theophylline are minor methylxanthines reported in a different type of teas (Fig. 6.3) (Alves and Bragagnolo 2002). Likewise, in leaves, fruit, and flowers also contain caffeine (Yang et al. 2009). In tea fruits, caffeine is accompanied by theobromine, which is instantaneous precursor of caffeine synthesis. The content of these alkaloids increases up to complete growth and then become stagnant. Studies revealed maximum content in pericarps of the fruits and less in seeds coat (Suzuki and Waller 1985). In tea plants, these nitrogen-containing compounds do not serve purpose as nitrogen reserves and might have some other ecological significance like in coffee (Suzuki and Waller 1985). Tea flowers also contain caffeine, theobromine, and 3, 7–dimethylxanthine alkaloids. Tea flower contains around 0.3–1.1% caffeine content (Chen et al. 2018). In an early report on flowers of *C. sinensis*, a substantial increase in caffeine content was observed up to October, while theobromine was found with little alteration in contents. The maximum content of alkaloids is present in stamens followed by petals of tea flowers. Caffeine is reported for good antimicrobial, antianxiety, anti-tremor activities (Nurminen et al. 1999). (Table 6.2).

6.5.6 Saponins

Saponins are an important class of compounds in tea (Fig. 6.3). It contains aglycone unit that is linked to the carbohydrate chain. These are glycoside compounds present in higher plants and mainly distributed in Araliaceae, Campanulaceae, Caryophyllaceae, Leguminosae, Scrophulariaceae, and Theaceae families (Man et al. 2010). Saponins are of two types, triterpenoid type, and steroid type. Pentacyclic triterpenoid saponins are the most abundant saponins in genus *Camellia*. In tea, mainly triterpenoid type saponins have been reported. Sapogenin (aglycone) unit is attached to carbon 3 position of carbohydrate moiety and is high molecular weight compounds (Yoshikawa et al. 2005). Carbohydrate unit is water-soluble and sapogenin is fat-soluble hence possess detergent like property. The tea leaves contain little content of saponins as comparison to other parts of *C. sinensis*. Leaves account 0.04–0.07% saponins on dry weight matter (Chen et al. 2018). Around 100 saponin molecules have been isolated till date. Theasaponin, isotheasaponins, foliatheasaponins, floratheasaponin and cinnamic acid containing theasaponins are reported in leaves of *C. sinensis*. Pentacyclic triterpenoids saponins are important bioactive molecules, and used due to their therapeutic potential for diabetes, liver-related problems, and wound healing purposes (Table 6.2). Due to increasing interest in saponins, recent studies are concentrating to locate them in different parts.

Flowers of *C. sinensis* contain a higher content of saponins than shoots. Floratheasaponin, chakasaponin, floraassamsaponin and assamsaponin are tea flower saponins (Fig. 6.3). In countries like China and Japan, saponins are incorporated in soft drinks for frothing properties. Compositional studies of floratheasaponins and their comparison in different regions of the world such as India, China, and Japan had also been performed previously.[49]

Extraction and purification of saponins from tea seed cake are well studied and are mostly of pentacyclic triterpenoid types or oleanane type. Further, they contain ligand, glycosides, and organic acid moieties (Zhang et al. 2019). Saponins from plant sources have been reported to impart anti-fungal, anti-microbial, insecticidal activities (Augustin et al. 2011). Few studies have also proven the anti- tumorigenic effects of triterpenoid molecules (Dinda et al. 2010). Isolation and purification of these molecules have been performrd using macroporous resin, although these are bulky molecules, and separation is quite difficult.

6.5.7 *Phenolic Acids*

Quality of tea is assessed by its flavour, chemical constituents and taste. Along with various phenolic compounds, phenolic acids are one of the significant contributors in tea leaves. Phenolic acids are naturally occurring molecules distributed in two main groups, hydroxycinnamic and hydroxybenzoic type (Yao et al. 2004). In tea hydroxybenzoic acid type of phenolic acids are abundant. They are ubiquitous and associated with various beneficial effects such as antioxidant and nutritional (Das and Eun 2016). Phenolic acids present in tea are mainly gallic acid derivatives. *Camellia sinensis* flush showed the presence of gallic acid, galloylquinic acid, vanillic acid, coumaryl quinic acid, protocatechuic acid and galloylated glucose derivatives. Studies revealed the predominance of gallic acid aglycones (Yao et al. 2004; Joubert et al. 2012; Del Rio et al. 2004). In fresh tea leaves, a trace amount of gallic acid has been recorded, while an increase in its content was observed during the tea manufacturing process (Del Rio et al. 2004). This is due to the formation of theaflavic acid via auto oxidation. Theaflavic acids oxidise the gallocatechins, and produced gallic acid. Hence, content of gallic acid depends on the auto-oxidation process. The phenolic acids present in C. sinensis flowers are quinic acid, shikimic acid, gallic acid, fumaric acid, glycolic acid, and p-coumaric acid (Fig. 6.3) (Muhlemann et al. 2012). Few metabolomic studies have revealed only the little information on their presence in tea flowers. Health beneficial effects are presented in Table 6.2.

6.5.8 *Organic Acids*

Organic acids are non-volatile compounds that play an essential role in the respiration process and involved in flavanol biogenesis (Neish 1960). Tea plant is a rich cradle of organic acids. Dicarboxylic acids, as well as tricarboxylic acid like malic, citric, succinic, oxalic, isocitric acids were reported to present in the tips of tea shoots (Fig. 6.3) (Sanderson and Selvendran 1965). Recently, metabolomics studies of tea leaves also reported to contains good amount of organic acids (Jia et al. 2016). It is known that few organic acids have aroma (Sanderson and Selvendran 1965). Moreover, tea leaves contain shikimic acid and quinic acid which are essential for the biosynthesis of polyphenols (Zaprometov 1967). Flowers have been reported to show the presence of malic acid, citric acid and succinic acid. Citric acid decreases with the growth of flowers but maximum amount of organic acids is reported in *C. sinensis* flowers . This is the key component for the tricarboxylic acid cycle during the flowering stage (Muhlemann et al. 2012). This cycle is driven by the organic acids, and required in an additional amount in the flowers.

6.5.9 Chlorophyll and Carotenoids

Plants contain various types of pigments includings chlorophylls. Chlorophylls have been studied for numerous epidemiological studies (Table 6.2). Mainly six chlorophylls and 13 species of carotenoids have been identified in tea leaves (Zhang et al. 2019). Chlorophylls and carotenoids are reported in tea leaves and made teas. Carotenoids are colored pigments made up of 8 isoprene units and called as tetraterpenoids. Carotenoid content in tea leaves ranges between 36 to 73 mg/100 g (dry weight). β-carotene, lutein, and zeaxanthin are significant carotenoids. During the tea manufacturing process, these metabolites get converted to their derivatives and aroma molecules (Sandeep and Nisha 2012). Further, the increase of these metabolites were also observed upto 10%. Pheophorbide, chlorophyll a, chlorophyll b, pyropheophytin a, are present in tea leaves while tea flowers also contain carotenoids in stamin part which impart color (Zaprometov 1967). The carotenoid profile in tea flowers has also been reported earlier and alteration observed in carotenoids content at different developmental stages (Suzuki and Shioi 2003). Carotenoids are mainly xanthophyll and carotenes. Neoxanthin, lutein, zeaxanthin are xanthophylls and α-carotene and β-carotene are the carotenes that have been reported in *C sinensis* flowers (Baldermann et al. 2013).

6.5.10 Amino Acids

Amino acids are primary metabolites and play a very significant role in cellular development. They are present in living cells and provide energy. Amino acids are building blocks for protein formation and other secondary metabolites synthesis (Zhang et al. 2019). These are precursors of various reactions that result in the establishment of color, odor, and other relevant secondary metabolites. In tea, amino acids are the precursors of aroma which define the quality of tea and responsible for umami taste (Guo et al. 2018). Around 26 amino acids are found in tea and theanine showed the dominancy in that (Guo et al. 2018; Sharma et al. 2018a, b). Theanine is non-proteogenic amino acid having various biological effects (Table 6.2). Free amino acids in leaves are theanine, glutamic acid, aspartic acid, serine, glutamine, alanine, arginine, and threonine. These amino acids, along with theanine, account for around 60–70% of free amino acids (Chen et al. 2018). Studies have demonstrated that during the time for processing of leaves to different kinds of teas (Tuan et al. 2016). Tea flowers contain free amino acids similar to their leaves, but little information is available in the literature. The amount of free amino acids reported in flowers per dry weight basis is around 0.8% (Wang et al. 2010). Theanine is the most abundant amino acid, followed by histidine while tryptophan, phenylalanine, isoleucine, leucine and lysine are present in trace amount in the tea flowers (Wang et al. 2010). Asparagine, glutamic acid, serine, arginine, alanine, threonine, tyrosine, methionine are the other minor amino acids present in the tea flowers. Theanine is also acts as a natural relaxant and showed its cooperative effect with an anti-tumor agent for cancer treatments (Juneja et al. 1999). Bioactivities related to aminoacids are depicted in Table 6.2.

6.5.11 Spermidine Derivatives

Putrescine, spermidine, spermine and spermidine derivatives are polyamines that are distributed in leaves and flowers of the *C. sinensis* (Fig. 6.4) (Chen et al. 2018). The dietary tea polyamines are mostly found in the floral parts and have significant uses. Some spermidine derivatives such as coumaroyl di-feruloyl spermidine, N1, N5, N10-tri-coumaroyl spermidine, tri-feruloyl spermidine and feruloyl di-coumaroyl spermidine are characteristic to *C. sinensis* flowers that are not reported in leaves (Chen et al. 2018). Moreover, spermidine-phenolic acid conjugates were

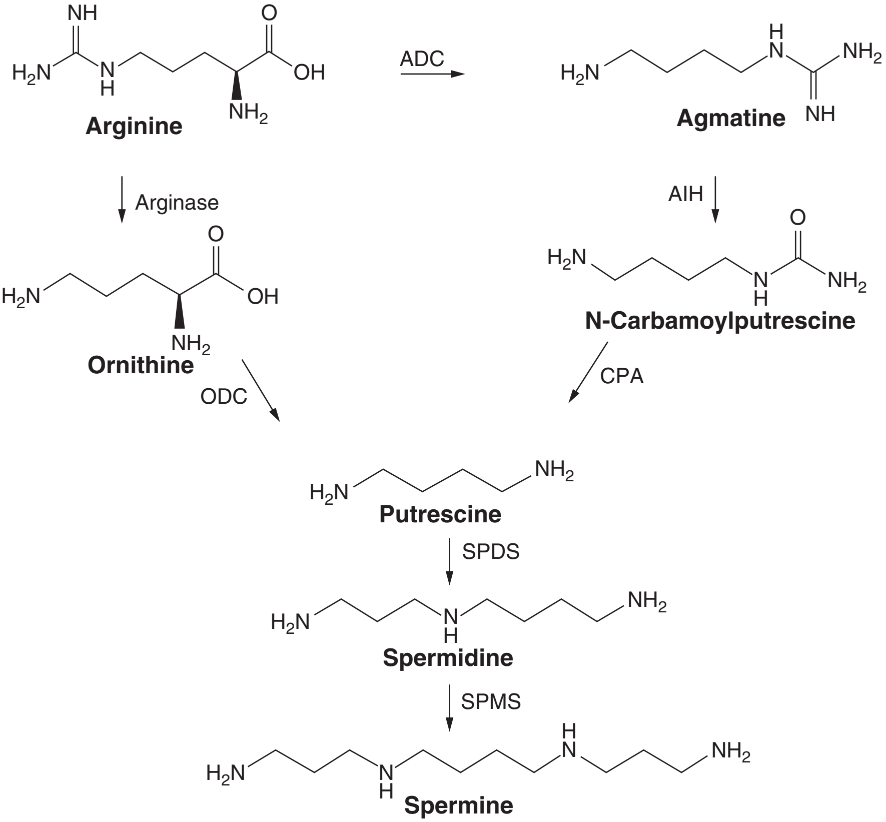


Fig. 6.4 Schematic view of biosynthesis of polyamines
ADC arginine decarboxylase, *AIH* agmatine iminohydrolase, *CPA- N* carbamoylputresine, *ODC* ornithine decarboxylase, *SPDS* spermidine synthase, *SPMS* spermine synthase

reported in *C. sinensis* flowers (Yang et al. 2012). Diversified roles of spermidine and its phenolic conjugates have been explored (Facchini et al. 2002). Hydroxycinnamic acid-spermidine derivatives contributed to the chemotaxonomic classification in the plant families. Thus spermidine derivatives and its phenolic conjugates can also be useful for the characterization of tea diversity.

6.5.12 Vitamins

Water soluble and fat soluble vitamins are necessary for the sustenance of body functions like growth and maintenance (Table 6.2). Tea leaves contain fat soluble vitamin K, E, A and water soluble vitamins B1, B2, B3 and C. Ascorbic acid (vitamin C) is core vitamin reported in black and green teas along with its different parts such as fruits and leaves (Liang et al. 1990; Sanderson et al. 1972). Different type of made teas also reported the presence of Vitamin C, but during the process of tea fermentation these vitamins get decomposed and reduced in their content (Gramza-Michałowska and Bajerska-Jarzębowska 2007). Green tea has been listed as good source of vitamin K but studies revealed its trace amount. Vitamins are detected and quantified by analytical tools like high performance liquid chromatography, solid-phase microextraction followed by gas chromatography combined to flame ionization detector (Reto et al. 2007).

6.5.13 Minerals

C. sinensis plant is rich in minerals (such as potassium, calcium magnesium, manganese, iron, phosphorous, nickel, sodium, boron, molybdenum, sulphur and Zinc (Li and Wang 2009). Cobalt, lead, cadmium are also reported but their presence is dependent on soil (Li and Wang 2009). Consumption of tea leaves beverage fulfils the daily requirement of essential minerals and Tea leaves are good source of potassium, manganese with positive effect on high blood pressure patients (Schwalfenberg et al. 2013; Fernandez et al. 2002). The content of minerals are more abundant in flowers than leaves (Muhlemann et al. 2012). Minerals reported in tea flowers are aluminum, zinc, calcium, sulphur, manganese, magnesium, boron, phosphorous, copper and iron. Among all, phosphorous and copper are present in the majority.

6.6 Biological Activities of Metabolites

In the past few years, research have been performed to establish the potential of *C. sinensis* and its phytochemicals against various diseases such as diabetes, arthrosclerosis, obesity, hypertension and cancer. Different molecules have diverse

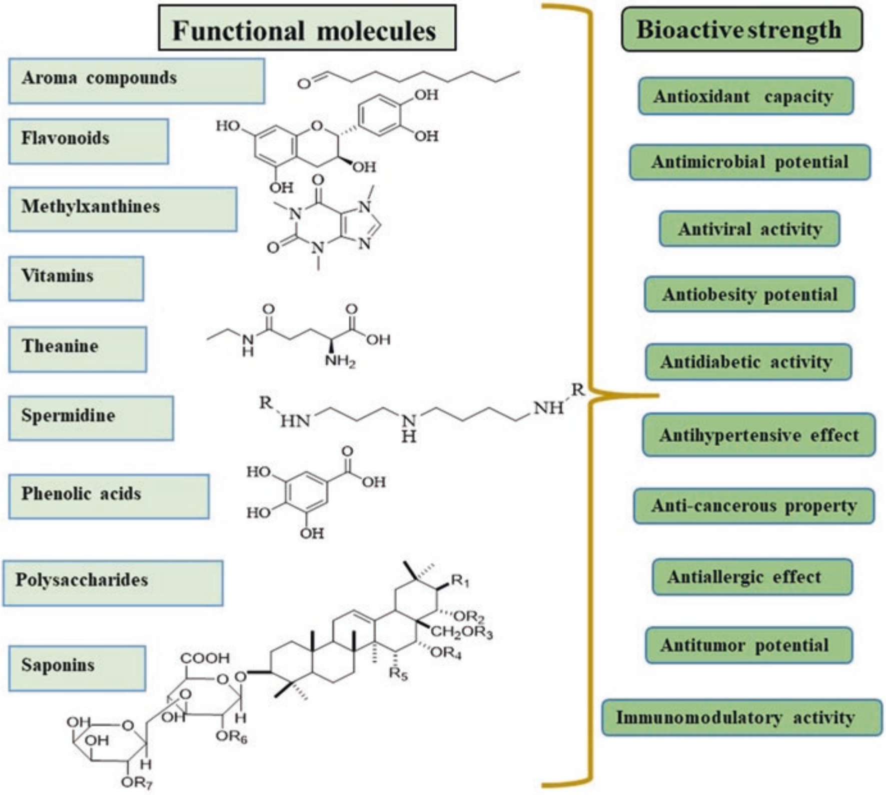


Fig. 6.5 Major phytoconstituents of tea and their pharmacological properties

biofunctional effects, hence bioactivities of major tea phytoconstituents (Fig. 6.5) is discussed (Table 6.2). The volatile components of leaves and flowers of *C. sinensis* provide protection aginst stress, protect plants from herbivours and act as good antimicrobial agents (Zhao et al. 2020; Kubo et al. 1992). Phenylpropanoid derivatives present in tea flowers posses diverse bioactivities (Neelam and Sharma 2020; Commisso et al. 2016; Hemaiswarya et al. 2011). Simillarly fatty acids and terpenes from *C. sinensis* reported for antioxidant, antimicrobial and anticancer activities, that further expans the significance (Mandal et al. 2019; Karimi et al. 2015; Guimarães et al. 2019; Paduch et al. 2016). Long chain fatty alcohols (Polycosanols) are reported for low-density lipoproteins cholesterol lowering effect, increase high-density lipoproteins and inhibit the oxidation of low-density lipoproteins colesterol oxidation. These are also considered as potent dietry suplements. *In vivo* studies in rats and human, reported the reduction of platelets aggregation (Narayan et al. 1988). The most common studied class of compounds in tea is flavonoids. These are widely known for their numerous health benefits. Various flavonoids like catechins, quercetin, rutin, apigenin have been reported for their hepatoprotective activity. Anthocyanins increase hepatic Gclc expression by enhancing the level of cyclic adenosine monophosphate that activates protein kinase A. This further upregulates cyclic adenosine monophosphate response element-binding protein phosphorylation to promote cyclic adenosine monophosphate response element binding - deoxyribonucleic acid binding and results in increasing glutamate-cysteine ligase catalytic transcription. With the increase in glutamate-cysteine ligase catalytic expression, hepatic reactive oxygen species level and proapoptotic signaling get decreased. Cyanidin-3-O-β-glucoside anthocyanin treatment decreases hepatic lipid peroxidation and inhibits the release of proinflammatory cytokines. Likewise other metabolites covering the class of flavonoids are potential bioactives (Alrawaiq and Abdullah 2014; Semwal et al. 2016; Chen and Chen 2013; Kumar and Pandey 2013; Agarwal et al. 2017). Polysaccharides, methylxanthenes and saponins contributing major part of phytochemical constituents of tea plant with functional properties (Nie and Xie 2011; Huang et al. 2013; Martínez-Pinilla et al. 2015; Fredholm 1985; Abdou et al. 2013). Polysaccharide play an important role in the anti-hepatotoxicity activity. The immunomodulatory activity of polysaccharides has been reported along with catechins. All the bioactivities of tea plant are credited to its phytochemical constituents. Activities like antioxidant potential, antimicrobial activity, antiviral activity, anti-covid activity, antiobesity, antidiabetic effect, antihypertensive effect and anticancer activity are associated with different phytochemicals of *C. sinensis* and elaborated here. While other activities such as immunomodulation, antidiabetic potential, antiinflamatory activity,antivenome property, hepatoprotective effect, skin protection, anti-allergic effect, antidiarrheal, anti-hyperglycemic activities etc. are dipicted in Table 6.2 (Heleno et al. 2015; Rice-Evans et al. 1996; Dhananjaya et al. 2009; Yin et al. 2009; Heleno et al. 2014; Khan and Iqbal 2016; Stahl and Sies 2005; Van et al. 2013; Maqbool et al. 2018).

6.6.1 Antioxidant Activity

Polyphenols are known for excellent antioxidant potentials. The antioxidant activity has been evaluated by using different *in-vitro* experiments. Antioxidant potential of polyphenols depends upon occurence of hydroxyl groups on benzene molecule. Number of hydroxy groups present on these molecules impart antioxidant potential by scavenging free radicals or by chelation effect (Hollman et al. 1997). This functional group influences numerous mechanisms of antioxidant activities. The B ring hydroxyl configuration of flavonoids is substantial determinants for free radical scavenging activity. These antioxidant molecules donate hydrogen or electron to free radicals and resulting in the formation of relatively stable flavonoid radicals. Flavonoids protects the plants against abiotic and biotic stress. Both glycon and aglycon forms of flavonoids are excellent antioxidants. Polyphenolic molecules especially epigallocatechin gallate and epigallocatechin contribute for the most antioxidant activity (Xu et al. . 2017). These molecules provide more interaction sites for free radicals to bind (Koch et al. 2018). Flower extract of *C. sinensis* showed antioxidant activity against 2,2-diphenyl-1-picrylhydrazyl free radical at IC_{50}

19.7µg/ml. The 2,2-diphenyl-1-picrylhydrazyl free radical scavenging activity of *C. sinensis* essential oil is reported at IC_{50} value of 13.22 mg/mL (Chen et al. 2014). Hetero-polysaccharides of tea bind with proteins that relieve the oxidative stress and leads to antioxidant activty. The activities of polysaccharides vary with the molecular weight. The monomeric units of tea leave polysaccharides exhibited good antioxidant property (Wang et al. 2010). *In vivo* hepatoprotective activity and *in vitro* antitumor activity studies along with antioxidant potential have been performed with purified polysaccharides (Xu et al. 2012). Thus, suggested polysaccharides is a powerful natural polymer along with bioactive effects. Tea polysaccharides were extracted and characterized from low grade teas. Further they were characterized from the tea flowers which seems to be additional alternate source of polysacharrides (Quan et al. 2011). The saponins, phenolic acids, organic acids from *C. sinensis* have been reported for their anti-oxidant potential (Stahl and Sies 2005). Phenolic acids contain carboxylic acid group along with hydroxyl group and contribute towards antioxidant property by inhibiting oxidative damage (Heleno et al. 2015). Vitamins contribute to minimize the deoxyribonucleic acid damage, oxidative cell damage and decrease the risk of cancer and other degenerative diseases (Sies et al. 1992). Hence tea is excellent source of antioxidants (Table 6.2).

6.6.2 Antimicrobial Activity

Plants synthesize few secondary metabolites in response to microbial infection (Zhang et al. 2019). Plants containing flavonoids are good antimicrobial agents. *In vitro* and *in vivo* studies showed inhibition of pathogens by made tea extracts (Bansal et al. 2013). Previous studies reported infusions of herbal teas as good antibacterial (Da Silva 2013). Different category of flavonoids shows antimicrobial activity against different bacterial and fungal stains. These have numerous cellular targets. Their molecular action is to form complex with proteins via hydrogen bonding, covalent bonding and hydrophobic effect. Thus their ability to adhere protein transport, disruption of microbial membrane, inactivation of microbial adhesion results in antimicrobial activity (Kumar and Pandey 2013). Flavan-3-ols, mainly catechins are well known antibacterial molecules that show activity against, *Shigella, Bacillus subtilis*, *Staphylococcus aureus, Streptococcus mutans, Escherichia coli* and *Klebsiella pneumonia, Vibrio cholera, Streptococcus sobrinus, Micrococcus luteus* (Rana et al. 2016; Kumar and Pandey 2013). Water extract of different tea combination have been optimized against antimicrobial activity (Zhang et al. 2019). Study coupled with electrospray ionization mass spectrometry characterized compound responsible for the activity (Granato et al. 2016). 2-phenyl ethanol as one of the important compound in tea flowers which seems to be exhibitsted the antimicrobial potentials. Triterpenoid molecules from tea seeds showed antimicrobial potential. Organic acids have good antimicrobial activities and used to protect meat and poultry products from *Salmonella* (Table 6.2) (Mani-López et al. 2012).

6.6.3 Antiviral activity

Living organisms have their own defence system that protects them from various conditions. Viruses have negative impact on plants, animals and other organisms. It can cause acute to chronic diseases (Schinzari et al. 2015). Hepatitis, liver cirrhosis and liver carcinoma and acquired immunodeficiency syndrome are some virus caused disorders (Coffin and Lee 2015). The cause of chronic diseases is invasion of virus to vital organs of the body. Catechins from green tea are effective against some viruses such as Zika virus, Chikungunya, dengue, fish, and livestock viruses (Carneiro et al. 2016; Xu et al. 2017). Green tea has differential effects on various types of viruses. Green tea extracts containing epigallocatechin gallate and epicatechin have reported for their inhibitory effects on influenza virus (Sur et al. 2001). Epigallocatechin gallate is the most studied catechin in tea showed docking to binding pocket of E protein. It also causes damage to virus particles with the help of interaction with lipid envelop (Carneiro et al. 2016). The activity of epigallocatechin gallate against adenovirus is demonstrated in different levels like direct inactivation of virus, protease adenine inhibition or intracellular growth inhibition. Epigallocatechin gallate is most potent antiviral molecule because of its structure having paragalloyl and galloyl moieties (Deryabin et al. 2008; Ishii et al. 2010). These groups are responsible factor for antiviral activity. It interacts with the surface of viron and cause interruption between interaction of viron and host cell. Tea extracts interferes with the adsorption of viruses like Rotavirus, Enterovirus EV71 (Mukoyama et al. 1991). Monoterpenes and triterpenoids in essential oils also have good antiviral activity against herpes simplex virus type 1(Table 6.2) (Bayala et al. 2014).

6.6.4 Anti-COVID Activity

World is facing new threat in the form of novel etiological virus. The virus is identified as COVID- 19 commenced in Wuhan city of China during year 2019–2020 and now spreaded in more than 180 countries. To discover rapid and effective treatment virtual screening of phytochemicals have been underway (Jin et al. 2020). Among various natural molecules, tea polyphenols was identified as one of the positive lead against main protease (Mpro) inhibitor of the virus. As per the recent studies on tea polyphenols bioactivities, around 65 phytochemicals of tea have been tested against main protease of severe acute respiratory syndrome coronavirus-2 (Bhardwaj et al. 2020). With the help of molecular docking three main active constituents of tea were studied in comparison with atazanavir, darunavir, and lopinavir (repurposed drugs) against the virus. The oolonghomobisflavan-A, theasinensin-D, and theaflavin-3-*O*-gallate were found with the maximum docking score than compared drugs. These molecules have been reported in different teas like oolong tea, green tea, and black tea manufactured from the leaves of *C. sinensis*. Thus bioactive constituents of *C. sinensis* are valuable and can became saver from dreadful virus.

6.6.5 Antiobesity

Obesity is growing metabolic syndrome worldwide, and antiobesity drugs from synthetic origion are available in the market but have adverse effects. Therefore, the activity of natural compounds against obesity is an advantage over synthetic drugs. Green tea has extensively studied against obesity and resulted in promising outcomes (Kao et al. 2006). Epidemiological and clinical studies of epigallocaetchin gallate have shown its effects on reducing obesity. However, the mechanisms are related to energy balance modulation, metabolism of carbohydrates, and lipids or via the endocrine system (Chen et al. 2018). The consumption of green tea and black tea is also reported to increase fat metabolism by enhancing postprandial thermogenesis (Henning et al. 2018). The caffeine and epigallocaetchin gallate were found to decrease human body weight at doses of 270 mg, epigallocaetchin gallate +150 mg caffeine/day/78.7 ± 4.3 kg body weight (Dulloo et al. 1999). Caffeine was found effective against obesity via raising AMP-activated protein kinase phosphorylation in visceral adipose tissues (Pang et al. 2008). The recent findings suggested the ability of polyphenols to regulate obesity by activating adenosine 5′monophosphate-activated protein kinase (Eng et al. 2018). Moreover, the *in-vitro* study of complex polyphenols (tannins) showed effects on 3 T3–1 pre-adipocyte cells and revealed the antiobesity activity of tannins (Sung et al. 2015). Flavanoids and saponins help to delay fat absorption from the diet in the intestine through inhibition of pancreatic and lipase activity and minimizing the fat deposition. Further, saponin enriched fractions were suggested to suppress mRNA of a neuropeptide that monitor body weight., regulate food intake and energy expenditure. The tea saponin enhances the release of serotonin, as observed in the *in-vitro* studies on isolated ilea of mice. Thus the tea saponins are in agreement with its good antiobesity activity (Hamao et al. 2011). Conclusively, it is observed that tea phytochemicals comprehensively helps to combat obesity (Table 6.2).

6.6.6 Antidiabetic Effect

Diabetes is a metabolic syndrome and results in the irregular production of insulin. The insulin resistance and decreased function of beta cells secreted in the pancreas are the major problem in Type–II diabetes. The recent research has illustrated flavonoids as good antidiabetic agents, and the National Institute of Health Clinical Centre have exploited the use of quercetin over glucose absorption in obesity-related type 2 diabetic patients by oral glucose tolerance test (Song et al. 2005). The consumption of a flavonoid enriched diet helps to lower blood sugar levels.

Epigallocatechin gallate retard the formation of glycation end products, and further studies suggested its role in declining the production of glucose in hepatoma cells of rats (Waltner-Law et al. 2002). The green tea extracts reported to alter glucose metabolism in diabetes mellitus conditions (Wu et al. 2004). The phenolic acids have a different mechanism of action for its antidiabetic potential. The chlorogenic acid decreased the glycemic index in the body of diabetic rats by reducing intestinal glucose absorption while caffeic acid enhances the hepatic glucose utilization and inhibition of the overproduction of glucose (Jung et al. 2006; Bassoli et al. 2008). Similarly, sinapic acid ameliorating hyperglycemia through phospholipase C-protein kinase C signals and enhanced the glucose utilization and act as potential antidiabetic (Cherng et al. 2013). Tea polysaccharides suggested antidiabetic potentials (Wu et al. 2004). They are reported to have α-glucosidase and α-amylase activity. The regular administration of tea flowers polysaccharides showed a decrease in blood glucose levels in alloxan-induced diabetic mice. Chakasaponins obtained from tea flowers have also been reported to elevate the glucose level and plasma triglycerides. The finding documented for its antihyperlipidemic and antihyperglycemic activities. Further, the primary metabolites such as amino acids have shown its role in nutrient management, which supports life. They exhibited antidiabetic potential by removing excess glucose from the blood and an unregulated IR system (Sulochana et al. 2001). Administration of amino acids reported to decrease the postprandial blood glucose levels in type 2 diabetes mellitus (Table 6.2).

6.6.7 Antihypertensive Effect

Hypertension refers to an increased rate of blood pressure that is now a global health problem. Hypertension is also a metabolic syndrome that results in various health effects such as diabetes, cardiovascular diseases (Eng et al. 2018). Catechins reported for the decrease in systolic blood pressure without any adverse effect to hypertensive patients (Nagao et al. 2007). Caffeine and methylated catechins present in tea have intense angiotensin-converting enzyme inhibitory activity. Meta-analysis performed for green tea consumption resulted in a significant decrease in blood pressure. Green tea phytochemicals were reported to maintain vascular tone by harmonizing vasoconstriction substances (angiotensin II) and vasodilating substances (prostacyclin). Further, flavonoids (Quercetin) showed a decrease in pregnancy-induced hypertension (Ozarowski et al. 2018). However, extensive multilevel studies are still required to explore its exact mechanism of action for antihypertensive effects. Tea enriched with flavonoids also helps to protect against coronary heart diseases that are resultant of high blood pressure. Tea phenolic acids and other polyphenols improve endothelium-dependent vasodilation in the aorta, activate vascular endothelial nitric oxide synthase, and decrease blood pressure. Tea seed oil as a rich source of oleic acid, have a cholesterol-lowering effect, which reduces the blood pressure and cuts down the risk of heart stroke (Wang et al. 2011).

6.6.8 Anticancer Activity

Cancer is a major health problem and plant secondary metabolites are directed as a good source of anticancer agents (Table 6.2). Extensive studies are carried out for the phytochemical evaluation against fatal diseases like cancer. *C. sinensis* contain phytochemicals that inhibit chemically induced carcinogenesis among mice models (Yanaida et al. 2002). The anticancer studies of flavonoids have widely studied, and multiple mechanisms of actions have been reported, such as cell cycle arrest, down-regulation of protein (p 53), inhibition of tyrosine kinase, expression inhibition of Ras protein (Davis et al. 2000). Antioxidant compounds are potent anticancer agents, and activity depends on the competence of metabolites as radical oxygen inhibitors (Mishra et al. 2013). Flavanones, isoflavanones, and complex polyphenols (lignans) are reported to decrease their cell proliferation and prevent the binding of estrogen to cancer cells. Caffeic acid, quercetin, and their derivatives act on NF-κB signaling and give anticancer activity. Another flavonoid called apigenin target leptin receptor pathway and induced apoptosis in lung adenocarcinoma cells (Davis et al. 2000). Luteolin obstructs epithelial-mesenchymal transition. Flavanones, isoflavones, and lignans prevent the binding of the estrogen to the cancer cells and reduce their proliferation (Mishra et al. 2013). Both *in vitro* and *in vivo* studies showed suppression in Lung, bladder, skin, prostate, and breast cancer by epicatechin gallate, epicatechin, epigallocatechin extracted from leaves of C. sinensis. Whereas, *in-vivo* studies of theobromine showed suppression in lung cancer (Seo et al. 2015). Cyanidin-3-*O*-glucoside that is reported in purple leaves and inhibit cell growth induced apoptosis in highly tumorigenic rat esophageal epithelial cell line named as RE-149 DHD. It stops matrix metallopeptidase-9 expression in bladder and lung cancer (Singh et al. 2016). Phenolic acids also help to delay in tumor progression (Kumari et al. 2017). Further administration of polyphenol enriched diet is reported to inhibit the progression of 4-nitroquinoline-1-oxide induced tongue cancer (Yanaida et al. 2002).

6.7 Conclusion

Tea plantations leftover highly valuable bioresources in form of flowers, fruits and coarse leaves after harvesting of tender leaves for tea manufacture. Undoubtedly these plant parts have emense prospective for diverse utilization. The tea is recognized globally due to the presence of potential bioactive metabolites such as polyphenols, methylxanthine, unique amino acid, terpenoids and various other valuale chemical entites. Similarly, polysaccharides, saponins, and fatty acids are the chemical representatives of tea fruits and ripe seeds. Furthermore amino acids, phenolic acids, organic acids, vitamins, minerals are other essential phytochemicals that are less explored from fruits and flowers. Evergrowing global population has created scarcity of bioresources and highlights the need for exploring the existing resources to their fullest capacity. Since the occurence of highly valuable bioactive metabolites in abandoned parts of the tea plant can serve the purpose by their valorization. Tea based products are ever increasing area of new business avenues. The different bio-functional effects of phytoconstituents present in the tea flower, fruit, and leaves have versatile potential for their utilization. Therefore, exploration of these economically underutilized parts of *C. sinensis*, have huge future perspectives.

Acknowledgments Authors are also thankful to Council of Scientific and Industrial Research (CSIR) New Delhi India and Department of Science & Technology, New Delhi, for award of Women Scientist Scheme (WOS-A) to RS (GAP- 0239). AR is thankfull to BIRAC, DBT India for financial support through BIPP scheme.

Conflict of Interest Authors have no conflict of interest.

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Chapter 7
Recycling Nutraceuticals from Agro-Industrial Residues

Gargi Ghoshal

Abstract Agro-industrial residues contain lignocellulose and bioactive compounds that could be recycled as enzymes, vitamins, dietary fibers, pigments, organic acids, bio-fuels, antioxidants, antibiotics, and animal feed, for example. Here we review the fermentation of agricultural waste for the production of food additives, antibiotics, antioxidants, enzymes and biosurfactants.

Keywords Agro-industrial residue · Bio fuels · Enzymes · Fermentation · Lignocellulosic waste · Organic acids · Vitamins

7.1 Introduction

Huge amount of ago-industrial residues produced every year by different food and agro-processing industries. Agro-industrial residues are exonerated surroundings devoid of following appropriate discarding system eventually ecological fault and harmful consequences on fitness of living being. Majority of these wastes are natural and unused, thus it is discharged by incineration, discarding or by land filling. Natural wastes generate diverse inconvenience with weather by raising percentage of greenhouse gases. Also, the use of fossil fuels has remarkable influences on greenhouse gases production (Bos and Hamelinck 2014). Therefore the global apprehension is to find out the improvement or alternative resources for cleaner and renewable bio-energy as agro-wastes cause a severe disposal difficulty. The juice industries produce fruit peels in huge quantity, coffee industry produce coffee pulp in vast amounts and cereal industries generate husks which are considered as waste. Globally total fiber residue wheat straw, rice straw are found about 147.2, 709.2 and

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable
Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_7

673.3 million metric tons respectively (Belewu and Babalola 2009). But proximate study revealed that these residues are highly nutritious, thus it accomplished additional concern in quality protection (Table 7.1).

Earlier reports described that diverse categories of fruits and nuts waste for example green walnut husks, pomegranate peels, lemon peels successfully utilized as standard antimicrobials (Adámez et al. 2012). Organic compounds produced from wastes though it is a hazard to the environment, but they characterize potential resources for cultivation of mushrooms as food as well other bio-based stuff in terms of energy and fertilizers. Several agricultural residues are utilized for making animal feed. Nonetheless, these wastes have lot of variations in composition for example large quantities of carbohydrate, proteins, and minerals.

Considering presence of highly nutritious components, these residues and not described as "wastes" but as essential/optional ingredients for another produce. The accessibility of these nutrients in unrefined form such as cereal industries generate husks. A range of studies informed that various kind of fruit waste e.g. pomegranate, lemon peels and green walnut husks employed as natural antimicrobials. These nutrients in peel or husks provide suitable environments and solid support for microbial growth in SSF system for manufacturing diverse valuable goods likefermentable sugars by dropping the manufacturing charges depending on the food crops (Adámez et al. 2012; Katalinic et al. 2010).

7.2 Agro-Waste

About 1.3 billion tonnes is wasted yearly which is approximately 33% of the food manufactured globally for eating of mankind. The tubers, roots as well as fruits and vegetables, have recorded highest (40–50%) wastage rates as compared to any other food, representing (520–650 million tonnes) globally per year. Food wastage of European Union recorded 39% or 89 million tons of food waste occurs during preparation annually, whereas 367 million tons per year inedible in the European Union (Panesar et al. 2016). However, highest quantity of agro-waste dedicated for animal bedding and fodder, and diverse horticulture purpose.

7.2.1 Valorisation of Agro-Industry Wastes

According to various earlier studies performed in last decades investigating the efficient consumption of agro-waste, the prospective ingredients for manufacturing of important produce to add value. Largely agro-waste utilization have been done in agriculture rich countries as their economies are greatly dependent on agriculture. Currently, bioethanol and other liquid-fuels are industrial functioning procedure to utilize agro- waste as major starting ingredients. Largest manufacturer and exporter of sugar cane is Brazil and eventually, Brazil also the second biggest maker of

Table 7.1 Production of food grade enzymes and Applications

Enzymes	Substrate	Organisms used	Fermentation type	Activity	Industrial Applications	
					Industry	Application
Pectinase	Orange bagasse	*Thermoascus aurantiacus* 179–5	SSF	19,320 Ug-1 (PL)	Fruit Industry	Clarification of the fruit juices
	Wheat bran 10% sugarcane bagasse +90% Orange bagasse		SSF	11,600 Ug-1 (PL) 40, 180 Ug-1 (PL)		Enhanced levels of fruit juice volume when fruit pulps treated with pectinase
	Lemon pulps	*Trichoderma virde* *Aspergillus niger*	Slurry state	9.01 Uml-1		Soften the peel of citrus fruits
	Orange bagasse: wheat bran (1:1)	*Penicillium viridicatum RFC*	SSF	346.4 Ug-1 (Exo-PG) 314.4 Ug-1 (PL) 5.6 Ug-1 (Endo -PG) 71.2 Ug-1 (Exo-PG) 480 Ug –1 (PL)		Enhances the citrus oil extraction such as lemon oil
	Deseeded sunflower head with green gram husk	*Aspergillus niger DMF 27*	SMF	30.3 Uml^{-1} (Exo-PG) 18.9 Uml^{-1} (Endo-PG)	Beverages industry	Accelerates tea fermentation
		Aspergillus niger DMF 45	SSF	45.9 Uml-1 (Exo-PG) 19.8 Ug-1 (Endo-PG)		Reduces foam forming property in instant tea powders
	Orange bagasse	*Botryosphaeria rhodina MAMB-05*	SSF	32 Uml-1		Remove mucilaginous coat from coffee beans
	Orange bagasse: wheat bran (1:1)	*Thermomucor indicae_seudaticae*	SSF	120 Uml-1	Wine industry	Imparts stability of red wine

(continued)

Table 7.1 (continued)

Enzymes	Substrate	Organisms used	Fermentation type	Activity	Industrial Applications	
					Industry	Application
			SMF	13.6 Uml^{-1}		
	Orange bagasse: Molokhia Stalks (1:3)	*Penicillium pinophlilum* Hedg 3503 NRRL	SSF	3270 Ug-1 dry solid substrate		
	Orange peel	*Aspergillus niger*	SMF	117.1 ± 3.4 μmml-1 min-1-1		
	Orange peel	*Bacillus licheniformis* SHG 10		2.69 μg galactouronic acid min-1 mg 1		
	Citrus pulp and sugarcane Bagasse	*Aspergillus. Oryzae* CPQBA 394–12 DRM 01	SSF	45 ± 4 Ug-1		
	Orange peel and groundnut oil cake	*Saccharomyces cerevisae PVK4*	SMF	6285 Uml-1		
Amylase	Coconut oil cake	*Aspergillus oryzae*	SSF	3388 Ugds-1	Brewing industry	Fermentation of alcohol by converting starch to sugars
	Wheat bran	*Thermomyces lanuginosus ATCC 58157*	SSF	4.946 × 105 Ukg-1	Baking industry	Breakdown of starch into simple sugars; thereby allowing the bread to rise and impart umigat
	Wheat bran	*Bacillus* sp. PS-7	SSF	4,64,000 Ug-1 dry bacterial bran		Dough conditioning
	Potato peel	*Bacillus subtilis* DM-03	SSF	532 ± 5 Ug-1		Generates additional sugar in the bread, which improves the taste, crust color and toasting quality
	Rice bran	*Streptomyces* sp. MSC702	SMF	373.89 Iuml-1		Anti-staling effect during bread making; improves the softness and shelf-life

	Rice bran: wheat bran (1:2)			549.11 Iuml-1	Fruit and brewery industry	Clarification of beer and fruit juices
	Wheat bran 1	*Aspergillus oryzae* IIB-6	SSF	7800 Ugds-		
	Soyabean meal	*Aspergillus. oryzae S2*	SSF	22118.34 Ug-1 dry substrate		
	Rape seed cake, potato peel and feather	*Bacillus subtilis* PF1	SMF	16.39 ± 4.95 μgml-1		
	Brewery waste	*Bacillus subtilis* UO-01	SMF	9.35 Euml-1		
Laccase	Barley bran	*Trametes versicolor*	SMF	500–600 Ul-1	Wine industry	Removal of polyphenol, thereby providing stability to wines
	Banana leaf biomass	*Pleurotus ostreatus*	SSF	1.7106 Umg-1 protein		Preparation of cork stoppers of wine bottles
		Pulmonarius sajorcaju		1.6669 Umg		Reduces cork taint generally imparted to aged wine bottles
	Groundnut seeds	*Trametes hirsuta*	SSF	600–700 nkatl-1	Brewing industry	Removal of oxygen at the end of beer fermentation process
	Oat husks supplemented with combined fiber and deinking sludge	*Cerrena unicolor T 71*	SSF	178 nkatg-1 DW		Prevent the formation of off-flavors (trans 2-nonenal)
	Banana peel: mandarin peel: cantaloupe peel (5:3:2)	*Pleurotus florida NCIM 1243*	SSF	6.8 Ug-1	Fruit industry	Juice clarification
	Brewary waste	*Phanerocheate chrysosporium*	SSF	738.97 Ugds-1	Baking industry	Increase strength, stability and reduce stickiness Increase volume, improved crumb structure and softness of the product

(continued)

Table 7.1 (continued)

Enzymes	Substrate	Organisms used	Fermentation type	Activity	Industrial Applications	
					Industry	Application
Lipase	Babassu cake	*Penicillium simplicissimum*	SSF	26.4 Ug-1	Fats and oils	Production of mayonnaise and other emulsifiers,
	Wheat bran: gingelly oil cake (3:1)	*Aspergillus niger MTCC 2594*	SSF	384.3 Ug-1		Triglycerides synthesis and trans-esterification of triglycerides in non-aqueous media; specially fat production
	Palm oil mill effluent	*Candida cylindracea ATCC 14830*		20.26 Iuml-1	Milk	Production of milk with slightly cured umigat for use in milk chocolates
	Wheat bran, coconut oil cake and wheat rawa	*Aspergillus niger MTCC 2594*	SSF	628.7 Ugds-1	Cheese	Aging, ripening and general umigat characteristics
	Defatted rice bran	*Aspergillus umigates* MTCC 9657	SSF	8.13 Iuml-1		Lecithin modification
	Castor oil cake and sugarcane bagasse	*Trichoderma harzianum*	SSF	4 Ugds-1	Meat industry	Degumming during the refining of vegetable oil
	Olive oil with crambe meal	Fusarium	SSF	5.08 Ugds-1		Fat removal
	Crambe meal		SMF	3.0 Iuml-1		
	Seasame oil cake	*Candida rugosa NCIM 3462*	SSF	22.40 Ug-1		
	Palm oil industry waste	*Aspergillus niger*	SSF	15.41 IUml-1		

Tannase	Cashew apple bagasse	*Aspergillus oryzae*	SSF	4.63 Ug-1	Brewing	Removal of polyphenolic compounds
	Rice bran	*Aspergillus oryzae*	SSF	14.40 Ug-1 min-1	Tea	Manufacture of instant tea
	Bahera fruit powder :wheat Bran (3:7)	*Aspergillus heteromorphus* MTCC 5466	SSF	1060 Ugds-1		
	Tamarind seed powder	*Aspergillus flavus MTCC 3783*	SMF	139.3 Uml-1		
	Coffee pulp	*Penicillium verrucosum*	SSF	115.995 Ugds-1		
	Wheat bran	*Foetidus. terreus*	SSF	47.3 Umg-1		
Invertase	Red carrot jam processing residue	*S. cerevisae NRRL Y-12632*	SSF	272.5 Ug-1 dry substrate	Sweetener, sugar	Invert sugar production
	Orange peel .	*Foetidus. flavus*	SSF	25.8 IUml-1	Confectionery	Production of high fructose syrup Manufacturing of soft-centered candies
	Pressmud and spent yeast	*Saccharomyces cerevisae*	SSF	430 Umg-1		Manufacture of artificial honey
	Carrot peels	*Aspergillus. niger*	SSF	7.95 ± 0.1 Uml-1	Other	Production of alcoholic beverages, lactic acid, glycerol produced from the fermentation of sucrose
Protease	Pigeon pea waste	Bacillus sp. *JB-99*	SMF	12,430 ± 120 Uml-1	Dairy industry	Prevent coagulation of casein during cheese production
	Green gram husk	*Bacillus circulans*	SSF	32,000–73,000 Ug-1		Flavor development
	Green gram husk	Bacillus sp.	SSF	9550 Ug-1 biomass	Meat industry	Meat tenderization

(continued)

Table 7.1 (continued)

Enzymes	Substrate	Organisms used	Fermentation type	Activity	Industrial Applications	
					Industry	Application
	Potato Peel: *Imperata clyindrica* Grass (1:1)	*Bacillus subtilis DM-04*	SSF	2382 Ugds-1	Baking industry	Assures dough uniformity
	Castor husk	*Bacillus altitudinis GVC11*	SSF	419,293 Ug -1of husk		Improve dough consistency
	Wheat bran	*Pseudomonas aeruginosa*	SSF	582.25 ± 9.2 Uml-1		Gluten development
	Dal mill waste	*Fusarium oxysporum*	SSF	8.8 μgml-1		Improve texture and flavor
	Cotton seed cake	*Bacillus subtilis K-1*	SSF	1020 Uml-1		Reduce mixing time
Naringinase .	Grapefruit rind	*Foetidus. foetidus*	SSF	2.58 Uml-1	Fruit industry	Debittering of citrus fruit juices
	Rice bran	*Aspergillus niger MTCC 1344*	SSF	58.1 ± 1.6 Ug-1 dry substrate	Wine industry	Enhances the aroma in the wine
	Sugarcane bagasse+ soyabean hulls+rice straw	*Aspergillus niger*	SSF	3.02 Uml-1		Production of pruning, a flavonoid
	Orange rind	*Aspergillus niger*	SSF	13.89 Uml-1		
β-galactosidase	Whey	Kluyveromyces. marxianus MTCC 1388	SMF	1.68 Umg-1	Dairy industry	Production of low lactose/ lactose free milk
	Whey	Kluyveromyces.. *marxianus* NCIM 3551	SMF			Production of prebiotics
	Whey and parboiled rice effluent	*K. marxianus* ATCC 16045	SMF	10.4 Uml-1		Prevents crystallization of lactose
	Acid whey	Streptococcus thermophilus	SMF	7.76 Uml-1		Production of ice creams, sweetened flavor and condensed milks
	Whey	*Bifidobacterium animalis* ssp. lactis Bb12	SMF	6.80 Uml-1		Improves the scoop ability and creaminess of the product

		Lactobacillus delbruckii ssp. *bulgaricus* ATCC 11842		7.77 Uml-1		
	Cheese whey	Kluyveromyce. *marxianus* CBS 6556	SMF	21.99 Uml-1		
	Wheat bran and rice husk (1:1)	*Aspergillus oryzae*	SSF	386.6 µmoles of ONP released ml-1 min-1		
	Wheat bran	*Aspergillus tubingensis*	SSF	15,936 Ugds-1		
	Wheat Bran and whole wheat (7:3)	*Penicilium canescens*	SSF	5292 ± 111 Ug-1		
Papain					Meat industry	Tenderizing of meat
					Brewing industry	Prevents haze formation in beer; thereby resulting in shiny bright beer
					Baking industry	Breakdown gluten proteins in the dough in case of waffle and cracker production

Modified after Panesar et al. (2016)

Table 7.2 Nutraceuticals food additives used in food Industries

Additives	E-number	Properties	Sources
Tocopherol	E306	Antioxidants, vitamin E	Vegetable oils; cranberry seeds; nuts
Carotenoids (a-carotene, b-carotene, g-carotene, astaxanthin)	E160e161	Antioxidant, coloring agent, precursor of vitamin A (except astaxanthin)	Astaxanthin can be extracted from crustacean shells or algae or Obtained by fermentation of carbohydrates by Phaffia rhodozyma; Carotenes in general are extracted from vegetables (carrots, tomatoes)
Citric acid	E330	Flavoring and preservative agent	Fruits; fermentation of carbohydrates by aspergillus Niger, Candida spp., or bacillus licheniformis
Lactic acid	E270	Preservative, curing and flavoring agent	Fermentation of carbohydrates by lactic acid bacteria
Malic acid	E296	Source of extreme tartness	Fruits; fermentation of carbohydrates by aspergillus flavus
Tartaric acid	E334	Flavoring agent, antioxidant, emulsifier	Vinification lees, fruits
Fumaric acid	E297	Acidity regulator, flavoring agent, antioxidant	Fermentation of carbohydrates by Rhizopus plants (Fumaria officinalis)
Natural emulsifiers (pectins, gelatin, gum, xanthan, carrageenan, alginates)	E440e449	Stabilizers, emulsifiers	Fruits, porcine, bovine, fish, algae, microorganisms
Xylitol	E967	Sweetener	

bio-ethanol worldwide (da Silva 2016) using hydrolysis of waste further by simultaneous saccharification and fermentation (Ravindran et al. 2018). However, researchers start looking at feasible alternative to translate polysaccharides rich lignocellulose residues produced from agrowaste as a starting material for manufacturing of diverse enzymes shown in Tables 7.1 and 7.2 (Ghoshal et al. 2012; Bos and Hamelinck 2014).

7.3 Solid State Fermentation

In biotechnological method when microorganisms grow on solid insoluble object without free water or limited water, known as solid state fermentation (Bhargav et al. 2008).

Legume seeds, cereal grains and other lignocellulosic materials e.g. straws, sawdust or wood shavings, and other of plant and animal byproducts are considered as generally used raw material in solid state fermentation. The substrates are polymeric and reside as stoutly packed or hardly water soluble usually due to low cost and easily accessible but as an intense nutrients rich ingredients for microbial growth. Manufacturing of foods using fermentation technique is oldest technique. Earlier literature illustrated small quantity of water otherwise deficiency of water suggests numerous reward like simple product revival, low expenditure for whole manufacturing procedure, small size reactor, compact downstream procedure, and also diminution of need of power during agitation and autoclaving (Pandey 2003). For fruitful implementation of solid state fermentation, diverse factors such as microorganisms, solid support used, water activity, temperature, aeration, and type of fermenter utilized must be standardised prior to fermentation. Single pure cultures, individual mixed cultures or a group of mixed original microorganisms can be used in solid state fermentation. Some solid state fermentation practice, e.g., tempeh and oncom manufacturing, involve multiplication of microorganisms like fungi which needs lower water activity for fermentation using extracellular enzymes produced by fermenting fungi (Table 7.1). Fungi, bacteria and yeasts diverse microorganisms are used in solid state fermentation method. Molds are often used in solid state fermentation to get highest yield of value added produce due to generation of unsurprisingly on solid support made of lignocellulosic agro-waste. Nevertheless, bacteria and yeasts, which necessitate reasonably elevated moisture concentration in effectual fermentation, can also be utilized in solid state fermentation, with smaller yield. Solid state fermentation consists of following five steps

1. Choice of substrate.
2. Mechanical, chemical or biochemical pre-treatment of substrate by processing to perk up the entrenched nutrients accessibility as well as to diminish particle size, e.g., ground straw and cut fruits and vegetables peels to optimize the physical characteristics of the procedure. However, the expenditure of pre-treatment should be reasonable with ultimate product value.
3. Hydrolysis of main polymeric substrates, including carbohydrates and proteins.
4. Fermentation routes for exploiting degradation of commodities by hydrolysis.
5. Downstream processing for refining and quantitative analysis of finish goods.

Majority of the Asian and African countries include diverse fermented foods in their daily diet. Diverse types of active oxygen e.g. superoxide anion radicals (O^{2-}), singlet oxygen (O_2), hydroxyl radicals (OH^-) and H_2O_2 which stated that these can direct oxidative damage to living being. Therefore, these free radicals are the cause of many deadly diseases such as cancer, atherosclerosis, arthritis and emphysema (Jacobs et al. 1999). Since time immemorial solid state fermentation is found mostly in food processing application, but currently it is achieving tremendous awareness because of the mounting utilization of diverse types of organic wastes and the greater manufacturing of value-added end product (Pandey et al. 2000; Wang and Yang 2007). The hunt for sustainable and green method for bio-translation of organic wastes into important produce could replace non-renewable resources and also convert chemical method to green method in commercial scale which emphasizes the potential of solid state fermentation. Scrupulous attention of solid state fermentation is because of its comparatively easy method which utilizes plentiful cheaper biomaterials of negligible or no pre-treatment for biotransformation, lower waste water production, capability for reproducible comparable micro-environments, suitable for microbial growth. Additionally, solid state fermentation has introduced a novel perception for bio transformation of solid organic wastes during manufacturing of purely vigorous metabolites in lab scale and large scale. Purpose of solid state fermentation in the manufacturing of diverse innate products have been extensively stated including enzymes, organic acids, biofertilizers, biopesticides, biosurfactants, bioethanol, bioflavour, animal feed, pigments, vitamins, and antibiotics. Similarly, solid state fermentation reproduce normal microbial techniques such as composting and ensiling. Thus, solid state fermentation and development of value-added goods are reviewed.

7.3.1 Substrate for Solid State Fermentation

In SSF solid industrial waste generated from diverse manufacturing unit such as paper, textiles, agriculture, alcoholic beverages, detergent, food, and animal feed processing are utilized as solid support. Raw materials that stay on solid also have low moisture intensity which are chosen for SSF. Figure 7.1 showed diverse category of the hard support used for SSF. Many researchers utilized miscellaneous

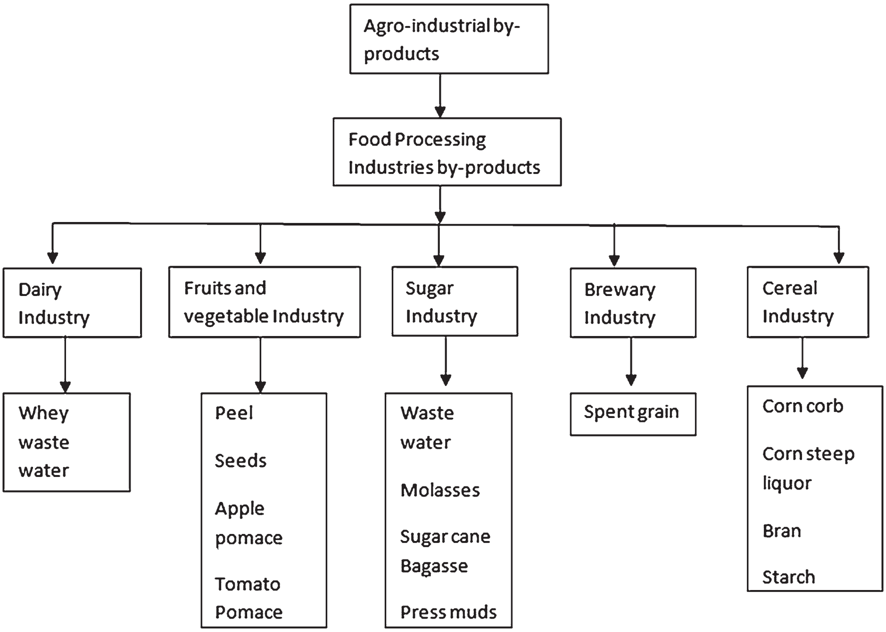

Fig. 7.1 Production of different agro-industrial by-products from different food processing industry. (Modified After Panesar et al. 2016)

ingredients considered for their study like black eyed pea (*Vigna unguiculata*), seim (*Lablab purpureus*), rice (*Oryza sativa*), peanut press cake (*Arachis hypogea*), (Sadh et al. 2017a, b, c, d). Diverse agro-industrial wastes intentionally utilized suitability for fungus immobilization delivery system for SSF (Orzuaa et al. 2009). They established few sabotage resources have superior probability using in immobilization delivery system in SSF, as they restrain large water assimilation capability, in addition to appropriate for superior multiplication rate for microbes.

7.3.2 Utilization of Agro-Industrial Wastes Using Solid State Fermentation

Agro wastes are utilized for generating huge commodities to add value. Figure 7.2 shows the schematic illustration of relevance from diverse raw materials. Maximum field wastes can be utilized internationally in manufacturing of biofuels, biogas in terms of heat, and power applying diverse technology. Diverse substrates have dissimilar composition and utilized in manufacturing of miscellaneous expensive stuff in terms of their composition (Table 7.2).

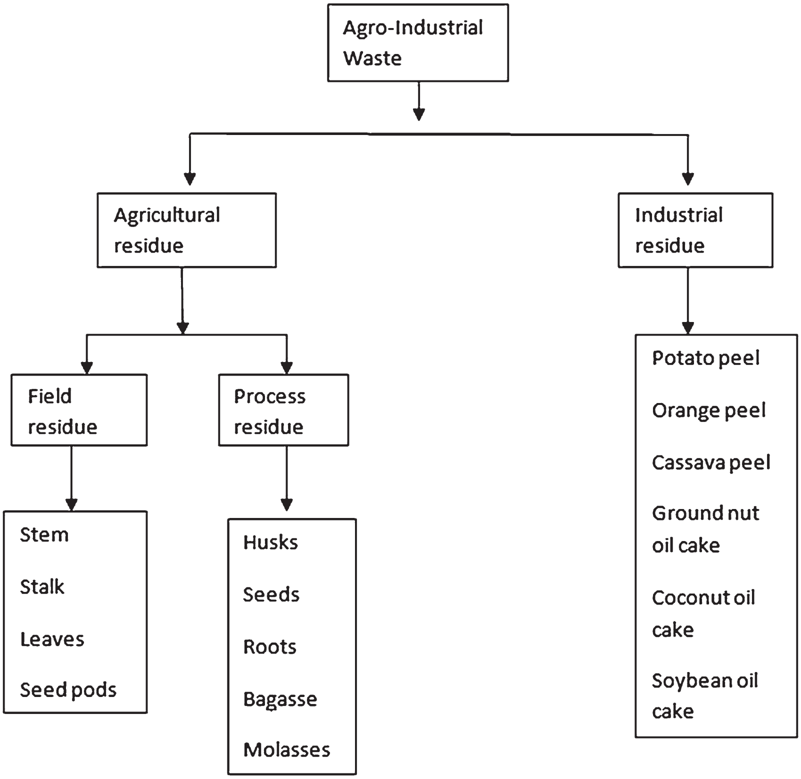

Fig. 7.2 Different types of agro-industrial waste

7.3.3 Antioxidant Properties

Antioxidants act as radical scavengers as they protect the human body from free radicals which causes numerous diseases such as asthma, anaemia, dementias, ischemia, arthritis, and aging. Lack of knowledge of composition of natural antioxidants, their application is restricted. As they are natural antioxidants therefore are safer and also have antiviral, anti-inflammatory, anti-cancer, anti-tumour, and hepatoprotective characteristics. Anti-carcinogenic and antioxidant agents was found in pineapple waste which is about 50% of the weight of pineapple, can be utilized as substrate and support in solid state fermentation. It was found that the pineapple waste after fermentation provides improved quantity of protein, fiber, phenolic and antioxidant activities too. So they recommended that the pineapple waste can be a substitute for novel advantageous stratagems (Rashad et al. 2015). Residues of various fruits and vegetables like peel is generally considered as a waste whereas various researches proved that fruits and vegetables peels though known as waste but considered as an important raw materials for the manufacturing of various food additives and pharmaceutical products (Parashar et al. 2014). Duda-Chodak and Tarko (2007)) explored the oxygen scavenging, total tannin and polyphenols in several fruits peels and seeds they found that nutraceutical content is higher in peels compared to seeds. The order of oxygen scavenging activity exits in different peels is Pomagranet> lemon> orange peel (Singh and Genitha 2014). Win et al. (2011) stated the occurrence of antioxidant activity and phenolic content in different parts of peanut and they found that maximum quantity is present in husk than other parts like hull, kernel. Field remainder like stem, leaves, and stalks were also be used for antioxidant and antimicrobial activities. A number of earlier reports revealed that the oxygen scavenging properties of numerous parts of *Argemone mexicana* and *Thuja orientalis* plants and found that compared to stem, leaf and other medicinal plant wheat, rice the fruit extracts have maximum antioxidant activity (Duhan et al. 2011a, b; Saharan et al. 2012; Saharan and Duhan 2013; Rana et al. 2014; Duhan et al. 2015a, b, 2016).

Sadh et al. (2017a, b) studied to find out the results of solid state fermentation on liberation of phenolics and subsequently the perfection of oxygen scavenging activity of *Lablab purpureus* (seim), *Oryza sativa* (rice), and their mixture using filamentous fungi, i.e., *A. awamori* and *A. oryzae* which is considered as generally recognized as safe. They found a considerable enhancement of total phenolic content level of fermented seed as well as flour with scrupulous culture as contrast to unfermented substrate. Rising total phenolic content concentration, the oxygen scavenging properties of fermented sample amplified in ethanolic extract of substrates with *A. awamori* and *A. oryzae.* Sadh et al. (2017c) used seim and rice mixture as substrate, i.e., to determine the influence of solid state fermentation on liberation of antioxidants and phenolics and also for some suitable feature. They established that fermented samples extract have high phenolic, antioxidant content and have functional properties better than the non-fermented sample as numerous biochemical alteration take place at the time of fermentation, thus fermentation has been utilized for advancement or to alter the percentage of nutritious and anti-nutritious components of substrates, which influence the product's biochemical or functional properties.

7.3.4 Antibiotic Production

Antibiotics are generated using diverse microorganisms that carefully hinder the multiplication or destroy contaminated microorganisms at extremely small amount (Tripathi 2008). Diverse agriculture wastes are utilized for the manufacturing of different antibiotics. Oxytetracycline were produced in solid state fermentation using corn cobs, sawdust, and rice hulls as solid support and in another study groundnut shell was used as solid substrate and effectively using *Streptomyces rimosus* culture (Ifudu Ifudu 1986; Asagbra et al. 2005). Contribution of exterior energy resource was utilized for improved manufacturing of antibiotic. Due to use of low cost carbon source like of varied agro-industrial residues the price of antibiotic production was reduced. For neomycin and other antibiotics production these residues can be used as an unexpected alternative sources (Vastrad and Neelagund 2011a). Same group also reported extracellular rifamycin B production in solid state fermentation using *Amycolatopsis Mediterranean* MTCC on oil pressed cake or oil industry waste as a raw material and found maximum antibiotic activity from coconut oil cake and ground nut shell (Fig. 7.2) Vastrad and Neelagund (2011b).

7.3.5 Oncom Production

Oncom, the traditional fermented produce of Indonesia made from numerous agro-industrial residues. Among three types of Oncom the popular majority is prepared from peanut meal. Oncom kacang is popular in West Java. Tahoo oncom well known in Jakarta, made from soya bean curd solid waste following same process as kacang. Oncom ampas hunkwe is made from mungbean (*Phaseolus radiata*) solid wastes and known as (Beuchat 1986; Steinkraus 1983).

7.3.6 Tempeh Production

Tempeh is very popular fermented food popular in Indonesia and Malaysia prepared domestically in home or in small scale industries. The smell and consistency of tempeh are superior. Boiled soya beans is better substrate as compared to steamed or sterilized soya bean for tempeh manufacturing. Soft tempeh is made from boiled soya bean using *Rhizopus* strains as they are capable to deteriorate the raw material based on their main nutrient components (Mak 1986). Earlier report suggested that the employment of soya milk waste formed a superior tempeh and it also prepared from unusual solid support or raw stuff for the manufacturing of cheaper, efficient and nutritionally superior tempeh. The amount of protein in tempeh improved considerably following using soya milk residues. Therefore, soya milk residues can be utilized as an alternative substrates for manufacturing a protein-rich food for human as a replacement for thrown out. Diverse types of tempeh and tempeh kind of products are popular in Indonesia (Lim 1991).

7.3.7 Enzyme Production

Composition of agro-wastes is not consistent and when wastes are used as a raw material which helps multiplication of different microbes thus diverse products e.g. valuable enzymes produced during fermentation. Multiplication rate of fungi is improved during utilization of these agro-waste and resulted alteration of lignocellulosic agro-wastes into low complex ones through inactivation of numerous enzymes. Amylase, was utilised for debranching of polysaccharides into lower sugar components during starch maufacturing. In another study cheaper nutritious agro-wastes are used to manufacture endoglucanase and β-glucosidase in solid state fermentation (Kalogeris et al. 2003) (Table 7.1).

Corn cobs were used for phenolics manufacturing in solid state fermentation as well as enzymic action (Topakas et al. 2004). Another study cinnamoyl esterase and xylanase were produced enzymatically using corn cobs, sugarcane bagasse, coconut husk and candelilla and they found production percentage increased in the following order of substrate used candelilla stalks<coconut husks<sugarcane bagasse<corn cobs. Oliveira et al. (2017) studied optimization of lipase manufacturing using oil cakes as substrate using *Aspergillus ibericus*, and they found maximum lipase production using palm kernel oil cake (PKOC). Saharan et al. (2017) studied to fermentation of cereals to release phenolics, flavonoids, and antioxidant activity and also investigated the role of α-amylase, xylanase, and β-glucosidase enzymes in SSF. A positive correlation was observed in concentration of polyphenols and activities of enzyme. To assays α-amylase, xylanase, β-glucosidase, and lipase during fermentation of peanut press cake using *A. oryzae*, resulting a considerable improvement in enzyme activities during analysis (Sadh et al. 2017d). Table 7.1 shows several studies that have been conducted on production of various enzymes with the using agro industrial residues.

In this section the important enzymes utilized in food applications reviewed, highlighted the innovation published in past years on baked goods, dairy, brewing, wine oleochemistry and in meat processing.

7.3.7.1 Lipases

Lipases are universal triacylglycerol acylhydrolases (EC 3.1.1.3) enzymes, which naturally biocatalyze the ester bonds cleavage of triglycerides and diglycerides, monoglycerides, or glycerol are generated. Lipases are believed multipurpose biocatalysts due to numerous attractive features like their chemo-, enantio-, and regioselectivity; its strength in organic solvents; their capability to catalyze reactions such as esterification, interesterification, and transesterification reactions; and their wide range of substrate specificity (Hasan et al. 2006; Jaeger and Reetz 1998). Extra application of these enzymes in diverse segment, holding third position on the basis of sales, because the significant applications in pharmaceutical, food, detergent, cosmetics industries (Table 7.1) (Houde et al. 2004; Gerits et al. 2014).

Lipases in Oil Industry

Lipids usually exist in living beings and the cause of lipolytic enzymes in the food sector is becoming a topic in limelight. The major research fields are the variation of vegetable and animal oils to achieve emulsifying complexes, to increase dietary importance, or else to reduce the amount of caloric. Purposely, diverse strategies have been planned, like the exclusion of injurious fatty acids or the enhancement of helpful complex such as ω-3 PUFA. The application of customary emulsifiers has triggered improved attention, and this market is acknowledged to exceeding 2.5 million tons in 2017 owing to their stabilizing and conditioning features in different dairy and bakery products (Naik et al. 2014). The use of lipase-catalyzed alcoholysis reactions monoacyl glycerides is a favourite choice than usual chemical substitute, due to the latter necessitate disadvantages like the necessity of metal catalysts, higher operation temperatures (210–240 °C), less alteration production, polymerization of unsaturated fatty acids, tedious refining steps, manufacturing of colour and fragrant stuff (Van der Padt et al. 1990). Thus, an improved research endeavour has been provided in the normal production of emulsifiers. Numerous studies have accounted the capability of fresh, unrefined lipases to catalyze the manufacturing of monoacyl glycerol and diacyl glycerol. To produce monoacyl glycerol and diacyl glycerols from the media containing glycerol and oleic acid at a fixed molar ratio of 11:1 using lipase from *Penicillium cyclopium* fermentation broths was studied. Chang et al. (2014) reported for the production of DAGs using recombinant *Candida rugosa* lipase as sub-product at the time of development of fatty acid methyl esters (FAME) attaining ratios of 1, 3-DAG to 1, 2-DAG of more or less 4:6. Occasionally, the use of immobilized lipases permit circumventing restrictions usually connected with free enzymes, like their non-recovery and unstable nature, encouraging the process to sustainable and economic by reducing operational costs and recycling of biocatalyst (Kamori et al. 2000). Eariler report by Naik et al. 2014 revealed that the most encouraging conditions of enzyme-catalyzed glycerolysis by varying lipase (Fermase CALB 10000) quantity, the oil-to-glycerol molar ratio (1:5), the solvent category, accomplish monoglyceride translation about 80% after 6 h duration of reaction. Correspondingly, Ghattas et al. (2014) utilized alginate-immobilized lipase extracted from *Rhizopus oryzae* for catalyzation up to 10 cycles of hydrolysis of olive oil to produce MAGs, DAGs, and (TAGs) from olive oil. They optimized the concentration of alginate (2% w/v), $CaCl_2$ (100 mM), and preliminary enzyme (2000 IU/mL) amounts. Previous studies (Zha et al. 2014) evaluated the capability of three immobilized lipases from *Candida antarctica*, *Rhizomucor miehei* and *Thermomyces lanuginosus* (from Novozym 435, Lipozyme RM IM, and Lipozyme TL IM respectively) to catalyze the glycerolysis of other vegetable oils such as coconut oil to achieve a correct MAG concentration at the time of two-step molecular distillations. The found that the optimum conditions are 8% enzyme, coconut oil to glycerol ratio 1:4, surfactant concentration 16% at 50º C temperature that yielded MAGs of 62.5%, DAGs of 30.4%, and TAGs of 5.8% after 5 h of reaction duration when lipase was used as biocatalyst. Ortega-Requena et al. (2014) utilized similar catalyst to accomplish polyglycerol polyricinoleate in a step in a vacuum reactor in inert atmosphere of dry nitrogen flow. In this technique circumvent the expensive conventional move concerning different steps in first step the ricinoleic acid polymerization and in the second step polyricinoleic acid esterification afterwards catalyzed by immobilized lipase extracted from *C. rugosa Rhizopus arrhizus*, *R. oryzae*, or *Mucor javanicus* (Gomez et al. 2011). Instead of the manufacturing of emulsifiers, many authors have given importance in FA modification using lipase as biocatalist to enhance the features of low nutritional value oils and accomplish health hassle of customers (Wang et al. 2012a, b). With this concern the manufacturing of low-calorie lipids controlled way containing medium-chain saturated fatty acids in the sn-1 and sn-3 positions as well as long-chain saturated or unsaturated fatty acids have been embattled in diverse study (Arifin et al. 2010). It is recognized easily when low dietary value avocado oil oils are used for etherification of capric and stearic acid with glycerol (Arifin et al. 2010; Caballero et al. 2014). This reaction is suitable for the commercial manufacturing of margarines. They found that interesterification is the process to to generate trans-free shortening and margarines with suitable characteristics in terms of melting, crystallization, textural and organoleptic characteristics (Zhao et al. 2013; Pande et al. 2012). The possibility of lipases has been exploited to manufacture esters with prominent odours and high molecular weight to extend the stability period. Due to the presence of meticulous organic acid and alcohol, post esterification different sensory properties can be identified. Li et al. (2014a, b)) reported 80% translation of butter oil using of immobilized *T. lanuginosus* lipase after 2 days (Li et al. 2014a, b). The same lipase for improvement of kojic acid esterfification yield and lipophilicity of ricinoleic acid was utilized by El-Boulifia et al. (2014).

Lipases in Bakery

Hitherto, mixture of several additives emulsifiers and enzymes has been believed to enhance the feature of baked products. Lipases also act crucial function during baking, as the lipid percentage of wheat grain create till 3–4%, that might be diminished to 1–2.5% post milling (Schaffarczyk et al. 2014). Therefore, the lipolytic enzymes addition might be regarded as precious for repairing, when conventional bread emulsifiers, diacetyl tartaric esters of monoglycerides (DATEM) was used. These entail immense storage space and shipping difficulties due to maintenance of lesser temperatures to circumvent caking, and their weight effectiveness is 10 times lesser as compared to the product when lipase (Novozymes 2003) is used as emulsifier. Another study when commercial lipase, Lipopan 50-BG was used, produced a very dense gluten complex that yielded a reduced volume of loaf (Martinez-Anaya and Jimenez 1997). Colakoglu and Özkaya (2012) used second generation lipases and observed that lipases generated altered structure of gluten proteins and starch which provide superior dough steadiness and a less soft and sticky as compared to application of DATEM, probably due to elevated affinity of outline amylose - lipid complexes. Presently, Lipopan Xtra, the third generation of bakery lipases also studied to achieve better compliance useful in miscellaneous flours, causing the development of the gluten network and improvement in wall thickness, to diminish cell density (Stojceska and Ainsworth 2008). Many earlier studies revealed that utilization of lipases along with novel emulsifiers e.g. inulin, confirmed health beneficial effects, providing the appropriate rheological features also better cake crumb with a dense homogeneous cell structure (Rodriguez-Garci et al. 2014).

Lipases in Dairy Industry

In cheese Lipolytic enzymes can hydrolyze milk fat and permit the maintenance of flavour or by making cheese ripening process faster. Thus, the incorporation of lipases is highly accurate for low molecular weight FAs which generate a strong as well spicy flavour, while that lipase catalyzing the hydrolysis of high molecular weight triglycerides grows a mild taste and flavour (Ferreira-Dias et al. 2013). In continuation, yeast lipase isolated from the digestive juice of *Sporidiobolus pararoseus* strain application in the mozzarella cheese-manufacturing practice formed a favourable cheese flavor (Mase et al. 2011; Mase et al. 2013). In composition of powdered babyfoods, fatty acids positions are not specific in the TAG configuration. Pancreatic lipase can hydrolyze the saturated fat if the position of saturated fatty acids at the sn-1,3 to release fatty acids, eventually cause constipation symptoms due to engagement of calcium soap in the intestine (Xu 2000).

In this circumstance, industrial structured lipids generated from Betapol, as milk fat alternative vegetable oils is permitted in Europe and Asia. Zou et al. 2014 have utilized an immobilized lipase extracted from *R. miehei* (Lipozyme RM IM) at the time of formulation the alternative human milk fat supplemented with medium-chain fatty acids delivering by acidolysis reaction of *Cinnamomum camphora* seed oil and oleic acid, optimizing the time, temperature, enzyme concentration and substrate concentration.

Lipases in Other Sectors

Lipolytic enzymes was generated with a huge deliberation to concentrate and/or transform fish oil-derived ω-3 fatty acids, like eicosapentaenoic and docosahexaenoic acids, which are extensively used as ingredients for functional food or nutritional supplements. They are traditionally accomplished by extraction using physical methods depending on temperature, pH etc. therefore concerning unexpected chemical reactions e.g. geometric isomerisation, polymerization and degradative oxidation which results in the production of bad odour. Thus, the application of lipases with ω-3 selectivity was planned by means of gentle processing conditions, size reduction of agro-wastes by lowering energy utilization, and improved features of the end products (Nalder et al. 2014). The application of these enzymes has also been anticipated in meat product preparation, due to the hydrolytic action contributes to incorporate an appropriate aroma of dry-cured meat produce for example like smoked-cured bacon, dry-cured ham and duck (Yang et al. 2005; Xu et al. 2008; Huang et al. 2014a, b). Ultimately, many reports stated about the utilization of lipases, incorporated in enzyme cocktails at the time of brewing procedure to transform white wine flavours and ensuring outstanding mouthfeel (Yu et al. 2011; Jiang 2010) or to obtain a creamy savour of coffee beverages and buttery consistency of toffees and caramel.

7.3.7.2 Amylases

The importance of starch, as polysaccharide chiefly made of amylose and amylopectin, in the diet of human being has encouraged a powerful investigation attempt to translate to diverse food ingredients such as glucose syrups, starch hydrolysates, fructose, cyclodextrins and maltodextrin derivatives (Souza et al. 2010). Although acidic hydrolysis has been traditionally used but the enzymatic catalysis has become appropriate alternative. Alteration of starch into oligosaccharides reasonable and environmentally responsive manner amylases has been used. Amylase can be classified into three types (1) hydrolytic α-Amylase (EC 3.2.1.1) that normally work on the cleavage of inner α-1,4- glycosidic linkages in starch to yield glucose and maltose. (2) α-1, 4-glucan linkages in non reducing ends is catalyzed by β-Amylase (EC 3.2.1.2) to convert polysaccharide chains to yield consecutive maltose units. (3) γ-Amylase (EC 3.2.1.3) directed to cleavage the non-reducing end of amylose and amylopectin to generate glucose after infringement of α-1, 6-glycosidic bonds and the last α-1,4-glycosidic linkages. Amongst the three classes, α- and $_{\beta}$-amylases are the favourite substitute for industrial application in the bakery goods, beverages, and in brewing (Table 7.1).

Amylases in Bakery

All the baked food products e.g. bread, cake, biscuits, crackers, cookies, etc., are made of cereal flour and starch is the major content of flour. Starch acts as gelling agent, thickener, water binder and emulsifier. Thus, the occurrence of α-amylases in cereal doughs is not desirable. In baking method the hydrolysis of starch to take place to yield small dextrins that can later be digested by yeasts at fermentation. In this technique, duration of fermentation are reduced to get and less viscous dough's are achieved, to get better final textures and superior loaf volumes (Patel et al. 2012). Another critical challenge of the bread is staling, that can be speeded up on the basis of both the baking practice and the storage period. Generally, this disadvantage is related to the recrystallization of the gelatinized amylopectin (AP) arrangement, which cause decrease of its shelf life. Grewal et al. (2015) have studied how mutagenic α-amylase manipulates the retrogradation of AP. The use of differential scanning calorimetry approved ultimately an outstanding hang-up of crumb set whilst the extent of hydrolysis was greater than 20%, due to a greater percentage of unit chains with a degree of polymerization lesser than 9 is identified, therefore hampering the small external AP chains to get double helices. An equivalent tendency was distinguished by Sozer et al. (2011) analyzed the effects of α-amylase incorporated to cakes, though they exhibited inferior staling rates as compared to bread, perhaps due to the superior ratios of sugar and shortening. Another interesting features of amylases is their probability to modify the fine starch structure of. Starch is divided in three main categories: (A) quickly digestible starch where part digested in less duration about than 20 min gradually (B) digestible starch require between 20 min and 2 h, and (C) resistant starch cannot be digested (Englyst et al. 1992). As the rapidly digestible starch produce a fast enrichment with postprandial glucose and insulin intensity in the bloodstream (Miao et al. 2014), the utilization of mutagenic amylases has been planned for enhancement of the quantity of gradually digestible starch from 11% to 20%. Sanz-Penella et al. (2014) pointed out the utilization of α-amylases to produce better quality bread devoid of visible transformation in the glycemic index. Nonetheless the main attempt for the use of amylases in baking is dealth with yeast-leavened doughs, the manifestation of frozen doughs or "ready-to-bake" limit the employment of chemical leaveners with indefinite effects when amylases are utilized. Patel et al. (2012) reported that the accumulation of additives like ascorbic acid and fungal α-amylases led to worsen dough viscosity, which exhibit growth during baking. Comparable satisfactory results of TPA analysis in terms of hardness, resilience, chewiness, cohesiveness and springiness were stated if these enzymes were applied in a mixture with lipases and proteases in gluten-free doughs (Martinez et al. 2013).

Amylases in Brewing

During brewing composition of wort is significantly exaggerated using the particular raw ingredients such as malt, adjunct, hops and yeasts. Though the malt has been conventionally prepared using barley, sorghum. It has also been used in lager beer manufacturing as a brilliant ingredient because of its cheaper price and appropriateness for manufacturing of beers of gluten-free in nature (Owuama 1997; Schnitzenbaumer et al. 2013). However, the superior gelatinization temperature > 70º C and the deficiency of amylolytic enzymes endanger its widespread submission (Ogbonna 2011). Thus, the accumulation of amylolytic exogenous enzymes which could sustain the reason for the use of sorghum as essential ingredient in countries when barley is not particularly cultivated (Schnitzenbaumer et al. 2013).

On the other hand accumulation of amylolytic enzymes has been confirmed as it is appropriate for manufacturing of light lager beers and carbohydrate-free in nature of lesser viscosity (Serna-Saldivar 2010). As the amylolytic enzymes modify substances made of fermentable sugars in wart, therefore leads to elevated ethanol percentage in beers. Higher maltose and glucose content linked with highest ethanol manufacturing and rates was found between 48 and 96 h for maltose and 72 and 120 h for glucose respectively, possibly due to osmotic stress based on glucose (Espinosa-Ramírez et al. 2014). Furthermore, the accumulation of these enzymes has also positively exaggerated the shelf life of opaque beers, as confirmed by Nsogning et al. 2015. One substitute for the consumption of amylolytic exogenous enzymes in brewing yeast is the establishment of amylase-encoding genes. Many authors have assured about the improvement using genetically engineered strains (Liu et al. 2008; Liu et al. 2009; Zhang et al. 2008; Wang et al. 2012a, b). Exceptionally, acetaldehyde generation in storage involve a pungent aroma that should be circumvent. Therefore, the plan demanding disorder of the ADH_2 gene encoding alcohol dehydrogenase projected collectively through the endorsement of glutathione synthesis, in a typically non-enzymatic defence structure extensively used by the brewery industry next to staling of beer, also an enhancement of amylolytic enzyme action (Wang et al. 2010). Wang et al. (2010) expressed gene encoding glutamyl cysteine synthetase uaing the organisms *Saccharomyces cerevisiae* GSH1 and the *Saccharomycopsis fibuligera* ALP1 gene encoding α-amylase in the brewing yeast strain aim the α-acetolactate synthase and alcohol dehydrogenase genes. In the fermentation media the amount of glutathione enhanced till 33%, while the α-amylase activity allowed after 5 days using roughly 50% of the starch leads to 30% upgrading of the stability index of flavor, approximately 80% lesser amount of remaining sugar, and 60% and 30% diminution of diacetyl and acetaldehyde concentration respectively. Amylolytic enzymes have been used not only in the beer industry, but also in other fermentation practices for the formulation of rice wine popular in China. The conventional manufacturing practices comprise raw rice pretreatment concerning elevated energy and labour expenses and generation of huge quantity of wastewater (Gohel and Duan 2012). Therefore, the application of enzymatic extrusion in the brewing of Chinese rice wine has been designed by Li et al. (2014a, b)), on the basis of optimizing amylase proportion, barrel temperature, and moisture percentage.

Amylases in Other Sectors

Damaging incidence of both starch soluble and insoluble present in sugarcane cause injurious effect during processing of sugarcane e.g. highly viscous and blockage in the filters, therefore declining the attaining quality of the sugar (Eggleston et al. 2010). Therefore, the function of α-amylases was planned to diminish these difficulty, enthralling into explanation that the action is robustly exaggerated by the feature such as the pH, calcium content, temperature, or degrees Brix (Eggleston et al. 2013). Maize starch was utilized by Cole et al. (2015)), in a media of model juices and syrups, estimating presentation of industrial α-amylases from *B. licheniformis* at miscellaneous stages of the sugarcane processing. An additional application of these enzymes is in the alteration of rice starch, as these constituents are used more and more in the manufacturing of infant formulations, bakery and breakfast cereal products (Zavareze et al. 2009). The enhanced significance in the development products that are gluten-free as a result of the increasing percentage of celiac disease infected people (Kurppa et al. 2010) have extra importance in enzymatically tailored rice flour. The aptness of rice flour customized with amylolytic enzymes from *A. niger* they have established *A. oryzae* to make a cereal cream, instantaneous milk powder, and purified sugar were taken with a good acceptance in sensory analysis (Martins Ferreira et al. 2014). In the advancement of novel application of amylases developing requirements in food safety have made positive impact. Thus, Gronqvist et al. (2014) have efficiently considered for the application of α-amylase extracted from *Bacillus amyloliquefaciens* in time-temperature integrators for confirmation of pasteurization criterion for fish burgers.

7.3.7.3 Hemicellulases

Enzyme-catalyzed hemicellulose hydrolysis reactions provide properties for example gentle working situations or the deficiency of poisonous deprivation commodities. Diverse hemicellulolytic enzymes have been defined (Table 7.3), although xylanases and endoglucanases are most useful (Kumar et al. 2008; Kuhad et al. 2011). In the last decades, these enzymes have prompted commercial importance in various sectors such as brewing, baked goods, animal feed, and or their manufacturing has been improved by development of fungal and bacterial strains suitable in to *Clostridium*, *Cellulomonas*, *Thermomonospora*, *Trichoderma*, and *Aspergillus genera* (Kuhad et al. 2011) (Table 7.1).

Hemicellulases in Bakery

Traditionally, xylanases have been added as a constituent of enzyme combination, along with other oxido-reductases and many other hydrolytic enzymes like amylases and lipases, to convert flow behavior and textural quality of doughs (Collins et al. 2006;), even though some authors have also reported their favourable properties when incorporated separately (Valeri et al. 2011). The main purpose of xylanases in wheat flour along with hemicellulases, catalyze the cleavage, permiting superior bread features on the basis of dough machinability, structure of crumb and firmness (Shrivastava et al. 2013). Furthermore, these enzymes transform water-insoluble hemicellulose into soluble form, allowing the bridge between water and dough, which leads to diminish the dough firmness, more uniform crumbs and greater loaf volume (Butt et al. 2008). Though xylanases is being added frequently

Table 7.3 Hemicellulases and peptidases

Sl no.	Hemicellulose	E. No.
1.	Endo-1,4-β-D-glucanase	EC 3.2.1.4
2.	Endo-1,4-β-xylanase	EC 3.2.1.8
3.	β-glucosidase	EC 3.2.1.21
4.	β-xylosidase (xylan-1,4-$_{\beta}$-xylosidase,	EC 3.2.1.37
5.	α-Arabinofuranosidase (α-L-arabinofuranosidase,	EC 3.2.1.55
6.	Acetylxylan esterase	EC 3.1.1.72
7.	Feruloyl esterase	EC 3.1.1.73
8.	Exo-1,4-$_{\beta}$-D-glucanase	EC 3.2.1.91
9.	Arabinanase (arabinan endo-1,5- α L-arabinanase,	EC 3.2.1.99
10.	α -glucuronidase (α -glucosiduronase,	EC 3.2.1.139
	Peptidase	
1.	Amino peptidase A	(EC 3.4.11.7)
2.	Amino peptidase B	(EC 3.4.11.6),
3.	Carboxypeptidase A	(EC 3.4.17.1),
4.	Carboxypeptidase B	(EC 3.4.17.2),
5.	Chymotrypsin	(EC 3.4.21.1),
6.	Papain	(EC 3.4.22.2),
7.	Pepsin	(EC 3.4.23.15),
8.	Subtilisin	(EC 3.4.21.62),
9.	Thermolysin	(EC 3.4.24.27),
10.	Plasmin	(EC 3.4.21.7),
11.	Trypsin	(EC 3.4.21.4)

to wheat flour bread dough but in rye bread making xylanase is extensively added globally. In this regards Banu et al. (2011) estimated the influences of variables like pH, enzyme concentration, and fineness modulus of flour to accomplish better texture in the final loaf.

The improvement of a competent bread manufacturing procedure encourages exploration of mutant yeasts, containing xylanases genes were determined. Therefore, Zhan et al. (2014) incorporated xylanase-expressing gene in *Kluyveromyces lactis* and established a development in sensory properties and bread size. The superior chearacteristics results because xylanases eliminate the arabinoxylans which is water insoluble persistent during the gluten development, which further leads to a elastic and steady dough arrangement (Sorensen et al. 2004; Ortiz Escobar and Hue 2008).

On the contrary, it has been hypothesized that the survival of these enzymes is important to activate an enhancement of arabino xylooligo saccharides in bread (Polizeli et al. 2005; Van Haesendonck et al. 2010), with established health beneficial effect. New development in bakery product manufacturing is decided to enhance the quality of prebaked bread. Generally, four different environmental factors are important for storage of prebaked breads such as at room temperature, refrigeration temperature, frozen temperature, and modified atmosphere (Barcenas and Rosell 2006a, b). The choice of the type of storage depends on shelf-life differences ranging few days to few months. Further explicitly, freezing storage results reducing loaf volume, moisture, flavor but modifications, and improvements in firmness of crumb (Barcenas and Rosell 2006a, b). The effect of storage at low temperature on the superiority of prebaked French bread was investigated by Lopes Almeida and Chang (2014) at varied concentration of hemicellulases produced by *A. niger* or *B. subtilis* were incorporated, additionally with other enzymes gluco-lipases, hexose-oxidases. Shelf-life expansion of prebaked rolls was achieved from 7 to 65 days devoid of considerable diminution in sensory characteristics.

Hemicelluloses in Brewing

Sukumaran et al. (2005) reported the advantages of extraction of glucanases from microbial source in alcoholic fermentation to produce beer and wine. Accumulation of glucanase has been established to reduce the viscosity of wort and circumvent filter blockage as they catalyze the glucan hydrolysis (Bamforth 2009). Additionally, the presence of hemicellulases has been help to remove color and clarification of must, producing a better ultimate wine feature and strength (Pinelo et al. 2009; Itu and Rapeanu 2011). Earlier study by Gambuti et al. (2007), Kelebek et al. (2007) established a positive correlation among the existence of macerating enzymes and color of wine as well as phenolic substances. Similar behavior was defined by Puertolas et al. (2009), to compare the enzymatic and physical (pulsed electric fields) healing for the separation of phenolic complexes during Cabernet Sauvignon vinification. An additional significant features to believe in vinification practices is the growth of a appropriate aroma, that is associated with occurrence of volatile notes recovered from grapes and flavourless non-volatiles, odourless glycoconjugates, known as glycosidic predecessor (Loscos et al. 2010; Pogorzelski and Wilkowska 2007). They can be chemically or enzymatically hydrolyzed and latter being mainly most suitable process circumvent for the development of unnecessary flavours, because of the alteration of aglycone structure (Hernandez-Orte et al. 2009). In this case, the utilization of β-D-glucosidase authorize the cleavage of glycosidic bond devoid of altering the aglycone, therefore being gorgeous to apply in flavour improvement of musts, juices, and wines (Wang et al. 2013).

Hemicellulases in Other Sectors

The most conventional utilization of hemicellulases consign to their utilization in extraction olive oil (Sharma et al. 2015), due to this the procedure bear an important consequences on the feature of the end product.

Even though expected approach for extraction on the basis of application of pressure followed by centrifugation has been ordinary (Vaz-Freire et al. 2008) diverse restrictions regarding the yields during extraction have additional employment of microbial or enzyme-catalyzed procedure (Najafian et al. 2009). Thus, extracellular hemicelluloses is being incorporated to destroy the oil bearing cell walls and better oil extraction without rancidity and better aroma (Najafian et al. 2009). This technique is applied to other variety of oils such as pumpkin seed oil. A blended application of microwave along with enzyme cocktail to attain 64.17% of oil followed by optimization of factors such as enzyme percentage (1.4%), temperature (44º C), time (66 min), and power of microwave radiation (419 W) was done. The extracted oil exhibited elevated oxidation stability possibly because of the superior antioxidant activities (Jiao et al. 2014). Similarly, the mixture of sonication and pH manupulation methods in addition of enzyme produced a multi fold improvement of lycopene separation from tomato peel (Konwarh et al. 2012; Cuccolini et al. 2013). Lycopene a carotenoid pigment having confirmed good antioxidant and anticarcinogenic activities (Kuhad et al. 2011). Same way β-carotene or chlorophyll separation was the objective in enzyme-catalyzed system (Ozkan and Bilek 2015).

Proteases

Protease known as peptidases, peptide bond hydrolases, or proteolytic enzymes, is one of the very demanding enzyme for food industries (Sawant and Nagendran 2014). These enzymes, also can be classified as exopeptidases or endopeptidases, based on the position where the cleavage is made (near the end or middle of polypeptide chains). Further, they are described as amino peptidases or carboxy peptidases when the peptide bonds is cleavaged at the N- or C-terminus, and some typical examples are shown in Table 7.3 (Tavano 2013). Though few enzymes are frequently achieved from plants or animal origin, present global needs induce the commercial manufacturing on the basis of microbial development, since it necessitate a superior biochemical variety and microorganisms can be hereditarily customized to increase the intensity of enzyme (Table 7.1) (Rao et al. 1998).

Application of Proteases in Bakery

Proteases have an imperative function in making baked goods (Gaenzle et al. 2008) as they certify superior dough consistency and superior bread texture (Goesaert et al. 2005). In this regards, one of the most important application is in gluten-free commodities. Currently, celiac disease activated in about 1% of the European and American population, due to the presence of gluten in food (Rao et al. 1998). Nevertheless, the gluten networks positively influence carbon dioxide maintenance throughout dough fermentation and due to its visco-elastic nature, as an unusual arrangement have to be improved to sustain these features. As earlier assured, rice flour is considered as excellent option for making gluten-free bread, its healing with enzymes, such as amylolytic and proteolytic enzymes, has been established to be valuable in terms of ultimate loaf quality. These enhancement rely on the deteriorating of the disulfide bonds exists in the gluten protein, therefore declining the gluten network (Katsube-Tanaka et al. 2004). Gathering of proteases extracted from

B. amylo liquefaciens (Protin SD-NY10) and *B. licheniformis* and papain concerned a diminution in time of mixing and dough texture and better consistency and pore unformity (Hatta et al. 2015). Their study confirmed that deterioration of the subunits of glutelin was requisite to fabricate the homogeneous network of tiny protein combined in rice (Table 7.1).

Application of Proteases in Dairy

Development of milk products is significantly affected by the action of protein degrading enzymes. Exclusively, plasmin was recognized as the chief endogenous protease present in buffalo milk, that positively modify the flavour and consistency of milk products. During the hydrolytic exploitation of the proteins can sustain the development of strong aromas in cheese, their presence in pasteurized milk could turn into upsetting due to gelation (Ismail and Nielsen 2010). Thus, the extent of hydrolysis should be cautiously guarded to accomplish the required consistency and aroma. Normally, cheese is formed due to the enzymatic coagulation, release of amino acids is stated as consistent due to the enhancement of cheesy flavor (McSweeney 2004). Distinguishing protein degrading enzymes such as chymosin and pepsin present in milk rennet, which attack on the k-casein's Peptide bond, diminution of coagulation of milk protein (Ripolles et al. 2015; Majumder et al. 2015). In this regards, it is significant to manage the proportion of pepsin and chymosin in rennet extracted in diverse supply.

Various proteases is expected as potential rennet alternative in halal, authentic vegetarian products, and they are deliberately used to generate novel aroma and consistency (Feijoo-Siota et al. 2014). The protein hydrolysis reaction is because of the continued existence of microorganisms for protease-manufacturing as present in particularly Camembert cheese (Aizawa et al. 2009). Five different proteases have been known all through ripening (chymosin, pepsin, plasmin, metalloproteinase, and aspartylprotease) (Tavano 2013). The improvement of accurate flavour in this cheese variety is challenging and dependent on the cautious accumulation of exogenous proteases (Wroblewska et al. 2004; Singh et al. 2003). Proteolytic enzymes are utilized for improvement of dairy allergens also, to hydrolyse that allergens up to molecular weights 3 kDa necessitates an insignificant allergenic prospective (Bogh et al. 2015). Some essential allergens are milk proteins such as caseins, lactalbumin, and lactoglobulin (Sharma et al. 2001).

Application of Proteases in Other Sectors

Several papers and patents stated that the purpose of use of proteases in meat industry is due to the enhancement of softness. In this case, the end users acceptance for red tender texture meats promotes analysis of stratagem connecting stiffness diminution (Polkinghorne et al. 2008). Similarly, Ryder et al. (2015) confirmed feasibility of proteases extracted from fungy and bacteria to hydrolyze myo-fibrillar and tissue proteins from connective tissue at altered temperature as well as pH values during post-mortem aging of meat. Another exceptional use of proteases is in the brewing. For example, one of commonly popular liquors in China (MouTai flavored) engages a complex impulsive fermentation, where a variety of proteases can be establish. Therefore, Huang et al. (2014a, b)) identified the appropriateness of a novel protease produced by SSF using *Aspergillus hennebergii* to extend a right liquor aroma as well as to alleviate microbial fermentation.

7.3.7.4 Other Enzymes

Another group of important enzymes claim an immense awareness in food industry are lipoxygenases (e.g. linoleate oxygen oxidoreductase, EC 1.13.11.12) (Kim and Oh 2013). Lipoxygenase can be established in plants, animals, fungi, algae, bacteria and coral. Though the distinctive industrial resources are soybean and fava bean flour that generally catalyze to produce fatty acids hydroperoxides by oxidation of polyunsaturated fatty acids in presence of oxygen radical. Oxygen radicals are capable to oxidize sulfhydryl of proteins and pigments in Carotenoids to hydroxyacids therefore they are used for bleaching in bakery products (Kang et al. 2010). As a results, their possibility to reduce mixing time and advance dough raising and foaming has been described (Patel et al. 2015). Their commercial expansion has been superior for farming by using *Penicilliumor Aspergillus* species. Their industrial application is largely committed in food conservation eliminating pathogens like *Campylobacter jejuni,Listeria monocytogenes, Salmonella infantis*, *Staphylococcus aureus* etc. (Rombouts et al. 2003).

Moreover, lipoxygenase expected to catalyze glucose elimination from dehydrated eggs or from wines, during gluconic acid manufacturing, to extend the shelf life of dairy goods, to eliminate air from fruit juices, to prevent rancid flavour development in mayonnaises (Wong et al. 2008; Bankar et al. 2009; Schmidtke et al. 2012). Other enzymes such as asparaginases, $_{\beta}$-galactosidases, laccases, and transglutaminases are responsible in different food production were highlighted. The effect of asparaginases have been studied and found to have develop carcinogens acrylamide during baking due to Maillard reactions between asparagine and carbon sources and therefore the use of asparaginase was restricted (Anese et al. 2011). If protein cross-linking reaction is catalyzed by transglutaminases (EC 2.3.2.13) it was reported that foaming, gelation function, solubility and emulsifying proficiency of protein can be altered (Giosafatto et al. 2012; Kieliszek and Misiewicz 2014). Hydrolytic enzymes β-galactosidases extracted using fungy and yeast from *Aspergillus* molds and *Kluyveromyces* yeasts have been utilized either in free form or in immobilized form for lactose elimination from milk and milk products (Wong et al. 2013; Messia et al. 2007).

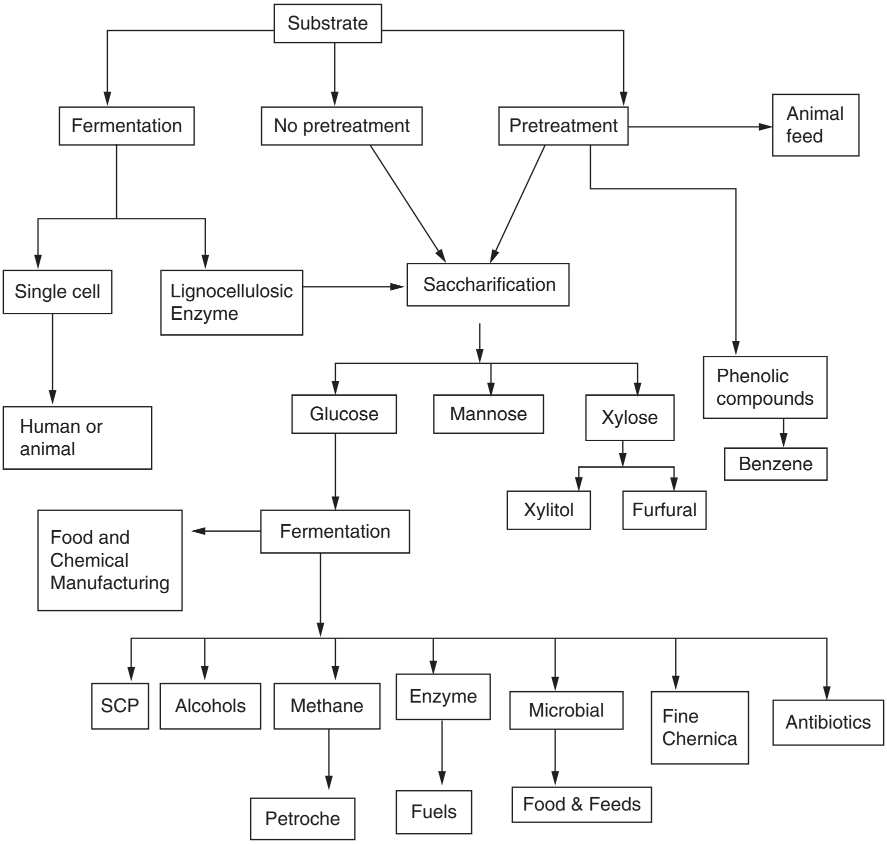

Fig. 7.3 Application of different agro-industrial substrates

7.4 Other Application of Solid State Fermentation

Some other functional advancement by SSF are also summarized here (Fig. 7.3).

7.4.1 Single Cell Protein Production

Mondal et al. (2012) studied the cultivation of single cell protein (SCP) utilizing fruit wastes like cucumber and orange peels using *S. cerevisiae* in SSF. They established that as cucumber peel generated in higher quantity and the protein amount as evaluated in the orange peels is higher. Therefore it was recommended that cucumber and orange peel can be translated to SCP by means of appropriate microbes. The final products achieved after transformation of agro- wastes are cheaper and nutritionally restricted to elevated protein percentage.

7.4.2 Manufacturing of Poly (3-Hydroxybutyric Acid)

The citrus fruits are utilized to manufacture fruit juice, and jams all over the world commercially. Thus citrus processing industries also produced a massive quantity of waste as peel residue or in other form but the citrus wastes can be utilized in SSF as they include huge quantity of carbohydrates. Orange peel waste was utilized for the manufacturing of Poly (3-HB) as a single carbon source after easy pretreament process as Orange peel has potential to utilize as underutilized agro-waste(Sukan et al. 2014).

7.4.3 Biosurfactant Production

Bacterial strain isolated in the oil polluted location as these bacterial strains have the capability to manufacture valuable or helpful products for human being. Saravanan and Vijayakumar (2014) isolated *Pseudomonas aeruginosa* PB3A and used for manufacturing of bio-surfactant using oil industry waste like defatted sunflower, castor, peanut cake, barley and rice bran. They utilized as a carbon rich substrate for fabrication of bio-surfactant using *P. aeruginosa* strain.

7.4.4 Xanthan Production

Xanthan, a exo-polysaccharides and important food additives, generated using *Xanthomonas* species. Therefore manufacturing of xanthan from cheaper diverse agro-waste is a precious advancement (Vidhyalakshmi et al. 2012). Vidhyalakshmi et al. 2012 yielded maximum xanthan by SSF on potato peels using following microbes *X. campestries (*2.87 g/50 g), *X.citri (*2.90 g/50 g), *X. oryzae* (1.50 g/50 g), and *X. musacearum*. (0.50 g/50 g).

7.5 Immobilization of Nutraceuticals

Ten agro-industrial wastes with physio-chemical treatment in SSF were studied for their suitability as immobilization delivery system by Orzuaa et al. (2009). Finally, they reported that among ten agro-wastes, *Citrus aurantifolia*, *Malus domestica*, *Citrus sinensis*, and *Cocos nucífera* have extreme possibility as immobilization media in SSF. These agro-industrial wastes can be utilized further for economical benefit environmental-friendly way for waste management as well.

7.6 Food Additives from Plants or Lignocellulosic Biomass

Lignocellulosic waste is probably extremely valuable resources for manufacturing and revival of numerous produce as raw material for food industry utilization, The resources include carbohydrates, proteins, lipids, amino acids, phenolic constituents and organic acids etc. (Ghoshal 2020). Several nutraceuticals, such as phenolic complex isolated from agrowaste lignocellulosic residues such as grape skin extract, carotenoids acquired from plants such as paprika extract, lycopene extracted from tomato skin and algae among others which can be utilized for other food product manufacturing as natural additives instead of artificial chemical additives (Table 7.2). Unusual property of barley husks antioxidants studied by De Abreu et al. (2011a, b) to stop rancidity of polyunsaturated fatty acids and also to extend the shelf life of cod liver oil by preventing oxidation. The lipid oxidation rate reduced with increasing antioxidant concentration though the major attractive result was that they were very efficient than chemical antioxidants like BHA and BHT in reducing oxidation reactions,

Antioxidant and antimicrobial properties of different spice extract from *Brassica nigra, Cinnamomum cassia*, *Origanum vulgare and Syzygium aromaticum* were studied by Krishnan et al. (2014). They evaluated the effect of spices in raw chicken meat stored at 4 °C for 15 days and also compared with positive control chemical antioxidant BHT and they were successful in diminishing microbial growth and lipid oxidation using spice extract in raw chicken. Thus applications of natural extract incorporated active packaging films were given priority to provide better oxidative potency and to protect sensory quality of meat, fish, chicken, and butter products. They developed brewery filtrate incorporated active packaging films to enhance the oxidative stability in beef stored at refrigerated conditions and 80% lipid oxidation was reduced. The heat stability of few nutraceuticals additives from beer, was studied and it was found that at 100-200º C along with antioxidant characteristics, they also acts as antimicrobial agent when incorporated into food, thus escalating the shelf life of processed foods. In another study Pereira De Abreu et al. (2011a, b) incorporated barley husks antioxidants in LDPE films and their effect on lipid oxidation in frozen blue shark (Prionace glauca) and frozen cod (Gadus morhua) and frozen swordfish (Xiphias gladius) were evaluated. In similar study by Romano et al. 2014 anticipated the incorporation of fructo-oligosaccharides in methylcellulose-based films as antimicrobial agents.

7.7 Food Additives from Lignocellulosic Biomass Produced Biotechnologically

Lignocellulosic agro-waste is considered to supply an economic resource of sugars that can be fermented with usual chemical or natural food additives to a variety of produce. The initial deliberation in achieving natural food additives from lignocellulosic residue after fermention is how to degrade lignocellulosic agro-waste materials to cellulosic, lignin, and hemicellulose sugars. Natural food additives extracted biotechnology are also have significance because of temporary set of laws, customer declare for normal constituent, and global awareness pertaining to sustainable development. Nonetheless, biotechnology based conduit and separation practice for natural add-mixture should be optimized to obtain a relation using low cost agro-industrial residue as substrate, with the final product yield, the application of microbes, and also the refining process. Novel bio-technology based processes are being comprehensive to realize diverse food additives which are presently formed industrially following chemical synthesis path. Natural additives for food processing and nutraceuticals isolated from plant sources e.g. astaxanthin, lactic acid, and xylitol can be recovered by fermentation with varied carbon sources with the suitable microbes, whereas like antioxidants are separated straight from fruits or other agro-industrial residues.

Xylitol, the polyalcohol, achieved by degradation of xylose, and can be utilized as sugar alternative in food industry due to its high sweetening index, gum and teeth protection characrterics, and suitable for diabetics. As xylose has the similar sweetening index as sucrose but low caloric value, with no carcinogenicity, but have a tremendous laxative effect. Xylitol is produced as an intermediate by using D-xylose catalyzed by xylose reductase extracted from *Debaryomyces hansenii* yeast. Some authors have studied the xylitol manufacturing using hemicellulosic low-cost carbon resources like sugars isolated from lignocellulosic residues (Rafiqul et al. 2015). Astaxanthin, the red-orange carotenoids is isolated from crustaceans or from variety of yeasts or microalgae biotechnologically (Liu et al. 2014). Astaxanthin is considered as significant biological antioxidants with encouraging nutritional property and clinical remedial for healing of diabetes, cancer, and ocular degeneration; improvement of immune system and preventing swelling. Furthermore, astaxanthin can be utilized as natural additive in foods to provide attractive red-orange color to foods like salmon flesh. Earlier reports projected on the utilization of lignocellulosic remainder to produce astaxanthin. Wood waste after acid hydrolysis in mild treatment conditions hydrolyzed followed by neutralization and treatment with charcoal to remove inhibitors finally enrichment using nutrients to use as culture media for growth of red yeast *Phaffia rhodozyma* to generate astaxanthin. One of the important food additive is lactic acid synthesized using synthetic chemicals or produced naturally in biotechnological path (Colakoglu and Özkaya 2012; Wang et al. 2010, 2012a, b; Gohel and Duan 2012; Li et al. 2014a, b; Eggleston et al. 2010). It is utilized to preserve pH in carbonated drinks, control acidity in cheeses, and as preservatives in olives and processed vegetables. In the form of calcium lactate it is utilized to metabolize hexoses (glucose, sucrose, or galactose) by lactic acid bacteria in the homo (e.g. *L. delbrueckii*, *L. rhamnosus*, and *L. jensenii*) or hetero fermentative (e.g., *Lactobacillus brevis)* path. Another path lactic acid bacteria (e.g., *Lactobacillus pentosus*) transform pentoses (e.g., xylose) instead of hexoses into lactic acid via pentose pathway. In this path lactic acid bacteria convert first D-or L-pentoses into lactate and acetate to produce intermediate D-xylulose 5-phosphate with conversion yield of 0.6 using winary snip as carbon source.

In this method hemicellulosic vines, hoots are first acid hydrolyse with sulfuric acid sugars, followed by neutralization and addition of nitrogen and then other minor nutrients, are sterilized prior to fermentation with *L. pentosus*. Another path lactic acid can be produced by simultaneous saccharification and fermentation using alfalfa fibers with pretreatment of liquid hot water (LHW) and non-LHW in homo or hetero fermentative *lactobacilli* strains (Eggleston et al. 2013).

Other acidulants used in food processing are ascorbic acid, citric acid, fumaric acid, and malic acid. Malic acid is a four carbon dicarboxylic acid frequently used as acidulant to enhance the taste of beverage or other food. *Saccharomyces cerevisiae* is used commonly to convert glucose to L-malic acid in four different metabolic pathways. *Aspergillus flavus* can also be used to generate L-malic acid with better yield as compared to *S. cerevisiae* without manufacturing of aflatoxin. Some reports are available for metabolic conversion of *S. cerevisiae* after genetic engineering to enhance yields of malic acid. Diverse substrate for example molasses, starchy materials, and hydrocarbons have been exploited as raw material for industrial citric acid manufacturing (Vidhya and Neethu 2009). About 99% of citric acid is produced globally by surface or submerged culture via biotechnological processes (Torrado et al. 2011). For citric acid manufacturing *Aspergillus niger* can be used in orange peel and cane molasses mixture as carbon source biotechnologically (Hamdy 2013). *Candida* and *Bacillus licheniformis* can also be used to produce citric acid. Fumaric acid, the four-carbon unsaturated dicarboxylic acid, is extensively used as food acidulant for beverage and can be generated biotechnologically using agro-industrial carbon sources. *Rhizopus oryzae*, the mycelial fungi, can be used as microorganisms to generate fumaric acid and chitin concurrently in same process. Fumaric acid fermentation consists of three steps, such as seed culture making, cultivation of fungal biomass in inert gas nitrogen environment.

β-carotene, ascorbic acid natural antioxidants are resource of natural vitamins can be produced in SSF using agroindustrial residues as food additives (Sharma and Ghoshal 2020a, b). Thus natural antioxidants diminish fatty acid oxidation rate also enrich the food products. Some culture of lactic acid bacteria generate diverse types of exopolysaccharides (EPS), which enhance rheology and improve textural properties of fermented food products (Trabelsi et al. 2015). EPS are generated by bacteria either by extracellular or intracellular method.

Lactic acid bacteria can generate bacteriocins, the generally recognized as safe (GRAS) additives. Bacteriocins (e.g. *Bacillus subtilis*, *E. coli*, and *Pseudomonas aeruginosa*) are imperative for maintaining the proportion of pathogenic and spoiling microbes in foods and feed (Muthalagu and Sinthyak 2015).

Certain lactic acid bacteria (*Lactococcus lactis*) can produced excess amount of B vitamins, folate (B11), riboflavin (B2), and cobalamin (B12), to supplement food stuff. Lactic acid bacteria metabolites are used as preservative in cereal processing as it is a dependable substitute to reduce fungal contamination at the time of pre or post harvest, with added benefits throughout the processing of cereals, to improve cereals products marketing. Microbial polysaccharides e.g. dextran, pectin, xanthan gum, gellan gum are the by-product of fruits can be used as food additives such as emulsifiers, gelling agents, texturizers, stabilizers, thickeners approved by the US FDA for food application. The majority of industrial gelatin about 41% of the produce globally is chiefly from pigskin. Fish gelatin is a substitute to mammalian gelatin for application in diverse food and pharmaceutical purposes (Schmidt et al. 2015). Other gelling, thickening and stabilizing polysaccharides such as alginate, carrageenan, and agar can be extracted from algae are widely used in food processing.

7.8 Conclusion

Most of the agro-waste residue are nutraceutical and natural bioactive enriched composition. They contain significant proportion of carbohydrates, proteins, lipids, minerals, and simple sugars, consequently, they are regarded as “raw material” instead of “wastes” in diverse industrial processes. Therefore presence of such beneficial nutrients in these residues recommended appropriate circumstances for abundant growth of diverse beneficial microbes. The microorganisms have favourable effect for recycling the same waste as substrate for their multiplication during fermentation process. The agro-industrial wastes can be utilized as solid hold up in SSF method for manufacturing of variety of important valuable composite. The application of agro-wastes residues as starting ingredients not only can assist to decrease the manufacturing cost also means of recovery of waste and its value addition by creating the environment eco-friendly as well.

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Chapter 8
Extraction of Bioactive Molecules from Food Processing By-Products

Yaseen Galali and S. Mohammad Sajadi

Abstract The food industry is generating huge amounts of by-products, about 1,890,000 tons, which should be better recycled into pharmaceuticals, cosmetics and functional foods, for instance, in order to save costs and avoid pollution. Here we review food by-products and methods of extraction. We present bioactive compounds from fruits, vegetable, tea, coffee, egg, nuts, meat and dairy products. Extracting methods include soxhlet, maceration, microwave, ultrasound, pressure.

Keywords Food by-products · Bioactive molecules · Novel techniques · Conventional techniques · Green techniques · Environmental pollution

Abbreviations

UAE	Ultrasound assisted extraction
EAE	Enzymatic assisted extraction
MAE	Microwave assisted extraction
PEFE	Pulsed electric field extraction
OHAE	Ohmic heat-assisted extraction
SFE	Supercritical fluid extraction
PLE	Pressurized liquid extraction
Thr	Threonine
Val	Valine
Cys	Cystine

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable
Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_8

Meth	Methionine
Isol	Isoleucine
Leu	Leucine
Phenyl	Phenylalanine
Tryp	Tryptophan
Lys	Lysine
DAH	Destroyed by acid hydrolysis
DW	Dry weight

8.1 Introduction

Food processing by-products are generated all over the world thorough the steps of food supply chain. The estimated percentages of waste is 20% along the whole chain, 38% generated during food processing, 42% of them is wasted by households (Fig. 8.1) (Baiano 2014). Furthermore, according to FAO data, one of the third of produced foods for human use wasted globally (FAO 2017). Food processing by-products is not just threatening food security; it also causes global environmental pollution and affects strategies and policies.

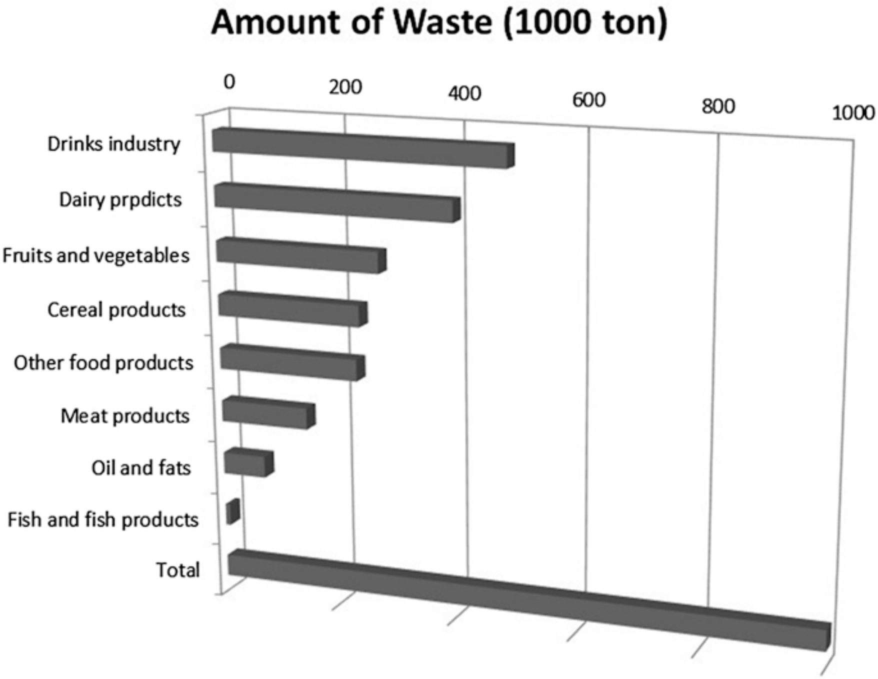

Fig. 8.1 Sources of bioactive components. (Baiano 2014)

Thus, policy makers globally at different scales target food waste in relation to food security and environmental pollution. Furthermore, United Nations sustainable development aims to minimize Food processing by-products throughout the entire food chain supply by 2030 as well as Food processing by-products at retailer and consumer stages reduction to half (United Nations 2015).

Biologically active molecules often mentioned bioactive molecules are agreed and defined as “non-essential and essential substances that presence in the nature as a part food composition that are proved to possess physiological benefits on human health (Hyun 2012). Coincidently, the communities’ information regarding non-communicable diet related diseases are increasing. Furthermore, the demand and use for natural, safe and health-improving products at ancient time until now a days is interest (Vuong 2017).

These products are used in different forms including powders, extracts and oils which contained many bioactive molecules. On the other hand, biologically active compounds from by-products have entered many biotechnical and industrial sectors in making many structured products such as adhesives, emulsions, gels, films, bioplastics, bio- composites and reconstituted fibers (Ryder et al. 2017).

Several extraction techniques have been used in order o extract bioactive molecules in food by-products. Thermal procedures like supercritical fluid extraction, Thermovinification, and non-thermal procedure Pulsed Electric Fields, Ultrasound some others have been developed in order to improve the extraction yield of bioactive molecules. The efficacy of both conventional and novel methods to extract maximum bioactive molecules relies on several factors such as nature of the by-product, bioactive molecule chemical structure and choosing reasonable techniques for extraction.

The main objective of this chapter is to show the main sources of bioactive molecules in agri-and food processing by-products. Also the chapter sheds light and identifies the main classes of the bioactive molecules in food by-products. Lastly, different techniques of the bioactive molecules extraction will be explained.

8.2 Sources of Bioactive Compounds

8.2.1 Bioactive Compounds in Fruits and Vegetables by Products

Fruits and vegetables are one of the most common agricultural products used globally in different forms row, minimally processed and processed that ultimately generate thousands of tons of by-products. The most common by-products include stones, skins, seeds, leaves, unused pulp and unsuitable parts. This causes a lot of environmental complication for the industry. Disposing agro-industrial fruit and vegetable by products with traditional methods is inappropriate which 25–30%

waste. This is not just causes environmental problems, it can also threaten food security (Ajila et al. 2010).

To overcome this issue, it reduction of waste or by-products is a global need. To transform by-products to valuable molecules, scientists, food technologists, and health professional have developed a few ways including extracting bioactive and phytochemicals molecules such as dietary fibers, minerals, phenolic compounds and carotenoids) that can be utilized as functional nutrients as anti-mutagenic, cardio-protective, antibacterial and anti-tumoral properties.

Furthermore, these functional nutrients can incorporated into food products to develop new functional foods, which has attained and of great interest these days (De Ancos et al. 2015).

Vegetable processing by-products possess different bioactive and biochemical molecules that can be utilized in various ways. Summer squash vines contained high percentage of Ash (23.3%) but lowest in organic material (77.8%). Furthermore the highest (94.8%) organic matter was detected in corn husk of baby foods. Snow peas protein seems to have the highest percentage of 23.2%. Moreover, pea vines cellulose and baby corn husk hemicellulose were highest by 36.8% and 32.1% respectively (Table 8.1).

Leaves of sugar beet contained the significant percentage table sugar by 24.9%. Regarding specific proteins, albumin in cauliflower leaves, globulin in cabbage leaves, prolamin in black chick pea plant and Glutelin in pea vines were found with 62.4, 16.2, 27.6 and 22.7 respectively (Table 8.2).

Phenolic compounds in leaves of radish represented the highest amount by 6.9% in comparison to other sources. The aforementioned results demonstrate that the by-products of vegetables contains significant amount of bioactive components and can be exploited as a great source of bioactive molecules.

Fruits by products including peel, skin, seed kernel and pomace are also rich sources organic matters including proteins, fats, carbohydrate and others. The highest amount of proteins and fats was found in watermelon seeds with 34.1% and 25.6 respectively (Table 8.3). Furthermore, highest amount dietary fibre (30.77%) and minerals (6.5%) was found in Jack fruit processing by-products. On the other hand mango seed kernel seemed to have the highest amount of carbohydrate.

Bioactive molecules can be exploited for various purposes including pharmaceutical, cosmetics and for developing functional food products. A number of studied researchers have used this products to create functional products (Al-Dmoor and Galali 2014a; Galali 2014).

8.2.2 Bioactive Compounds in Coffee Processing by Products

Coffee is one the most widely used beverages world wide. As a result, a large amount of coffee processing waste are generated which is 50 % is during green bean coffee production process (Mussatto et al. 2010). According to the type and amount, the by-products are dissimilar.

Table 8.1 Bioactive major and trace minerals in different fruits and vegetables byproducts extracts using anaerobic extraction methods (Asquer et al. 2013)

	Al	*As*	*B*	*Ba*	*Ca*	*Cd*	*Co*	*Cr*	*Cu*	*Fe*	*Hg*	*K*	*Li*	*Mg*	*Mn*	*Mo*	*Na*	*Ni*	*Pb*	*Se*	*Sn*	*Sr*	*V*	*Zn*
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg
Apricot	0.95	<0.05	0.10	0.014	3.67	0.002	0.029	0.648	0.04	2.37	<0.05	29.81	<0.005	1.31	0.31	0.022	0.08	2.88	0.04	<0.1	<0.25	0.01	0.007	0.08
Aubergin	3.40	<0.05	0.03	0.006	2.68	<0.001	<0.004	0.001	0.42	0.07	<0.05	20.75	<0.005	1.80	0.02	0.001	0.30	0.22	0.13	<0.1	<0.25	0.02	<0.001	0.49
Banana	0.68	<0.05	0.06	0.005	1.79	<0.001	0.015	0.033	0.44	0.26	<0.05	51.70	<0.005	4.35	0.08	0.012	0.08	2.58	0.08	<0.1	<0.25	0.03	<0.002	0.46
Broccoli	0.07	<0.05	0.06	0.015	14.03	<0.001	<0.006	0.002	0.31	0.11	<0.05	27.46	<0.005	4.36	0.02	0.008	3.28	0.27	0.06	<0.1	<0.25	0.08	<0.001	0.30
Cabbage	0.09	<0.05	0.04	0.006	7.96	<0.001	0.004	0.001	0.18	0.08	<0.05	21.15	<0.005	3.02	0.02	0.002	3.43	0.51	0.04	<0.1	<0.25	0.04	<0.001	0.22
Carrot	1.01	<0.05	0.03	0.021	6.27	<0.001	<0.004	0.004	0.15	0.12	<0.05	14.27	<0.005	2.24	0.03	0.003	8.75	0.16	0.02	<0.1	<0.25	0.03	<0.001	0.10
Cauliflow	0.12	<0.05	0.03	0.006	4.22	<0.001	0.005	0.000	0.37	0.08	<0.05	23.04	<0.005	2.87	0.02	0.003	2.89	0.72	0.03	<0.1	<0.25	0.02	<0.001	0.29
Clementin	1.07	<0.05	0.13	0.014	16.53	<0.001	<0.008	0.005	0.98	0.14	<0.05	16.78	<0.005	2.17	0.02	0.003	0.22	1.24	0.19	<0.1	<0.25	0.15	<0.002	0.98
Courgette	0.14	<0.05	0.02	0.002	2.38	<0.001	0.003	0.002	1.68	0.08	<0.05	18.51	<0.005	1.96	0.01	0.002	0.18	0.66	0.07	<0.1	<0.25	0.01	<0.001	1.16
Cucumbe	2.28	<0.05	0.02	0.004	3.78	<0.001	<0.002	0.001	0.05	0.05	<0.05	12.41	<0.005	1.85	0.01	0.002	1.19	0.07	0.01	<0.1	<0.25	0.02	<0.001	0.06
Endive	1.02	<0.05	0.01	0.000	3.68	<0.001	0.002	0.025	0.08	0.14	<0.05	12.49	<0.005	1.30	0.03	0.001	0.19	0.31	0.02	<0.1	<0.25	0.00	<0.001	0.08
Fennel	1.74	<0.05	0.02	0.007	5.47	<0.001	0.018	0.080	0.35	0.52	<0.05	21.62	<0.005	1.38	0.09	0.005	5.59	0.37	0.12	<0.1	<0.25	0.03	0.001	0.54
Lemon	3.16	<0.05	0.04	0.021	13.56	<0.001	<0.006	0.005	0.69	0.10	<0.05	19.71	<0.005	1.64	0.03	<0.001	0.42	0.41	0.31	<0.1	<0.25	0.07	<0.001	1.14
Lettuce	3.05	<0.05	0.01	0.005	6.93	<0.001	0.026	0.038	0.31	0.42	<0.05	30.11	<0.005	1.67	0.08	0.001	1.26	0.28	0.17	<0.1	<0.25	0.02	<0.001	1.13
Melon	3.43	<0.05	0.03	0.001	3.70	<0.001	0.010	0.001	0.80	0.19	<0.05	37.60	<0.005	3.60	0.02	<0.001	1.15	0.59	0.11	<0.1	<0.25	0.02	<0.001	0.93
Onion	0.78	<0.05	0.07	0.021	9.26	<0.001	0.004	0.001	0.51	0.11	<0.05	12.21	<0.005	1.73	0.02	0.002	0.97	0.54	0.13	<0.1	<0.25	0.05	<0.001	0.80
Orange	0.39	<0.05	0.05	0.016	17.61	<0.001	0.012	0.029	0.05	0.25	<0.05	11.85	<0.005	1.63	0.03	0.007	0.11	2.43	0.02	<0.1	<0.25	0.23	<0.001	0.05
Peach	0.68	<0.05	0.04	<0.002	1.28	0.001	0.020	0.001	1.31	0.24	<0.05	19.06	<0.005	1.28	0.01	<0.002	0.11	3.25	1.50	<0.1	<0.25	0.02	<0.002	8.40
Pear	0.12	<0.05	0.06	0.001	0.94	<0.001	0.007	0.006	0.49	0.08	<0.05	7.86	<0.005	0.68	0.01	<0.002	0.29	0.98	0.31	<0.1	<0.25	0.01	<0.002	1.25
Pepper	0.34	<0.05	0.01	0.001	0.61	<0.001	<0.004	<0.001	0.83	0.09	<0.05	15.84	<0.005	1.10	0.01	<0.001	0.18	0.77	0.09	<0.1	<0.25	0.00	<0.001	0.76
Pineapple	4.86	<0.05	0.02	0.009	3.08	<0.001	0.005	0.001	1.99	0.07	<0.05	12.90	<0.005	1.33	0.16	<0.001	0.08	0.51	0.05	<0.1	<0.25	0.02	<0.001	1.53
Potato	5.48	<0.05	0.07	0.017	4.86	<0.001	0.012	<0.001	0.41	0.19	<0.05	45.30	<0.005	3.33	0.03	<0.002	0.35	0.24	0.13	<0.1	<0.25	0.01	<0.002	0.70
Tomato	0.48	<0.05	0.01	0.000	1.23	<0.001	0.003	0.001	0.35	0.07	<0.05	9.97	<0.005	0.64	0.01	0.001	0.21	0.68	0.04	<0.1	<0.25	0.00	<0.001	0.39
Watermelo	2.08	<0.05	0.03	0.006	1.57	0.001	0.013	0.203	0.004	0.81	<0.05	17.13	<0.005	1.65	0.16	0.007	0.08	2.29	0.01	<0.1	<0.25	0.01	0.002	0.02

Table 8.2 Bioactive compounds and chemical composition of some vegetable by-products in leaves, husk, pulp and pomace (Wadhwa and Bakshi 2013)

	Ash	Crude protein	Organic matter	Neutral detergent fiber	Acid detergent fiber	Neutral detergent soluble	Hemicellulose	Cellulose	Total Sugar	Total phenol	Globulin	Albumin	Glutelin	Prolamin
Sugar beet leaves	21.0	21.9	78.9	42.3	21.1	57.8	21.2	11.4	24.9	2.9	12.7	60.6	14.7	12.0
Cauliflower leaves	13.7	17.0	86.4	27.5	19.4	72.5	8.1	15.2	18.6	5.9	12.9	62.4	15.6	9.1
Black chick pea plant	9.8	13.6	90.2	46.4	38.2	53.6	8.3	25.3	14.0	3.2	13.5	43.5	15.5	27.6
Cabbage leaves	15.8	19.9	84.2	33.7	22.6	66.3	11.1	13.7	20.6	5.9	16.2	54.3	21.3	8.2
Pea vines	10.0	11.8	89.9	60.0	49.9	40.0	10.0	36.8	6.4	4.5	12.4	56.9	22.7	7.9
Radish leaves	22.1	19.4	77.9	27.9	21.9	72.1	5.9	14.9	9.5	6.9	13.7	61.0	13.8	11.4
Summer squash vines	23.3	13.9	76.8	41.1	40.4	58.9	0.7	16.9	7.8	3.7	14.8	69.8	12.6	2.8
Baby corn husk	5.2	11.6	94.8	60.9	28.8	39.1	32.1	24.4	–	–	–	–	–	–
Carrot	8.2	9.9	91.8	9.0	8.0	91.0	1.0	7.0	–	–	–	–	–	–
Ensiled pea vines	9.0	13.1	91.0	59.0	49.0	41.0	10.0	34.0	–	–	–	–	–	–
Potato	4.8	9.5	95.2	–	–	–	–	–	–	–	–	–	–	–
Snow peas	5.2	23.2	94.8	23.1	14.4	76.9	8.7	21.6	–	–	–	–	–	–
Sugar beet pulp	7.3	10.0	92.3	45.8	23.1	54.2	22.7	–	–	–	–	–	–	–
Tomato pomace	6.0	22.1	94.0	63.0	51.0	37.0	12.0	12.0	–	–	–	–	–	–

Table 8.3 Bioactive analysis of various processed fruits by-product sources: pomace, kernel, seeds, flour, and peels (Verma and Joshi 2000)

Type of by products	Fruit	Moisture	Protein	Fat	Minerals	Fiber	Carbohydrate
pomace	Apple	–	2.99	1.71	1.65	16.16	17.35
seed kernel	Mango	8.2[a]	8.5	8.85	3.66	–	74.49
(inner and outer Portion)	Jack fruit	8.5	7.50	11.82	6.5	30.77	14.16
seeds	Jack fruit	64.5	6.60	0.40	1.20	1.50	25.80
flour	Jack seed	77	2.64	0.28	0.71	1.02	18.12
peel	Passion	81.9	2.56	0.12	1.47	5.01	–
peel	Banana	79.2	0.83	0.78	2.11	1.72	5.0
seeds	Sweet orange	4.0	15.8	36.9	4.0	14.0	–
seeds	Watermelon	4.3	34.10	52.60	3.70	0.80	4.50
seeds	Watermelon	6.8	21.0	33.0	4.0	30.00	–
seeds	Pumpkin	6.0	29.5	35.0	4.55	12.00	12.53
Central core	Banana	93.1	0.3	0.03	1.04	0.68	1.20

[a] Values are in percentage

Coffee dry processing by-product of is mainly husk which represents the pulp, dried skin and parchment by 0.18 /ton (Esquivel and Jiménez 2012; Murthy and Madhava Naidu 2012). Whereas, wet technique processing by-products is primarily include the silver skin, pulp and spent coffee ground is the end by-product after brewing process (Table 8.4). The total carbohydrate was ranged 35–72.3 and total dietary fibre was 24–43. Protein content ranged from 5 to 11 but the lowest compound by up to 10%.

Coffee by-products are a rich source of biologically active molecules. Different coffee by-products from different countries (China Mexico, and India) were analyzed for their Procyanidins and flavanols content. The minimum quantity of flavonols (0.1μg/g) detected in Chinese Robusta coffee (Table 8.5). Highest amount of flavanols was found in Arabica coffee husk in Mexico. The variations in the biomolecules components is attributed to different preparation processing bean green and degree of roasting (Mullen et al. 2013).

Attempts have been made to develop and create novel products from coffee processing by-products. Scientists endeavored to generate bioethanol from by-product of coffee using different steam, heating, and enzymes from coffee waste. The outcome results indicated that the yielded bioethanol amount extended between 0.426 ± 0.0015 g/L. from 83% per glucose amount (Arrizon et al. 2012). Shenoy et al. (2011) utilized sulfuric acid and pressure to hydrolyze low moisture coffee by-products, it was found that 0.45 g ethanol/g sugar was yielded (Shenoy et al. 2011). Earlier study optimized ethanol production condition from dry coffee husk and used *Saccharomyces Cerevisiae*, the optimum condition was 3 g yeast/L and 30 °C and bioethanol yielded was 8.49 ± 0.29 g/100g dry husk (13.57 ± 0.45 g ethanol/l).

Table 8.4 Bioactive molecules in coffee by-products of various researches between the years of 2000 and 2009

Components	Pandey et al. (2000, 2000)	Brand and Pandey (2001)	Ferraz and Silva (2009)	Gouvea et al. (2009)	Bekalo and Reinhardt (2010)	Shenoy et al. (2011)	Murthy and Naidu (2012)	Murthy and Madhava Naidu (2012)	Srinivas Murthy et al. (2013)
Total carbohydrate	57.8	35.0		72.3	–	–	–	–	–
Total fibre	–	30.8		–	–	–	24 ± 5.9	43±0.5	24.0
Cellulose	–	–	23.1	16.0	24.5		43 ± 8.0	–	43.0
Hemicellulose	–	–	23.8	11.0	29.7	28.0	7.0 ± 3.0	–	–
Lignin	–	–	28.3	9.0	23.7	72.0	9.0 ± 1.6	–	9.0
Pectin	12.4	–	–	–	–	–	1.6 ± 1.2	–	–
Protein	9.2	5.2		7.0	–	–	8.0 ± 5.0	–	11.0
Minerals	–	10.7	–	–	–	–		–	

Table 8.5 Flavanols and procyanidins composition in Mexico, India and China Arabica and Robusta coffee by-products

Procyanidin and flavonoids	India		Mexico		China	
	Arabica	Robusta	Arabica	Robusta	Arabica	Robusta
Quercetin-3-O-rutinoside	1 ± 9.2*	4.7 ± 2.5	153.8 ± 62.4	3.7 ± 0.2	9.8 ± 2.2	2.6 ± 0.5
Quercetin-O-rutinoside	3.9 ± 2.2	6.4 ± 3.5	23.1 ± 9.9	8.1 ± 0.9	2 ± 0.5	0.7 ± 0.2
Quercetin-3-Ogalactoside	0.8 ± 0.3	2.9 ± 1.7	1.4 ± 0.7	2.9 ± 0.3	0.2 ± 0	0.1 ± 0
(+)-catechin	37.3 ± 15.6	7.7 ± 1.3	32.4 ± 7.8	n.d.	21.1 ± 6.2	0.1 ± 0.1
(−)epicatechin	4.6 ± 2.1	n.d.	17.9 ± 2.6	n.d.	16 ± 2.5	0.5 ± 0.5

Values are expressed as (µg/g)
nd non detected

Another useful aspect of coffee by-products is using it nutritionally and pharmaceutically due to high amount of bioactive molecules. Sliver coffee skin can be used a functional ingredients to produce functional foods. Previous study by (Jiménez-Zamora 2015) stated that both coffee spent grounds and coffee silver skin can be utilized as prebiotic source but after melanoidins was removed. They also can be used food preservatives if used in high amount. Biologically active molecules of coffee processing by-products also showed antimicrobial activity against some pathogenic microbes *E. coli, S. aureus Candida sp*. growth (*C. albicans, C. Krusei and C. parapsilosis* (Sousa et al. 2015).

8.2.3 Bioactive Compound in Tea Processing Byproducts

Alongside with coffee, tea with different stages of processing is one of the most commonly drunk beverages. It is estimated that up to 20 million of cups are consumed. These could left behind magnificent amount of waste (Hussain et al. 2018). It has been reported that 30,000 tons of waste in Turkey (Yagmur et al. 2008), 100,000 of rejected tea processing waste in Malaysia (Nasuha and Hameed 2011) and 190,000 tons in India (Wasewar et al. 2008) are generated annually.

Tea by-products are normally not used and are either burned or dumped into grounds which leads economic and environmental problems (Hossain et al. 2012). This needs to be resolved and alternatives should be found in order to recycle these by-products into useful components.

Several studies have attempted to determine analyze and identify various biologically active molecules. Since it is tea by-products it is possibly contained similar molecules. It has been reported that valuable molecules like catechins (i.e. epicatechin and epigallocatechin gallate) can be extracted from tea by-products (Serdar et al. 2017). A group of researchers analyzed black tea by-products, grade and oven waste. Similar phenolic compounds were found (Güçlü Üstündağ et al. 2016) (Table 8.6).

Another important biomolecules in tea by-products are amino acids in different amounts. The most prevalent amino acid in tea by-products is glutamic acid by

Table 8.6 Oven waste and grade waste phenolic biomolecules of tea by-products based on dry weight

	Phenolic compounds (mg/g DW)	
Compounds	Grade waste	Oven waste
Catechins		
Epicatechin	n.d.	n.d.
Catechin	n.d.	n.d.
Epigallocatechin	n.d.	n.d.
Epigal-locatechingallate	0.91 ± 0.08^{b}	1.05
Gallocatechin	3.99 ± 0.21b	4.69
epicatechingallate	0.31 ± 0.02^{a}	0.26
gallocatechingallate	n.d.	n.d.
Total theaflavins	11.53 ± 0.50^{c}	16.00 ± 0.59^{b}
Total catechins	5.21 ± 0.28^{b}	6.01
Caffeine	16.09 ± 1.29^{b}	16.59 ± 0.50^{b}
Gallic acid	0.59 ± 0.03^{b}	0.65

Values with different letters are significantly different
nd non detected, *DW* dry weight

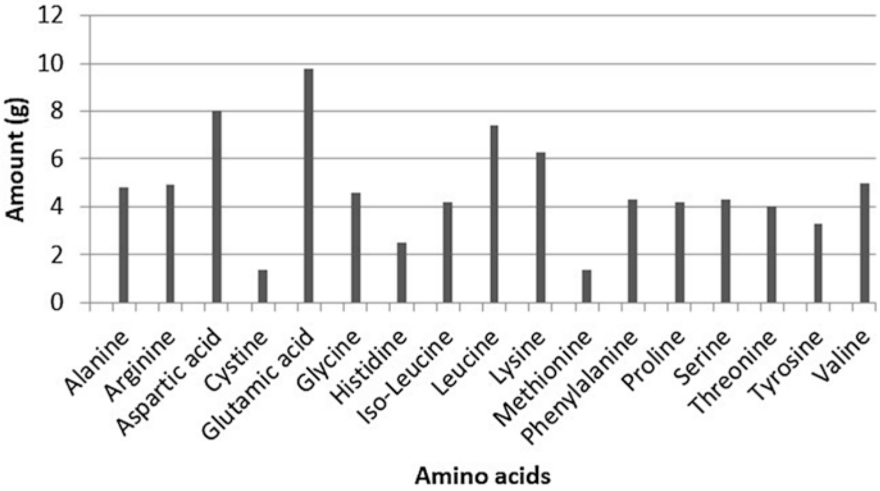

Fig. 8.2 Amino acid composition of tea leaf waste. (Konwar and Das 1990)

9.8 g/100g and least ones are cysteine and methionine with 1.4 g/100g protein (Fig. 8.2)

It has been stated that biomolecules in tea-products is similar but in a lesser amount. The authors included that the biomolecules can be exploited as preservative in agricultural products, pharmaceutical and for cosmetic purposes (Güçlü Üstündağ et al. 2016).

8.2.4 Bioactive Compound in Egg Processing Byproducts

Egg is one of the products that are used across the globe in different cuisines. It has entered industry and the processing which generates waste. The main by-products of egg processing include water in egg industry (Xu et al. 2002), refused eggs, egg shell and membrane (King'ori 2017) and unsuccessfully processed eggs and thrown away (El-Deek et al. 2011).

At different levels processing likes food industries, hatcheries and even at home, egg shell waste is generated which if not treated properly not merely causes pollution to the environment, but it also problematic in terms of disposal place, cost, smell and flies, abrasiveness and cost (Amu et al. 2005). Thus, recycling and re-using for animal nutrition, plant fertilizing and cosmetic purpose can be a reasonable justification.

Researchers have attempted to study and analyze egg shell chemical and nutritional composition. King'ori (2017) has reported that egg shell contains a number of elements such as calcium, boron, magnesium, iron, zinc manganese and copper. Egg shell sometimes is used as plant fertilizer. Eggshell of medium sized egg contains up to 80 mg of calcium. Furthermore, egg shell and membrane contains various amino acids (Nakano et al. 2003). The amino acids content in inner and outer egg and decalcified shells are dissimilar. It seems glycine; glutamine and proline are higher all three groups comparing to the rest of amino acids. It is also obvious that amino acid content in inner and outer egg shell is similar (Fig. 8.3).

Researchers have also analyzed biologically active molecules in waste water of egg industry using acid hydrolysis. It has been found that contains different amino

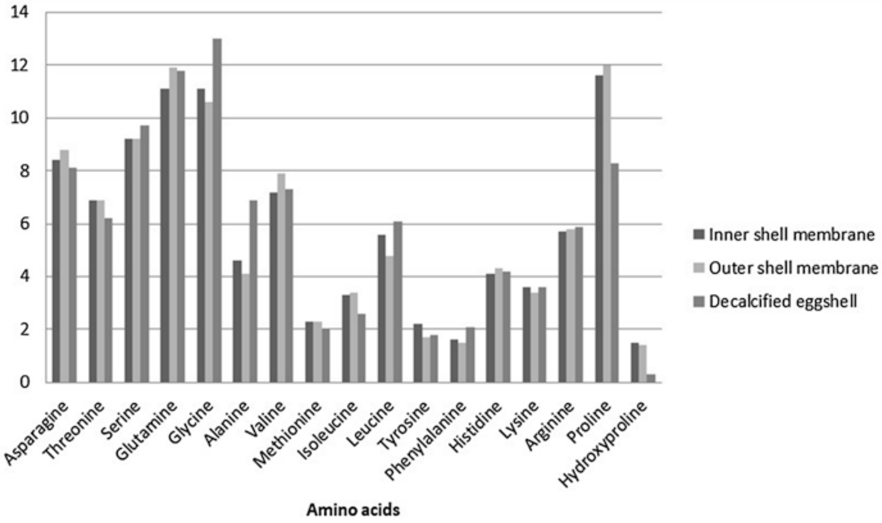

Fig. 8.3 Bioactive amino acid content in egg processing by-products

acids including Leucine (8.44), Lysine (6.47), Valine (6.14), Isoleucine (5.63) and Threonine (4.11 g amino acid/100 g total protein) (Xu et al. 2002).

Peptides as biologically active molecules are part of the egg processing by-products. Different peptides like AGTTCLFTPLALPYDYSH, LAPSLPGKPKPD, RNDDLNYIQ and RASDPLLSV are identified from egg yolk by products which they possess different functional properties (Eckert et al. 2014). Previous study also investigated that egg yolk by- products are source of lipid (56.1) protein (36.3) carbohydrate (4.3) and ash (3.3 g/100 g dry weight) (Hiidenhovi et al. 2005).

Proteins and are bioactive components are extracted from egg processing by-products. In a research to discover the egg-yolk protein as by-product and source of bio active compounds, various sequences of peptides was found as followings RASDPLLSV; RNDDLNYIQ; LAPSLPGKPKPD and AGTTCLFTPLALPYDYSH. It has been stated that aforementioned peptides possess medicinal, pharmaceutical and functional properties (Eckert et al. 2014) (Table 8.7).

8.2.5 Bioactive Compound in Meat Processing Byproducts

Meat and meat related products are essential partners of usual daily diet and they offer important macro and micro nutrients which are not usually available in other sources (Kushi et al. 2012). For that reason, the demand for meat over the past few decades has raised in different place of the globe including Africa, Europe and America.

Animals and livestock conversion to meat their meat at home or abattoir undergo different processing and causes by-product generation at different stages of

Table 8.7 Protein composition of wastewater from egg by-products (Xu et al. 2002)

Protein composition	Electrocoagulation
Thr	4.11[b]
Val	6.14
Cys[a]	DAH
Meth[a]	DAH
Isol	5.63
Leu	8.44
Phenyl	5.17
Tryp[a]	DAH
Lys	6.47

Thr Threonine, *Val* Valine, *Cys* Cystine, *Meth* Methionine, *Isol* Isoleucine, *Leu* Leucine, *Phenyl* Phenylalanine, *Tryp* Tryptophan, *Lys* Lysine

[a] DAH; destroyed by acid hydrolysis

[b] Values are based on g amino acid/100 g total protein

production (Alao et al. 2017). Meat by-products are also generated according to religion, traditions and culture. Despite that, bones, skin, blood, fatty tissue, horn, hoofs, feet, internal organs and meat trimmings are common by-products of meat processing (Toldrá et al. 2012) (Fig. 8.4).

Researchers have exert efforts to understand the nature and composition of these by-products and their potential use in human consumption, industrial or agricultural sectors (Jayathilakan et al. 2012) These by products are rich in different bioactive molecules with having important physiological properties (Fig. 8.5)

Another by-product of meat processing is blood that contains high amount of bioactive molecules (Table 8.8). Blood is a rich source of hemoglobin, albumins, fibrinogen and globulins (Bah et al. 2013). Blood also contains several important bioactive peptides with important physiological properties opioid, anti-oxidant and microbial activities. Skin, bone and horn by-products are rich in different molecules including collagen, glue and gelatin that can be extracted from them biologically active compound with several used in cosmetic and pharmaceutical and nutraceutical aspects. Furthermore, Collagen is a precursor for several nitrogenous molecules (Minkiewicz and Dziuba 2011).

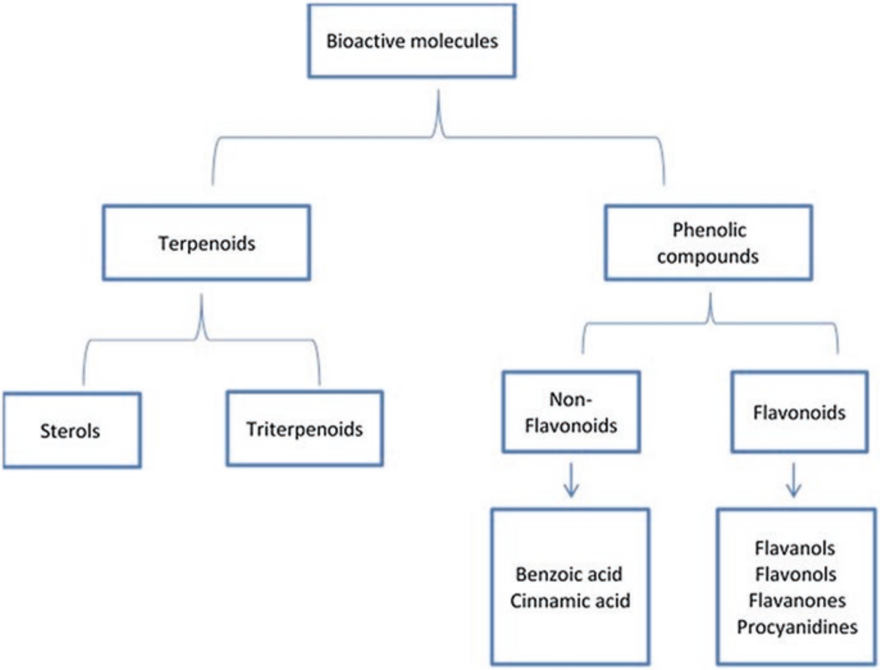

Fig. 8.4 Bioactive molecules of nuts by-products present in testa, hull and kernel

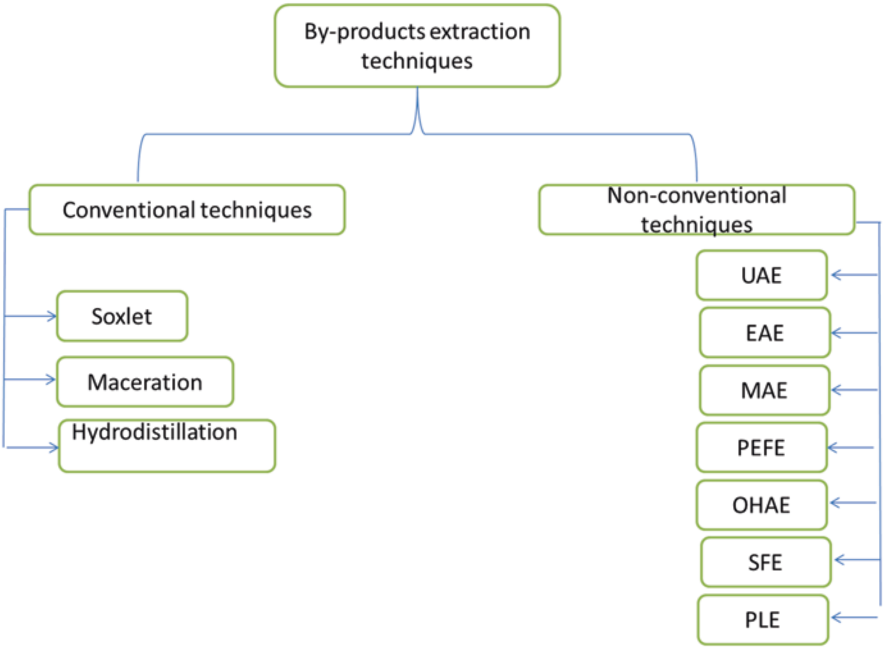

Fig. 8.5 Conventional and non conventional extraction techniques used to extract bioactive. molecules in food by-products of food processing. *UAE* Ultrasound assisted extraction, *EAE* enzymatic assisted extraction, *MAE* microwave assisted extraction, *PEFE* Pulsed electric field extraction, *OHAE* Ohmic heat-assisted extraction, *SFE* Supercritical fluid extraction, *PLE* Pressurized liquid extraction

8.2.6 Bioactive Compound in Dairy Products Processing Byproducts

Dairy products are a part of daily diet of majority of the cultures and of great interest. Furthermore, converting raw milk to dairy products results in large amount of by-products. These by products if not treated and recycled properly, it costs a lot as well as results in magnificent environmental pollution.

One of the most predominant by-products of dairy processing by-products is whey. It is a watery waste remained after cheese manufacturing process (Table 8.9). Whey is of great interest by food professionals since it contains important bioactive proteins such serum albumin, α-lactalbumin, β-lactoglobulin, and immunoglobulins (Galali and Hanee 2019; Conrado and Veredas 2005) and they possess several physiological functions (Asghar et al. 2011).

Casein is another component of dairy industry by-products. It contains many biologically active components. Previous review has concluded that casein by-products can be used in several different industries including the structure of adhesives, emulsions, gels, films, bioplastics, bio- composites and reconstituted fibers

Table 8.8 Prevalence of bioactive compounds of meat- by products (Lafarga and Hayes 2014)

Types	Source	Bioactivity	Parental protein
Bovine	Brain	PEP-Inhibitory	38–55 Glial fibrillary acidic
	Blood	Opioid	Hemoglobin
	Blood	Opioid	Hemoglobin
	Muscle	Antioxidant	1–12 Myoglobin
	Muscle	Antioxidant	1–13 Myoglobin
	Blood	Antimicrobial	33–61 α-Hemoglobin
	Blood	Antimicrobial	1–23 α -Hemoglobin
	Blood	Antimicrobial	107–136 α -Hemoglobin
	Blood	Antimicrobial	107–141 α -Hemoglobin
	Blood	Antimicrobial	137–141 α -Hemoglobin
	Blood	Antimicrobial	133–141 α -Hemoglobin
	Blood	Antimicrobial	126–145 β-Hemoglobin
	Blood	Antimicrobial	α-Hemoglobin
	Brain	PEP-Inhibitory	38–55 Glial fibrillary acidic
Porcine	Muscle	Antithrombotic	–
	Muscle	Antioxidant	Integrin α-3
	Muscle	Antioxidant	Collagen α-1 (VII)
	Blood	Antioxidant	Plasma proteins
	Muscle	Antioxidant	–
	Muscle	Antioxidant	Actin
	Muscle	Antioxidant	Tropomyosin
	Muscle	Antioxidant	Tropomyosin
	Muscle	Antioxidant	Myosin heavy chain
	Muscle	Antioxidant	–
	Blood	Antioxidant	Hemoglobin
	Skin	Antioxidant	Collagen
	Blood	Antioxidant	Plasma globulin/albumin
Venison	Muscle	Antioxidant	–
	Muscle	Antioxidant	–
Buffalo	Horn	Antioxidant	–
	Horn	Antioxidant	–
	Horn	Antioxidant	–

Table 8.9 Bioactive components in cheese processing by-products

Bioactive compounds	Quantity (g/l)
lacto globulin (*α*)	1.5
lacto globulin (B)	3–4
seruma lbumin (Bovine)	0.3–0.6
Lactoperoxidase	0.06
IgM IgG, IgA	0.6–09
Lactoferrin	0.5

Table 8.10 Hydrolyzed bioactive peptides using enzymes and microbes from casein and whey processing by products

	Peptides	Microorganisms/enzymes
1	a- Lactoalbumin, b-lactoglobulin	Trypsin
2	a-Lactoalbumin, B- lactoglobulin Na-Casein, b-casein	Trypsin , pepsin, thermolysin LYQQP and K-proteinase
3	as2-Casein	Lactobacillus different
4	b-lactoglobulin	Pepsin, *Lactobacillus rhamnosus*, and corolase PP
5	k-Casein	*Lactobacillus delbrueckii bulgaricus* IFO13953
6	b-Casein	*Lactobacillus bulgaricus*
7	b-Casein	*Streptococcus thermophilus* and þ *Lactococcus lactis* biovar diacetylactis
8	a-Casein	Trypsin
9	b-Casein	Proteinase from E. faecalis
10	b- lactoglobulin	Thermolysin
11	Na-casein	Alcalase
12	b-Casein	Pepsin
13	Na-casein	Na-casein Enzyme culture of bacterium and plants

(Ryder et al. 2017). Furthermore, casein is also a rich source of many bioactive peptides molecules when treated with different enzymes and microbes (Table 8.10) (Muro Urista et al. 2011). Lactobacillus species, pepsin and trypsin are the most common microbe and enzymes used to hydrolyze and b-casein and Na-casein and lacto albumin and lacto globulin are the most common types of peptides.

8.2.7 Bioactive Compound in Cereal Products Processing Byproducts

Cereal products are staple foods and present on meal table every day. There are hundreds of product of cereal processing sing different cereals particularly wheat varieties (Al-Dmoor and Galali 2014b). Cereal products such as bread, pssta and other products are submitted to different processing like milling and flouring and producing different products that causes generating various by products. On of the major bioactive molecules of cereal processing by-products is dietary fiber.

Different cereals have different dietary content and leaves behind. It has been reported that corn has the highest amount of dietary fiber by 87.86 g and in lesser amount wheat bran, sesame coat, rice bran and oat bran by 44.46, 42, 27.04 and 23.8 (g /% on dry matter basis) (Elleuch et al. 2011). These by products have several functional properties and can be used in different cereal products (Galali 2014).

Phytosterols are another biomolecules in cereal by-products particularly in their bran part. It was seen that rice bran contains the largest amount of phytosterols by

Table 8.11 Phytosterol composition of different cereal by-products (Jiang and Wang 2005)

[a]Bioactive phytosterols	Rice bran	Wheat germ	Durum wheat	Wheat bran	Oat bran	Oat hull	Corn fine fiber
Campesterol	2.61	4.7	2.18	3.66	0.22	0.68	4.85
Comapestanol	0.36	0.67	2.9	1.74	0.04	0.09	1.14
Stigmasterol	1.8	0.22	0.35	0.27	0.13	0.53	5.01
Sitosterol	4.94	11.23	4.71	4.53	1.56	4.09	27.63
Sitostanol	0.84	0.83	2.1	2.45	0.07	0.49	4.15
Cyclo-artenol & like phytosterols	3.33	0.69	0.31	0.48	0.26	0.53	1.44
24-Methylenecycloartanol-&like	5.25	1.03	0.70	3.01	0.38	0.85	0.82
Brassica-sterol	n.d.	0.15	0.57	0.56	n.d.	n.d.	n.d.
Total lipids (mg/m)	20.33	21.28	15.07	17.67	3.41	8.18	1.14
Total raw material (mg/g)	4.5	2.4	1.8	1.2	1.5	0.7	0.3

nd not detected

[a] phyto sterols are determined as mg free sterols/g lipids

4.5 mg/g bran and the lowest was out hull with 0.7 mg/g. Moreover, phytosterols content of wheat bran, oat bran, durum wheat and wheat germ with 1.5, 1.5, 1.8 and 2.4 mg/g respectively (Table 8.11).

Oil is another bioactive substance that is extracted from cereal processing by-products. The amount of oil content varies between the cereal products. Oil content of by products of cereal products were as follows; rye bran 27, spelt bran 39, buckwheat bran 41, oat bran 58, corn bran 74, wheat germ 112 and rice bran 189 (g kg^{-1} dry weight). Additionally, the most abundant fatty acids components seemed to be linoleic by 35.54–62.65%, oleic 11.76–42.73%, palmitic by 11.39–17.23% and α-linolenic by 1.05–9.46%. Furthermore, the total phytosterol and tocochromanols were 1.19–35.24 and 0.369–3.763 (g kg^{-1} of oil) respectively. The study further analyzed biomolecule content and found that tocopherols is prevalent in buckwheat, wheat germ and corn bran by 99.9%, 96.5% and 84.2% respectively. On the other hand tocotrienols present commonly in spelt bran, rice rye and oat and wheat bran by 90.6%, 79.6%, 73.9% and 73.8 % respectively.

Therefore, it is now very clear that cereal by-products are rich biologically active molecules. They can be supplemented with different products to develop functional foods with important physiological and health benefits instead of disposing that cause both economical and environmental problems (Górnaś et al. 2016).

8.2.8 Bioactive Compound in Nut Processing Byproducts

Nuts are a group of seeds that have important nutrients and have gained popularity in the last few years due to physiochemical, sensorial and nutritional properties (Özcan et al. 2011). Therefore it has entered food industry in different processing.

the main edible part is the kernel a seed with layers of cotyledons (Gradziel 2009). The majority of the nuts are either protected by shell and hull.

Nuts are eaten in different forms, raw, roasted and sliced and milled used in different products: bakery and confectionary. These processes generate various by-products mostly green leafy cover, hard shell, skin or testa and hull.

These by-products can be considered of bioactive molecules resources with having several functions including anti-mutagenic, anti-proliferative properties and anti-carcinogenic (Shahidi and Ambigaipalan 2015). There are several bioactive molecules in nuts by-products; Terpenoids (Triterpenoids and Sterols), flavonoids including epicatechin, quercetin- 3-O-rutinoside catechin, , eriodictyol-7-O-glucoside, quercetin-3-Oglucoside and quercetin-3-O-galactoside,) and other non flavonoids like benzoic acid and cinnamic acid (Fig. 8.4). Furthermore, procyanidin trimers, dimers, and tetramers along with dihydrochalcones including phloretin-2-O-glucoside were merely determined in hazelnut pellet.

Luteolin and 5,7-dihydroxychromone as flavones have only been determined in peanut shell. Moreover, diosmetin was discovered only in peanut skin and apigenin was determined in pistachio hard shell (Table 8.12). Almond hull shell Brazilian, pea nut and cashew by-products have not specified for having flavonoids content (Chang et al. 2016). For that reason they have not been mentioned.

8.3 Conventional and Non Conventional Extraction Techniques for Biomolecules Extraction

Biologically active compound are commonly extracted from food processing by products using conventional and novel techniques (Fig. 8.5). Each method has drawback and side. It is of interest to use reasonable techniques to extract maximum amount of bioactive molecules as well as extraction conditions (Barba et al. 2016)

Conventional techniques (Fig. 8.5) were widely used with alcoholic solvents to extract bioactive compound from by-product of food processing. However, this method could degrade the bioactive compounds if exposed for along time with increase temperature (Putnik et al. 2018a, b). Furthermore, conventional methods can be unsafe due to utilizing toxic solvents (i.e. propane). On the other hand, non conventional methods (also known as green extraction methods such as ultrasound-assisted extraction, microwave-assisted extraction, supercritical fluid, high pressure, pulsed electric fields was later invented for extraction of bioactive compounds from both raw and food by-products.

These novel techniques has superiority on conventional techniques with since they are extract bioactive molecules which are safe, and higher quality biomolecules, higher yield, more selectivity and alternative solvents, less environmental problem and less and time energy requirement (Putnik et al. 2018a, b; Zhang et al. 2018) (Table 8.13)

High-pressure assisted technique has shown to enhance extraction efficacy of polyphenols from 2% to 64% in different products including citrus fruits (Casquete

Table 8.12 Bioactive molecules of nuts by-products of pistachio (Fabani et al. 2013), Walnut (Slatnar et al. 2015), Pecan nut (do Prado et al. 2014), Hazal nut (Ciemniewska-Zytkiewicz et al. 2015) and Brazilian nut (John and Shahidi 2010)

	Bioactive compounds	Skin	Hull	Shell
Pistachio	[a]Gallic Acid	75 ± 5	n.d	n.d
	Procyanidin dimer	55 ± 3	n.d	n.d
	(+)-catechin	140 ± 10	n.d	n.d
	( )-epicatechin	27.53 ± 0.03	n.d	n.d
	Eriodictyol-O-hexoside	3.35	n.d	n.d
	Eriodictyol-O-hexoside	0.21	n.d	n.d
	Quercetin-O-hexoside	2.68	n.d	n.d
	Isoquercitrin	49.3	n.d	n.d
	Myricetin	1.6 ± 0.1	n.d	n.d
	Eriodictyol	13.7	n.d	n.d
	Quercetin	13.7	n.d	n.d
	Naringenin	1.9 ± 0.2	n.d	n.d
	Luteolin	30.4	n.d	n.d
	Cyanidin-O-galactoside	21.14 ± 0.05	n.d	n.d
	Cyanidin-O-glucoside	0.55	n.d	n.d
Walnut	Galloyl bis HHDP glucose 2	n.d	50.85	n.d
	[b]Galloyl bis HHDP glucose 1	n.d	95.48	n.d
	Glansreginin (B)	n.d	22.01	n.d
	Glansreginin (A)	n.d	597.44	n.d
	HHDP digalloyl glucose (isomer 3)	n.d	14.53	n.d
	HHDP digalloyl glucose (isomer 2)	n.d	47.49	n.d
	HHDP digalloyl glucose (isomer 1)	n.d	35.51	n.d
	HHDP galloyl glucose 1	n.d	22.00	n.d
	Di-galloylglucose	n.d	21.32	n.d
	HHDP galloyl glucose 2	n.d	57.52	n.d
	Di-HHDP glucose isomer 4	n.d	27.83	n.d
	Di-HHDP glucose isomer 3	n.d	43.45	n.d
	Di-HHDP glucose isomer 2	n.d	133.54	n.d
	Di-HHDP glucose isomer 1	n.d	115.00	n.d
	Vescalagin(isomer 6)	n.d	17.09	n.d
	Vescalagin(isomer 5)	n.d	35.30	n.d
	Vescalagin(isomer 4)	n.d	100.40	n.d
	Vescalagin (isomer 3)	n.d	22.69	n.d
	Vescalagin (isomer 2)	n.d	49.42	n.d
	Vescalagin (isomer 1)	n.d	32.42	n.d
	[a]Hydrolysable tannins	n.d	1610.87	n.d
	Procyanidin (dimer 2)	n.d	1.19	n.d
	Procyanidin (dimer 1)	n.d	156.92	n.d
	Procyanidin trimer	n.d	1.76	n.d
	Procyanidin tetramer	n.d	281.11	n.d
	Catechin	n.d	26.92	n.d
	[a]Flavanols	n.d	467.90	n.d

(continued)

Table 8.12 (continued)

	Bioactive compounds	Skin	Hull	Shell
Pecan nut	[c]Gallic acid (g/mL)	n.d	n.d	828.68 ± 32
	Chlorogenic acid (g/mL)	n.d	n.d	137.91 ± 6.44
	Epigallocatechin (g/mL)	n.d	n.d	120.21 ± 29.72
	Epicatechin gallate	n.d	n.d	0.34 ± 0.01
Hazal nut	Gallic acid	n.d	n.d	2.7 ± 0.0 d
	Protocatechuic acid	n.d	n.d	0.5 ± 0.0 e
	Catechind	n.d	n.d	0.8 ± 0.0 c
	Vanillic acid	n.d	n.d	0.4 ± 0.0 e
	Sinapic acid	n.d	n.d	<LOQ
	p-coumaric acid	n.d	n.d	<LOQ
	Myricetin-3-O-rhamnoside	n.d	n.d	0.2 ± 0.0 c
	Quercetin-pentoside	n.d	n.d	1.0 ± 0.0 b
	Phloretin-2-O-glucoside	n.d	n.d	0.1 ± 0.0 c
Brazilian nut	[d]Gallocatechin	1316.32	n.d	n.d
	Protocatechuic acid	1319.95	n.d	n.d
	Gallic acid	1638.92	n.d	n.d
	Vanillic acid	285.53	n.d	n.d
	Catechin	2874.55	n.d	n.d
	Taxifolin	333.16	n.d	n.d
	Quercetin	28.15	n.d	n.d
	Ellagic acid	76.99	n.d	n.d

nd not determined
aConcentration (lg/g dw)
[b]Concentration(mg kg^{-1} FW)
cEthanolic extraction (g/mL)
[d]Concentration of bound phenolics (lg/g defatted meal)

et al. 2014; Casquete et al. 2015) and tomato pomace (Strati et al. 2015) (Table 8.12) . Furthermore, using electric pulsed field techniques improved anthocyanins extraction yield. Similarly, electronically cooperated pulsed field techniques enhanced color extraction (Praporscic et al. 2007) Particularly with increasing temperature (Brianceau et al. 2015). Earlier researches have found that in blackberries using ultra sound assisted extraction increased recovery of total protein, total phenol, total anthocyanin (Barba et al. 2015) and required less extraction time. Similarly, the methods improved extraction yields in carrot pomace (Jabbar et al. 2015).

Microwave assisted extraction is another novel techniques has been used. It has proved to be dependable methods with less interaction between solvents and high quality bioactive molecules. (Putnik et al. 2017). Researchers have shown that flavonoids yield extraction was more efficient and reached 80.78% in barley leaves (Gao et al. 2017).

Ohmic heat-assisted extraction seems also to be efficient in extracting materials from food processing by-products. Using Ohmic heat extracted increased polyphenol extraction yield in frape pomace (El Darra et al. 2013) and colorant from rice bran (Serdar et al. 2017). In contrast using conventional methods need more time, solvents and less extraction yield (Table 8.14).

Table 8.13 Conventional and non-conventional extraction techniques of bioactive molecules from food by-products

Techniques		Solvent	Temperature condition	Pressure	Time consuming	Amount of solvent requirement	References
Conventional technique	Soxlet	Aqueous and non-aqueous solvents	Under heating	Ambient	High	Moderate	Murugan and Parimelazhagan (2014)
	Maceration	Water, aqueous and non-aqueous solvents	Ambient	Ambient	High	High amount	Murugan and Parimelazhagan (2014)
	Hydro distillation	Water	High	Ambient	High	None	Zhang et al. (2018)
Non conventional methods	Ultrasound assisted extraction	Non-aqueous and aqueous solvents	Ambient and under heat	Ambient	Low	Moderate	Zhao et al. (2012)
	Enzyme assisted extraction	Non-aqueous and aqueous solvents	Ambient and heating after enzymatic treatment	Ambient	Moderate	Moderate	Zhao et al. (2012)
	Microwave assisted extraction	Non-aqueous and aqueous solvents	Ambient	Ambient	Moderate	No solvent or moderate	Balaky et al. (2020)
	Pulsed electric field extraction	Non-aqueous and aqueous solvents	Under heat or ambient	Atmospheric	Low	Moderate	Baiano (2014)
	Ohmic heat-assisted extraction	Non-aqueous and aqueous solvents	Under heat	High	Low	Moderate	Loypimai et al. (2015)
	Supercritical fluid Extraction	S-CO2	Around ambient temperature	High	Low	No solvent or little amount	Zhao et al. (2012)
	Pressurized liquid extraction	Non-aqueous and aqueous solvents	Required heating	High	Low	little	Baiano (2014)

Table 8.14 Conventional and non-conventional techniques to extract bioactive compounds

Bioactive molecules	Extraction techniques	Performance	References
Essential oil from C. microcarpa peel	Hydrodistillation	Using water as solvent for eight hours extract.	Md Othman et al. (2016)
Phenolic acids and flavonoids of Kinnow peel	**Maceration**	Extraction (80% ethanol) resulted in the highest yield with 18.46%	Safdar et al. (2017)
tetramethyl-2-hexadecen- 1-1, Squalene, n-hexadecanoic Acid and octadecatrienoic acid from agarwood leaves	Soxhlet	Extraction with hexane as solvent resulted in highest percentage of oil yield	Lee et al. (2016)
	Novel techniques		
Polyphenols from red grape pomace	Ohmic heat-assisted extraction	The highest extraction efficacy were attained at 400 V/cm	El Darra et al. (2013)
Colorant from rice bran		50, 100, 150, and 200 V cm were used and high yield and high concentration of bioactive molecules was obtained	Loypimai et al. (2015)
Anthocyanins from black rice bran		Both low and high concentration bioactive compounds were extracted. The highest level of bioactive compounds were observed at OHM with 40% MC ($E = 50$, 100, and 150 V cm^{-1}) and 30% MC ($E = 100$, 150, and 200 V cm^{-1})	Md Othman et al. (2016)
Grape pomace polyphenols	Pulsed electric fields	Extraction can be increased with increasing temperature	Brianceau et al. (2015)
Flavonoids from young barley leaves	Microwave-assisted extraction	Method was more efficient than conventional, and maximum flavonoids yield obtained (80.78 ± 0.52%)	Gao et al. (2017)
Total tannins, total and total phenol and flavonoids of mandarin peel		Ethanolic extraction had more efficiency over water extraction of tannin, phenols and flavonoids were 0.082 ± 0.0006, 1.871 ± 0.0000 and 0.197 ± 0.0004 respectively	Balaky et al. (2020)

(continued)

Table 8.14 (continued)

Bioactive molecules	Extraction techniques	Performance	References
carrot pomace total phenols, antioxidant capacity, caffeic acid, chlorogenic acid, epicatechin and catechin,	Ultrasound assisted extraction	Extraction time and improved the extraction yield	Jabbar et al. (2015)
Fatty acids, b-sitosterol, a-tocopherol, squalene, total phenolics and carotene from palm pressed fiber		Bioactvie molecules with antimicrobial activity were determined	Dal Prá et al. (2017)
Lycopene from tomato waste	High pressure-assisted extraction	led to higher yields (from 2% to 64%	Strati et al. (2015)
Citrus peel fruits polyphenols		More extraction yields	Casquete et al. (2014)

8.4 Conclusion

This chapter presented the importance of various processings food by-products as a cheap and rich of bioactive molecules resources source. It is no longer a practical solution disposing in to the environment and cause pollution. These bioactive molecules can be utilized in different areas; functional product development, cosmetics, pharmacognosy and other sectors. These applications require non-degraded bioactive compounds for better performance. Several methods of extraction have been used and each method has own strength and weakness in relation to interested bioactive molecule. Despite that, a number of parameters decide on suitability of extraction techniques including; by-products type, bioactive molecule structure, the scientific skills. It is very important to choose suitable methods particularly novel techniques which are quicker and safer. It is decisively crucial to consider aforementioned parameters prior to select any extraction techniques

Acknowledgments The author appreciate support of Salahaddin Univeriy-Erbil and Cihan university-Erbil, Iraq

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Chapter 9
Plant and Food Waste as a Source of Therapeutic Compounds

Divya Vanoh, Jahidul Islam Mohammad, and Mogana Das Murtey

Abstract The global agriculture industry produces tens of millions of plant waste every year, which environmental issues, yet plant waste is rich in phytochemicals with various health benefits. Here we review plant and food waste as a source of therapeutic compounds with focus on phytochemicals and food by-products. Phytochemicals include phenolics, alkaloids and terpenids. Food by-products include compounds from tomato, carrot, onion, potato, pumpkin, maize, paddy, asparagus, cocoa, tea, coffee, buckwheat, almond, walnut, pistachio, cashew nut, hazelnut, and peanut. Medicinal properties include anticance, antimicrobial, anti-inflammatory, anti-viral, antiproliferative, and treating hyperglycaemia, hypercholesterolemia and cardiovascular diseases.

Keywords By-products · Agriculture waste · Fruits · Vegetable · Agro-plant · Nuts · Antioxidant · Antimicrobial · Anticancer · Anti-hypercholesterolemia

9.1 Introduction

There is a symbiotic relationship between humans and plants reaching well back into our shared evolutionary past. Plants have often been present as a human part of life, usually as food or medicine. The use and knowledge of the variety of healing

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9_9

properties of plants has been passed on through experience and study since ancient times. Over time, however, the plant structures and the presence of organic compounds responsible for the healing properties become the object of interest for researchers (Dreyfuss and Chapela 1994). This interest finally leads to the discovery of phytochemistry, a study of plant compounds.

Plants have two kinds of metabolisms: primary metabolism that exists in all living organisms and secondary metabolism that affects phytochemicals' development and storage. Many techniques have been developed over the years, ranging from plant tissue sample preparation to advanced techniques for the elucidation of organic structures (O'Shea et al. 2012).

The discovery of phytochemicals has led to significant advances in technology and advanced machinery in the pharmaceutical and agrochemical industries over the last few decades, resulting in an immense amount of agricultural waste and by-products. Inadequate waste disposal systems, combined with a lack of by-product management, pose a risk to the environment and sustainability, especially in the food processing industry (Jabeen et al. 2015).

In recent years, scientists around the world have focused efforts to harness the potential of agricultural waste by-products, which can become a lucrative source of income. Although by-products used to be a major concern for disposal for the sector concerned, growing interest in the function of plant phytochemicals in products and their possible effects on human health allows them a promising source of safe diets or supplements. Owing to higher incidences of co-morbid diseases such as cancer, diabetes, and coronary heart diseases, consumer health consciousness has risen in the last decade (Schieber et al. 2001).

Since nutritional recommendations encourage a diet rich in fruits and vegetables for a balanced lifestyle, this fuels the requirements for safe and healthy natural ingredients. Currently, one third of the components of fruits and vegetables such as peels, pips and skins are discarded as waste or by-product during preparation and processing, decreasing the overall nutritional potential (O'Shea et al. 2012). This review highlighted the availability and the potential to be readily capitalised as a healthy ingredient of untapped natural sources of phytochemicals from fruit, vegetables as well as nuts.

9.2 Major Group of Phytochemicals

A large range of organic compounds, including phytochemicals, are produced by fruits and vegetables, which is important for human diet. Of the 200,000 phytochemicals known so far, about 10% come from fruits, vegetables and grains (Patra 2012). Phytochemicals are natural active chemicals found in plants which are considered as non-essential nutrients, derived from the Greek word '*phyto*' (plant) (Alasalvar and Shahidi 2008; Hasler and Blumberg 1999). Phytochemicals are responsible for protecting plants from disease and harm, as well as contributing to the growth of plant phenotypes. Phytochemicals have recently been considered to play an important role in human health, depending on the dose of the supplement (Gibson et al. 1998; Samrot et al. 2010; Deepak et al. 2010).

Since phytochemicals, also known as secondary metabolites, tend to accumulate in the outer layers of plant phenotypes, there are studies done to identify and isolate the chemical components in order to establish their biological efficacy and to understand the mechanism of their action (Costa et al. 1999; King and Young 1999). Phytochemicals are classified by separate functions, but the inherent synergy between the individual compounds in the plant makes it exhibit more than one biological function. As a result of years of research, it is now known that phytochemicals have anti-cancer, anti-diabetes and heart disease benefits (Rao 2003; Mathai 2000).

It is possible to classify phytochemicals into two broad groups: primary and secondary metabolites. Sugar pyrimidine, amino acids, proteins, purines, and nucleic acids are found as primary metabolites. On the other hand, majority of the secondary metabolites can be categorised into three main groups: terpenoids, phenolic compounds, and alkaloids (Fig. 9.1). Other bioactive phytochemicals such as flavonoids, lignans, plant steroids, curcumin, saponins and glucosides are present in addition to the main classification. (Hahn 1998; Harborne 1999; Espín et al. 2007; Tomás-Barberán et al. 2004).

9.2.1 *Phenolic Compounds*

Plants will synthesise secondary metabolites called as phenolic compounds during normal growth or as a defence mechanism against environmental changes. Phenolic compounds are water soluble in their chemical structure, with at least one hydroxyl group connected to one or more aromatic rings (Naczk and Shahidi 2004; Shahidi and Yeo 2016; Shahidi and Peng 2018). Phenolic compounds derived from phenylalanine and tyrosine consist of a number of phytochemicals, from basic phenols to

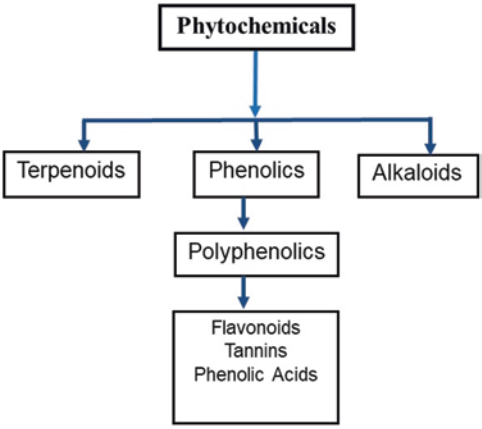

Fig. 9.1 Classification of phytochemicals of plant-based natural products. Phytochemicals are divided into three big groups with phenolics group by far, the largest and widely distributed in plant kingdom, comprises mainly with flavonoids, tannins and phenolic acids. (Modified from Shahidi et al. 2019)

complex compounds known as polyphenols in their natural state (Cowan 1999; Bravo 1998).

Many studies on the role of phenolic compounds against human ailments have been carried out. For example, Ouerghemmi et al. 2017 managed to prove the antioxidant and antimicrobial effects of phenolic compounds in the leaves and flowers of wild Tunisian *Rutar chalepensis L.* They analysed and found that flowers and leaves of wild Tunisian *Rutar chalepensis L.* showing high total polyphenol amounted to 168.91 and 129.69 milligrams catechin equivalent per gram of dry weight (mg CE/g DW) respectively and approximately have similar amount of flavonoid (50 mg CE/g DW) and tannin (435.89 mg CE/g DW) (Ouerghemmi et al. 2017).

During the experiment, the phenolic compounds in the flowers and leaves of wild Tunisian *Rutar chalepensis L.* reportedly exhibit significant total antioxidant capacity; 189.61 and 169.6 milligrams gallic acid equivalent per gram of dry weight respectively. This leads to high 2,2-diphenyl-1-picrylhydrazyl scavenging efficiency (ranging between 23.73–30.69 micrograms per millilitre) and reducing power (0.90 micrograms per millilitre) (Ouerghemmi et al. 2017).

In addition to that, phenolic compounds from the flowers and leaves of wild Tunisian *Rutar chalepensis L.* showed antibacterial properties against human pathogen strains such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. The inhibition zone diameter that exhibited by flower extracts were reported as follows: 15 ± 0.6 (*Staphylococcus aureus*), 16.3 ± 1.1 (*Pseudomonas aeruginosa*) and 15.7 ± 0.9 mm (*Escherichia coli*) while leaves extracts showed the inhibition zone diameter of 15.3 ± 1.2 mm (*Staphylococcus aureus*) 16.7 ± 0.6 mm (*Pseudomonas aeruginosa*) and 14.3 ± 0.4 mm (*Escherichia coli*) (Ouerghemmi et al. 2017).

Flavonoids, phenolic acids and tannins are the most significant dietary phenolics (King and Young 1999). Flavonoids, the main group of plant-derived phenolic compounds, found in a wide range of plants. It is synthesised through phenylpropanoid pathway and further subdivided into flavones and flavanols (Nichenametla et al. 2006). Research has shown that flavonoids are responsible for several medicinal and pharmacological activities such as anti-inflammatory, antimicrobial, anti-cancer and anti-diabetic (Kumar and Pandey 2013; Mahomoodally et al. 2005).

It is established that flavonoids are synthesised by plants to exert an antimicrobial activity against invasive microbial infections. An in vitro study by Xu et al. 2019 proved the fact by examining the chemical composition and antimicrobial activity of *Sedum aizoon L* flavonoids against *Aeromonas*. They found predominant flavonoids such as kaempferol, quercetin dihydrate, and catechin were displayed antibacterial activity on *Aeromonas* in vitro which affected the membranes of the bacteria, caused sugar leaks and protein depletion (Xu et al. 2019).

Recently, the possible health benefits resulting from antioxidant activity have generated interest in flavonoids. Jimenez-Aguilar et al. (2017) have measured the concentration of minerals such as calcium, potassium, magnesium, phosphorus, and phenolic compounds in the 15 leafy *Amaranthus* species. They found the concentrations of calcium, potassium, magnesium, phosphorus, and phenolic compounds were 1.5–3.5 milligram per gram on a fresh weight basis (mg/g FW), 5.5–8.8 mg/g FW, 1.8–4.5 mg/g FW, 0.5–0.9 mg/g FW and 3.2–5.5 milligram gallic acid equivalents per gram on a fresh weight basis respectively. This findings were equivalent to 13 to 34% of the daily value recommended by US Food and Drug Administration. The antioxidant activity of leafy Amaranthus species were at 38–90 micromole trolox equivalents per gram on a fresh weight. Presence of antioxidant minerals and phenolic compounds in amaranth leaves make them as ideal candidate as a food source for significant nutrients and health-beneficial compounds (Jiménez-Aguilar and Grusak 2017).

Another significant proportion of phenolic compounds are phenolic acids and tannin. The substituted forms of hydroxybenzoic and hydroxycinnamic acid derivatives are phenolic acids. They are found in plant sources, such as wheat, legumes and oilseeds in particular (Balasundram et al. 2006). In various agricultural, biological, chemical and medical studies, phenolic acid compounds have been the topic of interest. Phenolic acids have been reported to have many biological activities. Ashraf et al. 2015 used methanol, chloroform and hexane extracts to identify the chemical composition and pharmacological potentials. of dried *Eucalyptus camaldulensis* leaves. They found the dominating presence of phenolic acids such as palmitic acid (31.06%) together with traces of gallic acid, p-hydroxybenzoic acid, syringic acid and vanillic acid. Moreover, they found outstanding total antioxidant contents of dried *Eucalyptus camaldulensis* leaves at 34.81 ± 0.67 milligram gallic acid equivalents per gram of plant extract.

Tannins are an essential high molecular weight category of secondary plant metabolites. They range from dimers to large polymers and are abundantly present in both bark and wood (Shirmohammadli et al. 2018). Tannins shield plants from ultraviolet rays and free radicals, as well as animals, insects, fungi, and bacteria from various biological threats. Generally, tannins are categorised into condensed and hydrolysable tannins (Sieniawska and Baj 2017; Ambigaipalan et al. 2016). Tannins have shown a great deal of ability to deal favourably with human ailments and one of the tannin characteristics summarised by Ekambaram et al. 2016. The ability of hydrolysable tannins as an antimicrobial agent are due to the presence of nonahydroxyterphenoyl and hexahydroxydiphenoyl (Ekambaram et al. 2016).

In conclusion, phenolic compounds are consisting of three main groups; flavonoids, phenolic acid and tannin which are known to have antioxidant and antimicrobial properties.

9.2.2 Alkaloids

The alkaloids are a large phytochemical group which contain heterocyclic nitrogen atoms. The name of the alkaline was derived from its chemical structure which characterises its nitrogenous base properties (Mueller-Harvey and McAllan 1992). They have few common features: bitter taste, soluble in water, contain at least one atom of nitrogen in the molecule, and initiate biological activities such as anti-proliferative, anti-inflammatory, anti-bacterial and antioxidant effects (Rodriguez-Garcia et al. 2017; Rao et al. 1978).

As a protection for the plant, alkaloids are necessary to ensure survival against micro-organisms or natural pests and display antitumor and antibacterial effects at the same time (Molyneux et al. 1996). Liang et al. 2017 showed that diterpenoid alkaloids isolated from *Aconitum sinchiangense*, which shown significant anti-tumour activity against tumour cells such as adenocarcinomic human alveolar basal epithelial cells, human breast cancer cell line and immortalized human colon cancer cells while exhibit significant anti-bacterial activity against *Staphylococcus aureus* via the root bark with minimum inhibitory concentrations of 0.147 and 0.144 micro-mole per millilitre (Liang et al. 2017).

A further research by Feng et al. 2019 showed that plant-based alkaloids could exhibit antihypertensive effects where five aqueous extracts of plant-based alkaloids were administered orally to spontaneously hypertensive rats. They concluded that in each of the groups provided with plant extracts, sustainable reductions in systolic blood pressure (from 180 millimetre of mercury to 150 millimetre of mercury) were observed (Feng et al. 2019).

For decades, quinidine, a form of alkaloid, has been used as an anti-arrhythmic treatment. Reports by Viskin et al. 2019 who used quinidine on patients with polymorphic ventricular tachycardia due to coronary artery disease but in absence of acute myocardial ischemia. During the study, patients with cardiovascular disease who have ventricular arrhythmias responded better to quinidine than to any other antiarrhythmic medications. Three patients (16%) were discharged without recurrent polymorphic ventricular tachycardia developed by quinidine (Viskin et al. 2019).

Quinine is another popular example of alkaloid usage and become the gold standard treatment for malaria. Shanks 2016 summarises the historical review and benefits of quinine administration in malaria cases. Another review on the benefits of alkaloid were done by Alam et al. 2017. They reviewed extensively about the role of alkaloids from plant *Catharthas Rosas L.* which can give a therapeutic effects such as anticancer, anti-diabetes, antihypertensive, and antimicrobial activities.

In conclusion, alkaloids are useful for human health and in fact crucial to address co morbidities conditions since it exhibited anti-hypertensive, anti-arrhythmic as well as anti-tumour activities and also important for anti-malarial activities.

9.2.3 Terpenoids

Terpenoids are the greatest natural group of phytochemicals found primarily in plants with isoprene molecules. It is regarded as modified terpenes with shifted methyl groups. It is a liposoluble and volatile substance responsible for the odour of citrus, coniferous and eucalyptus plants and flowers (Bohlmann et al. 1998; Gershenzon and Dudareva 2007; Bonkanka 2007). Terpenoids are colourless important ingredients for the better quality of agricultural products since they are used as flavourings in food and fragrances in cosmetics (Harborne and Tomas-Barberan

1991). Terpenes are categorised according to their molecular formula (nC5H8) and are defined by the number of isoprene units (Langenheim 1994). Terpenoids can be derived from resins or tree gums as a non-volatile essential oils and subdivided into acyclic, monocyclic, bicyclic and tricyclic structures (Ludwiczuk et al. 2017).

In several trials, terpenoids have been used and have demonstrated numerous possible benefits for human health. Terpenoids have been shown to demonstrate strong inhibition responses against Gram-positive and Gram-negative pathogenic bacteria as summarized by Raut and Karuppayil 2014. They reviewed that since terpenoids are lipophilic, they easily permeate and damage the cell wall and cell membrane integrity, causing cellular material, cytoplasmic protein denaturation, and cellular enzyme inactivation, which eventually leads to apoptosis (Raut and Karuppayil 2014).

Terpenoids, particularly monoterpenes are heralded as an effective anticancer agent, found mainly in essential citrus fruit oils. They induced apoptotic reactions and cellular redifferentiation in cancer cells by modifying the gene expression. The manner of anticancer reaction of terpenoids was by increasing the synthesis of pro-apoptotic proteins which can be achieved by posttranslational modification of small guanine nucleotide-binding proteins. This process would significantly reduce the progression of cancer in animal models and induced regression of existing tumours (Huang et al. 2012; Lesgards et al. 2014).

Terpenoids can be suitable anticancer agents since it suppresses the proliferation of tumour cells by apoptotic induction or necrosis. The mode of actions by terpenoids are normally by caspases activation, cancer cell membrane depolarization (specifically mitochondria), angiogenesis inhibition and phosphoinositide 3-kinases/ protein kinase B/ nuclear factor kaffa beta pathway. The presence of good antioxidant agents such as beta-caryophyllene, thymol or eugenol are critical in stimulate selective oxidative stress which leads to decrease inflammation (Lesgards et al. 2014).

There are different studies that have illustrated the benefits of terpenoids on health betterments. Harpagoside, a terpenoid found in *Harpagophytum procumbens*, noted to inhibit the expression of cyclooxygenases as well as the nitric oxide production through peritoneal macrophages. It increases dopaminergic neurodegeneration and movement disorders in a model of Parkinson's disease by increasing neurotrophic factors derived from glial cell lines (Georgiev et al. 2013). In a series of vivo studies, another terpenoid, picrolia, an antioxidant and naturally occurring hepatoprotective agent, exhibited choleretic and anticholestatic action (Verma et al. 2009). Terpenoids have promoted a synergistic combination with flavonoids that has led to the gastrointestinal activity of pepper tea, reducing the influx of calcium and the non-competitive contraction block caused by 5-hydroxytriptamine (Raut and Karuppayil 2014).

Therefore, in fruits, vegetables and nuts, the presence of phytochemicals increases the consistency of food intake. In the agri-food sector, the rise in production, preparation and use contributes to the production of large quantities of solid and liquid waste. This chapter highlights the role of phytochemicals in selected fruits, vegetables and nuts by product/waste, which is useful for our health improvement.

9.3 By Products and Waste of Agricultural Plants and Vegetables

Vegetable consumption is inversely linked to many chronic diseases. Phytochemicals found in vegetables are responsible, through a variety of mechanisms, for health benefits. Lately, agro plant by-product and waste valorization are generating interest because they can be a renewable source, generate profit, and provide jobs. The bioavailability of phytochemicals such as phenolics, terpenoids, and alkaloids are high since it can be obtained from industrially derived plant by-products.

9.3.1 Tomato

The top crop grown in the world is the tomato (*Solanum lycopersicum*) which is a major food source for vitamins A and C. It accounts for more than 15% of the world's production of vegetables due to its high rate of food intake (Adams-Phillips et al. 2004). Tomatoes have substantial number of bioactive compounds such as carotenes (lycopene) and phenolic compounds (flavonoids and phenolic acids) and extensively used in the pharmaceutical and agro-food industries (Heuvelink 2018). Due to high demand, processed tomato products produced high-volume by-products; the skin, pulp and seeds which are collectively known as tomato pomace (Figueiredo-Gonzalez et al. 2016; Galanakis 2017).

Tomato pomace makes up about 4% of the weight of the fruit and consists mainly of fibre along with protein, fat, and mineral traces. Bioavailability of phytochemicals in tomato skin are similar with tomato flesh and in fact possess higher percentage of phenolic compounds than pulp and seeds. Recently, tomato pomace become interesting choice to be taken as a long-term health benefit supplement. The effect of tomato pomace extract on platelet aggregation in healthy human beings was investigated by Palomo et al. 2019. Their clinical research concludes that the daily consumption of one-gram tomato pomace aquatic extract results in reduction of platelet aggregation from 62% to 54% after 5 days of consumption (Palomo et al. 2019).

Tomato pomace was also used by Shao and co-researchers to observe the cholesterol-lowering effects of tomato pomace on male Golden Syrian hamsters. Faecal bile acid and total lipids are excretion increased 47% and 352% after treatment with tomato pomace supplements due to rises in bile acid and cholesterol in the faeces. It showed that in tomato pomace responsible for reducing cholesterol by increasing faecal bile acid and lipid excretion (Shao et al. 2013).

Warditiani et al. 2020 recently determined the effect of lycopene extracted from tomato pomace on minimizing the rat blood glucose in hyperglycaemia rats that were induced by a high-fat diet. They concluded that tomato lycopene extract doses (5, 15, and 50 mg/kg of body weight) managed to normalise the rat blood glucose level in 14 days of treatment (Warditiani et al. 2020).

In conclusion, tomato by products such tomato pomace consists of numerous vitamins and phytochemicals from phenolic compounds such as lycopene, beta carotene, lutein is good for hyperglycaemia, hypercholesterolemia as well as for platelet aggregation condition.

9.3.2 Carrot

The carrot (*Dakas carota L.)* is one of the most highly yield vegetable crops in the world and it is used as a fresh commodities or for industrial processed food. It belongs to the family of *Apiaceae* and consists of two parts, the stem and most importantly root which consists of a shell (periderm), a pulpy outer cortex (phloem) and an inner core like most roots (xylem) (Tiwari and Cummins 2013; Dawid et al. 2015; Nguyen and Nguyen 2015). Carrots has numerous phytochemical entities such as phenolic and carotenoids (Surbhi et al. 2018).

Annually, large quantities of carrots have been discarded for not reaching standard market requirement. In addition to that, high demand for carrot puree and juice leads to high amount of waste, namely carrot peel from industry. Carrot peel has numerous phytochemicals which can be useful against human diseases. Carrot peel which is just 11% of the total fresh weight, contains half of the total phenolic compounds such as ferulic acid, caffeic acid, chlorogenic acid, synapic acid, protochuic acid and p-kumaric acid. It also contains carotenoids such as saponin, lutein, lycopene, alpha and beta carotene. (John et al. 2017a; Zhang and Hamauzu 2004; Alasalvar et al. 2005).

Carrot peel has been used by John et al. 2017b to evaluate their antioxidant and antimicrobial activity. They analyse and found the total phenolic and flavonoid content of carrot peel extract are 106.36 milligrams of gallic acid equivalents and 27.83 milligrams of quercetin equivalents. They demonstrated greater antioxidant potential for the 2,2-diphenyl-1-picrylhydrazyl radical scavenging operation of carrot peel acetone extract. The carrot peel acetone extracts showed 96.95% scavenging activity and could inhibit the growth of *Shigella flexonari*, *Escherichia coli*, *Staphylococcus aureus*, and *Pneumoniae Clebisilla* ranged from 11 to 16 millimetre (John et al. 2017b; Gulsunoglu et al. 2019).

Meanwhile, Kamiloglu et al. 2017 demonstrated that carrot peel indeed has anti-inflammatory potential which can be useful for cancer research. They used polyphenol-rich black carrot peel to trigger the inflammatory response in endothelial cells treated with tumour necrosis factor alpha after gastrointestinal digestion. The result indicated that the transportation of anthocyanins and phenolic acids was greater for digested samples (1.3–7%) compared to undigested ones (0–3.3%).

The transported polyphenols were able to down-regulate the secretion of pro-inflammatory markers such as monocyte chemoattractant protein-1, interleukin-8, vascular endothelial growth factor and intercellular adhesion molecule-1 from 120–203% down to 34–144%. These findings have shown that black carrot peel can act by regulating endothelial cell inflammatory cascade inhibition. The capability of carrot peel makes them a good candidate to be used as functional food ingredients (Clementz et al. 2019; Kumar et al. 2019; Kamiloglu et al. 2017).

In conclusion, carrots by products such as peel which have phenolic and carotenoids which are useful for anti-inflammatory, antimicrobial and anticancer effects.

9.3.3 Onion

An onion (*Allium cipa L.*) is one of humanity's oldest vegetables. This included in the *Amerilidaceae* family and the Allium genus. Onions are available in various colour, size, firmness and pungency. It found in plenty of recipes and may be consumed as raw or as pickled food vegetable. Onion nutritional composition is very elaborated, but it has been proved to consist series of phytochemicals such as flavanol quercetin and quercetin derivates. There is a lot of environmental concern about onion waste or by-products in the industry and its disposal, as the market for onions rises every year. The food and agricultural products processing industries generate substantial vast amount of phytochemical rich onion by-products which can be beneficial for public health (Benítez et al. 2011).

The main by-products of the onion processing industry are brown skin or dried peel rich in quercetin, chorecetin glycosides which contain effective antioxidants against the lethal effects of oxidative stress. Singh et al. 2009 demonstrated the antioxidant potentials of onion-dried peel by examining the antioxidant activity of five fractions of red onion peel. They found red onion peel has high total content of phenolics (384.7 ± 5.0 milligrams of gallic acid equivalents) and flavonoids (165.2 ± 3.2 milligrams of quercetin equivalents). The antioxidant activity of red onion peel is 97.4 ± 7.6% and demonstrated dose-dependent antimutagenic activity 70.41 ± 4.79% of inhibition of tobacco-induced mutagens in the *Salmonella typhimurium* strain (Singh et al. 2009).

In another study by George et al. 2019, they used a unique carrier-based delivery of phyto-derived quercetin extracted from onion peel waste as an anticancer treatment. They reported that onion peel waste derivative showed better treatment ability with quercetin enrichment by obtaining optimum loading efficiency of 91.36% compared to pure chitosan cellulose hydrogel while maintaining an acidic anticancer environment at pH 5.0 (George et al. 2019).

Since onion wastes are not suitable for landfill disposal due to rapid growth of microorganism such as *Sclerotium cepivorum* (white rot), valorisation of onion by-products especially for profitable production of food-grade products will benefit the onion producers and processors (Benítez et al. 2011).

In conclusion, valorisation of onion by products will provide phytochemical compounds such as quercetin, chorecetin glycosides which will be useful for antioxidant activity and anticancer activities.

9.3.4 Potato

Potato (*Solanum tuberosum L.*) is a South American native crop, originated from central Andean area dated back around 500 B.C. It is now grown in most parts of the world and become a major source of human nutrition since the nutritional quality was well established and documented (Zaheer and Akhtar 2016). Potato is a great source of protein and contains many vitamins, such as vitamin C, vitamin B6 and vitamin B3, as well as potassium, phosphorus, magnesium and iron, in addition to supplying energy through its high starch content (Andre et al. 2007). Although generally, consumption of potatoes has decreased, processed products such as chips and French fries have showed growing popularity.

A large amount of potato peel waste is produced because potatoes are widely used in processed food products (Liang and McDonald 2014a, 2014b). Phenolic compounds such as gallic acid, caffeic acid, chlorogenic acid and proteolytic acid are the main phytochemicals in potato peel, but as they reach the middle of the potato flesh or tuber, the amount of phenolic compounds decreases (Dos Santos et al. 2016; Singh and Rajini 2008; Ezekiel et al. 2013). Potato peel contains essential bioactive compounds which can be extracted and used for health benefits as potential food additive substances (Alvarez et al. 2014; Singh et al. 2009).

In order to minimise oxidative stress and avoid chronic diseases, it can be used as a dietary antioxidant (Arun et al. 2015; Singh et al. 2005). As reported by Singh and Rajini 2004, the presence of high phenolic compounds having antioxidant properties are useful in inhibiting lipid peroxidation. They documented that dried aquatic extract of potato peel powder managed to inhibit ion chelating ability by 50% which eventually led to lipid peroxidation in homogenates of rat liver (Singh and Rajini 2004).

The fact that dietary fibre has a beneficial impact on blood glucose and insulin response is a well-known fact (Onyechi et al. 1998; Chandalia et al. 2000). Potato peel antioxidant activity was found to affect the condition of hyperglycaemia, particularly the glycaemic index. A 4-week streptozotocin induced study found that potato peel-powdered diets with diabetic male Wister rats showed a substantial decrease in blood glucose levels by 52%. The streptozotocin induced rats fed with potato peel-powdered diets managed to normalise the structure of the diabetic rats' liver by 13–17% and kidneys (19%) (Singh et al. 2005).

Since half of the potato peels is consist of dietary fibers, it was introduced as a promising fibre source (Camire et al. 1995). Potato peel are consisting primarily insoluble fibers which is useful in bile acid binding which is crucial in lowering plasma cholesterol (Camire et al. 1993). Another study on dietary fiber from potato peel by (Lazaro and Werman 1996) on hypocholesterol effect showed that rats, after feed with potato peels for 4 weeks, experienced significant reduction in plasma cholesterol content and hepatic fat cholesterol levels. Apart from being a good dietary source, potato peel also touted as an antimicrobial agent by acting positively against gram negative bacteria species at high concentration (De Sotillo et al. 1998).

In conclusion, potato by products such as potato peel are useful for hypercholesterolemia and antioxidant activities.

9.3.5 Pumpkin

Pumpkin (*Cucurbita*) is originated from American continent before spreading throughout world. It is a dicotyledonous seed vegetable that belongs to the family Cucubitaceae and has high production and economic value. Pumpkin is an annual trailing plant with flexible succulent stem with trifoliate leaves (Caili et al. 2006; Matsui et al. 1998). The most important part of the pumpkin is its low-fat and protein-rich seeds and followed by its fruits. Pumpkin seeds are a high energy source of the ferum and beta carotene which increasingly become a popular snack. Pumpkin seeds are consumed either raw or roasted and used as an ingredient of bread, cereals, salads and cakes (Xanthopoulou et al. 2009).

Pumpkin is primarily grown for human consumption as a vegetable crop and increasing demand resulting in increasing number of by-products of pumpkin processing industry which is cause environment hazard. Pumpkin peels and hull are the most common by-products of pumpkin processing industry. There are plenty of studies done by using pumpkin by product and credited with antibacterial, antiproliferative and antioxidant.

Pumpkin peels mainly composed of cellulose as well as small amount of flavonoids, saponins, tannins and alkaloids (Chonoko and Rufai 2011; Nyam et al. 2013). Generally, pumpkin peels showed greater phenolic amount than seeds which due to presence of tocopherols and beta sitosterol (Saavedra et al. 2015; Li et al. 2016a, b). Asif et al. 2017 showed that the pumpkin peel exhibited good antibacterial activities against four bacterial strains *E. coli*, *P. multocida*, *S.aureus* and *B. subtilis* by stop the growth (around 35%) and division of pathogenic bacteria. They proceed by proving pumpkin peel indeed possessed antiproliferative activity by tested against Madin-Darby bovine kidney cancer cell line. Pumpkin peel extract managed to show growth inhibition ranged 5% to 35% of viable cancer cells. Their result showed methanol extract of pumpkin peel exhibited an inhibitory effect on cancer cell line.

Pumpkin seed hull has plenty phenolic compound such as p-hydroxybenzoic which showed higher value of antioxidant activity and potentially a good sources of antioxidant compounds with health benefits (Saavedra et al. 2015). The study by Mala and Kurian 2016 reported the antioxidant potential of processing wastes from pumpkins. The pumpkin peel methanol extract exhibit inhibition of 2,2-diphenyl-1-picrylhydrazyl activity by 80% at higher dose. They concluded that pumpkin peel which has a good source of minerals like phosphorus, iron and dietary fibre exhibit antioxidant activity (Mala and Kurian 2016).

In conclusion, pumpkin by products such as peel, seed and seed hull are widely available as source of nutrients such as saponins, flavonoids, alkalis and tannins. This phytochemicals are useful for antioxidant, anti-inflammatory, antibacterial and antifungal.

9.3.6 *Corn/Maize*

Corn or maize (*Zea mays L.)* is one of the leading crop in terms of worldwide production after wheat and rice. Corn originated in Mesoamerica and usually used in starch production as well as oil producing industry. In terms of food, corn mainly consumed on the cob, food packages containing dry-milled fractions or as a starch as well as dry flour. Corn contains significant amounts of bioactive compounds in different parts of maize plant, providing desirable health benefits beyond its role as a major source of food. The health benefits of corn are further enhanced with presence of phenolic compounds such as vannilic acid, syringic acid, courmaric acid, ferulic acid and caffeic acid (Siyuan et al. 2018; Veljković et al. 2018; Serna-Saldivar and Carrillo 2019).

Since the demand on corn and its industry derivative products always high, this phenomena caused a serious environmental issue such as industrial corn waste management. Last few years, corn waste products such as corn tassel and corncob become subject of interest from scientist around the world. Corn tassel is a by-product from hybrid corn seed production and packed with phenolic compounds (Duangpapeng et al. 2018). Previous studies by Mohsen and Ammar 2009 reported that corn tassel has antioxidant capacity because the presence of total phenols extracted by methanol and water. They have reported that corn tassel inhibits 2,2-diphenyl-1-picrylhydrazyl scavenging activity at 85%.

Another corn waste product, corncob is account half of the waste production and considered as important agriculture by-product. Corncob is the central core of an ear of corn and contains significant number of phenolic compounds. It has proven to exhibit good antioxidant activity as reported by Hernández et al. 2018. They concluded that from the extracts of phenolic antioxidants from red corncob showed higher radical scavenging capacity using the 2,2′-azino-bis (3-ethylbenzo thiazoline-6-sulfonic acid technique (123.73 ± 6.42 milligrams of trolox equivalents) compared to the 2,2-diphenyl-1-picrylhydrazyl test (30.03 ± 4.19 milligrams of trolox equivalents).

This results were supported by recent study from Vazquez-Olivo et al. 2019 which reported that corncob has adequate total phenolic contents (219.67–1420.94 milligrams of gallic acid equivalent) and showed better antioxidant activity than other corn by-products.

In conclusion, corn or maize by products corn tassel and corncob are useful for biological activities such as antioxidant activities.

9.3.7 *Paddy*

In many Asian countries, Rice (*Oryza sativa*) is a major agricultural and staple food commodity for half of humanity (Henderson et al. 2012). Traditionally, rice is consumed in polished form and genus Oryza in rice has two cultivated species, Oryza sativa L. and Oryza glaberrima (Huang and Ng 2011; Fasahat et al. 2012). Like other major crops, rice undergoes losses in term of quantitative where presence of paddy waste during harvesting and qualitative during rice milling. This loss produces abundance of rice by-products that can be used in manufacturing, medicinal, cosmetic and nutritional products using modern technologies (Hasheminya and Dehghannya 2013).

Paddy by-products has potential based on chemo preventive studies done against different types of cancer but this study focused on the chemoprevention potential of paddy waste such as paddy husk and straw. Paddy husk is the outermost part of paddy grain which is used for production of livestock feed, construction fillers, co-filter for juice production and various industrial composites. The ash obtained from paddy husk is an effective alternative for cement consumed at concrete formulation due to inexpensiveness, ease of availability and proper technical properties (Hasheminya and Dehghannya 2013). The ash which contains biosilica, has high potential in food industry and medical appliances (Athinarayanan et al. 2015).

It is low in toxicity and recently, Chen et al. 2017 have used mesoporous bioactive glass manufactured from rice husk ash as a drug delivery vehicle for camptothecin (water insoluble anticancer drug). Rice husk ash has managed to increase the solubility of camptothecin which subsequently increased the cytotoxicity of camptothecin toward the cancer cells (Chen et al. 2017). Paddy husks were pyrolyzed to produce bio-oil which is like other bio-oils in chemical composition and basic fuel properties (Qiang et al. 2008).

Paddy husk being a potential source of energy, also been used in brewing industry, as a building material, fertilizer and substrate, fireworks and as pet food fiber (Li et al. 2011). Previous research done by Asamarai et al. 1996 and Huang and Ng 2011 reported paddy husk to have traces of Vitamin E isomers such as tocotrienols, tocopherols and oryzanols (Huang and Ng 2011; Asamarai et al. 1996). Apart from Vitamin E isomers, earlier reports show that heated paddy husk can produce lignin-derived components such as ferulic acid and caffeic acid which are protective against photooxidative damage (Saija et al. 1999; Mochidzuki et al. 2001; Garrote et al. 2007). Paddy husk has been used in the antioxidant study by Jeon et al. 2006 which reported that phenolic compounds in the methanolic extract of paddy husk inhibited high hydrogen peroxide-induced damage which revealed by deoxyribonucleic acid strand breaking decreasing from 38% to 22% in human lymphocytes (Jeon et al. 2006).

In the tropical world, ruminants depend on natural pastures to graze year-round or animals are fed with cut grass and crop residues. Most of these regions are experiencing seasonal dry periods where pasture supply decreases and the quality of pasture decreases as digestible energy and nitrogen content are reduced. As paddy straw is abundant from cultivation in the area, farmers supply their livestock and packaging industry with paddy straw as the main source of livelihood (Sarnklong et al. 2010).

Karimian et al. 2014 documented previous work on the existence of phenolic compounds in rice straw, such as gallic acid and caffeic acid, as well as fundamental flavonoid compounds such as epiginin and rutin (Karimian et al. 2014). Gallic acid, a plant phenol used by Liu et al. 2012 to treat human pancreatic carcinoma (MiaPaCa-2) cell line and it managed to increase the rate of cell apoptosis from 12.5 ± 0.72 to 78.3 ± 2.48% via mitochondrial-mediated pathways (Liu et al. 2012). Caffeic acid has been shown to inhibit oxidative deoxyribonucleic acid damage and apoptotic morphological changes in human fibrosarcoma cells, and has demonstrated anti-proliferative effects (Zhu et al. 2013; Chen et al. 2013).

In conclusion, paddy waste such as husk and straw are consisting of cellulose, lignin and silica which are useful for anticancer and antioxidant activities.

9.3.8 Asparagus

Asparagus (*Asparagus officinalis L.)* is an herbaceous vegetable originated from the eastern Mediterranean and Asia Minor for more than 2000 years. The edible part of the asparagus is about half of the full length of the stem and containing the remaining part always discarded as by-product (Wang et al. 2013). Edible part of the asparagus contains numerous vitamins, proteins, fat and mineral in addition to numerous bioactive phytochemicals such as flavonoids, phenolic and carotenoids (Fuentes-Alventosa et al. 2013).

Although industrial processing only needs the edible part of the asparagus, previous studies proved that variety of fibres and phytocehmicals compounds are mainly located in the lower portion of the plants which will be discarded during processing (Rodríguez et al. 2005; Al-Snafi 2015; Sun et al. 2005). The potential of asparagus by product as food supplement due to physiological properties that has been reported previously. In 2015, Elsaid et al. 2015 discovered the antioxidant capacity in aqueous extracts of asparagus where investigated tissue has showed an increase in total antioxidant capacity from 254 ± 17.2 enzyme unit per gram tissue to 304.6 ± 21.9 enzyme unit per gram tissue (Elsaid et al. 2015). In 2009, Visavadiya and Narasimhacharya reported the hypocholesterolemic potential of Asparagus roots. They concluded that presence of phytochemicals in asparagus root responsible for elevated bile production and cholesterol elimination in hypercholesterolemic conditions (Visavadiya and Narasimhacharya 2009).

Another study by Fuentes-Alventosa et al. 2009 reported that fibre from asparagus by-products can become a dietary fibre substitution source since it has oil and water holding capacities as well good glucose retardation index (Fuentes-Alventosa et al. 2009). Presence of dietary fibre in asparagus by-product leads to exhibition of hypolipidemia effect as much as 20% compared to control hyperlipidaemic mic as reported by Zhu et al. 2010. They concluded that oral administration of the aqueous extract of asparagus by-product had a potent hypolipidemic effect in mice fed a high-fat diet.

Meanwhile, Wang et al. 2013 identified that saponins from old stems of asparagus exerted potential inhibitory activity on tumour growth and metastasis. Saponins from stems of asparagus inhibits the motility of tumour cells by 14.54% after

48 hours of incubation through inhibition of cell migration and invasion (Wang et al. 2013).

In conclusion, asparagus by products such as roots and old stems are consisting of thiophene, thiazole, aldehyde, ketone vanillin, asparagusic acid and glucose which are useful for antioxidants, anti-inflammatory, antibacterial and antifungal activities.

9.3.9 Cocoa

Cocoa is an important material in chocolate processing and considered as lucrative agricultural commodity. Cocoa is originated from cacao tree (*Theobroma cacao L.*) beans, native to tropical regions of the Americas. The cacao is a small tree and its fruits are grown adjacent to the thicker branches (Rusconi and Conti 2010; Bernaert et al. 2012). Cocoa-rich chocolate has been popular for its good taste but recently become a source of interest for its good health effects (Corti et al. 2009). In the last century, the market for cocoa and chocolate has grown exponentially and the chocolate manufacturing sector is projected to increase its production. Cocoa (chocolate) has been able to shed its notorious tag in recent years, where considerable evidence supports the health benefits of cocoa and its position as a potentially useful foodstuff (Rusconi and Conti 2010; Bernaert et al. 2012).

As the market for chocolates grows, the amount of by-product or waste also increases. Cocoa-based goods are produced worldwide from cocoa crops and discarded with a negative effect on the climate (Oddoye et al. 2013; Martínez et al. 2012). Cocoa powder, cocoa shell and cocoa leaves are waste of cocoa derived from frequent pruning of cacao tree to increase the production and cocoa industry. Cocoa by products are rich with polyphenols such as anthocyanins, catechins and proanthocyanidins (Miller et al. 2006; Payne et al. 2010) and other minerals such as theobromine, phosphorus and calcium, vitamins such as Vitamin D, amino acids, as well as dietary fibers. Polyphenols typically have antioxidant properties, reducing the development of reactive oxygen species and protecting cells from oxidative stress by inhibiting the activation of caspase-3 (Rodríguez-Ramiro et al. 2011; Handojo et al. 2019; Hernández-Hernández et al. 2019).

In recent years, cocoa waste has become a subject of interest. Previous study by Baba et al. 2007 examines the effects on the plasma lipid profile of average cholesterol and moderately hypercholesterolemic humans after long-term cocoa powder consumption. They found improved concentrations of high-density lipoprotein cholesterol by 24% that induced lower density lipoprotein oxidation suppression by 9% and concluded that the polyphenolic substances obtained from cocoa powder may increase high density lipoprotein cholesterol elevation (Baba et al. 2007).

Dhingra et al. 2012 reviewed the presence of dietary fibre in cocoa waste. They mentioned that the cocoa bean shell can be used as a source of dietary fibre since it has mixture of lignin, polysaccharides, and cellulose. This cocoa fibres have antioxidant and physicochemical properties that are ideal for use in the preparation of low-calorie, high-fibre foods such as chocolate cookies and chocolate cakes (Dhingra et al. 2012).

The prospect of cocoa waste having antioxidant properties were supported by few studies. Osman et al. 2004 used cocoa shoot and leaves which were processed according to green tea processing procedures and found similar type of antioxidants such as epigallocatechin, epicatechin, gallic acid, epigallocatechin gallate and epicatechin gallate, similar to green tea (Osman et al. 2004).

An earlier research by Altin et al. 2018 comparing liposomal fungi and powder systems with the supply of cocoa hull waste phenolics coated with iron liposomes (drinking yogurt). Their findings showed that the stability of phenolic compounds of cocoa hull waste in liposomal powders was better and that this analysis could be a guide for successful food production and nutraceutical field studies (Altin et al. 2018).

In conclusion, cocoa by products such as bean shell, hull, shoot, and leaves have variety of phytochemicals such as polyphenols, carbohydrates, alkaloids, tanning, organic acids as well as vitamins and minerals are useful to increase high density lipoprotein and for antioxidant activities.

9.3.10 Tea and Coffee

Tea, the second most popular beverage in the world, has been consumed and used as a possible health-promoting natural medicine for thousands of years (Kumar et al. 2011; Jobu et al. 2013). Tea is produced from processed dried leaves and buds of the *Camellia sinensis* plant, which was first grown in China (Forrest 1985; Mukhtar and Ahmad 2000). Black (fermented), green (undifferentiated) and oolong (semifermented) are the three primary forms of tea dependent on the processing of cut leaves (Lin et al. 2003). A spectrum of phytochemicals such as catechins, epigallocotchin gallate and gallic acid are found in tea (Lin et al. 1998; Stangl et al. 2006; Fei et al. 2014; Zhang et al. 2013).

Black tea are the main varieties of tea produced and consumed worldwide. All types of teas consist of different types of phytochemicals due to differences in manufacturing. Since tea is one of the world's most sought-after primary products, a lot of waste or by-products such as tea leaves are produced by its processing. Tea leaves produce a lot of waste from the tea processing sector, and several studies have shown the potential of tea leaves.

Farhoosh et al. 2007 tested the antioxidant activity of various extracts of old tea leaves and black tea wastes in comparison with that of green tea leaves. Hot water extracts of old tea leaves and black tea wastes showed the same statistically significant antioxidant activities as found in hot water extracts of green tea leaves. This means both old tea leaves and black tea wastes which normally considered as an agricultural wastes, can be used as potent natural antioxidative sources (Farhoosh et al. 2007).

This claim supported by work done by Ustundag et al. 2016. They managed to highlight black tea waste not only as source of antioxidant but also as an antimicrobial phenolic compounds. They managed to prove that black tea waste exhibited antioxidant activities which were comparable to those of black tea extracts. Black tea waste too showed positive reaction in antimicrobial activity against S. aureus (Üstündağ et al. 2016).

After water and tea, coffee is the third most consumed beverage in the world (Villanueva et al. 2006). It is famous for the acidity, aroma and taste. The coffee plant (undomesticated) is first cultivated in Africa – specifically in Kaffa (Ethiopian region) before spread to rest of Middle East, South India, Persia and Europe by sixteenth century. Coffee is processed from seed from coffee berries (genus Coffea) roasted at various temperatures to the desired flavour before ground and serve as a brewed beverage. The two most common species of coffee berries are coffee Arabica and coffee Rustica and abundant with polyphenols like caffeic acid and chlorogenic acids (Padmapriya et al. 2013; Patay et al. 2016; Clifford 1999).

Since coffee is one of the most sought-after primary products in the world, many waste or by-products such as bean processing (coffee husks and pulp) and coffee fruit are produced by its production (coffee cherry). Carbohydrates, proteins, lipids and organic functional compounds such as caffeine, chlorogenic acid and tannins are made from coffee by-products (Das and Venkatachalapathy 2016; Gouvea et al. 2009; Bondesson 2015; Cruz 2014).

Coffee pulp, comprises the exocarp (outerskin) as well as the mesocarp (fleshy portion, is the main by-product of the industry constitutes almost 40% of the wet weight of the coffee berry (Cruz 2014; Roussos et al. 1998). Coffee pulp produced carotenoids exhibited antioxidant and antimicrobial activities against pathogenic bacteria such as *Escherichia coli* and *Staphylococcus aureus* as well as toxigenic fungi (Moreira et al. 2018).

Other solid coffee waste such as spent coffee grounds became focus of interest by Silva et al. 2015. Spend coffee grounds showed antimicrobial activity by showed minimal inhibitory concentration of one milligram per millilitre on *Staphylococcus aureus* and *Escherichia coli* growth (Silva et al. 2015).

In conclusion, tea leaves and coffee by products such as coffee pulp and spend coffee grounds are full of nutritious phytochemicals such as gallic acid and polyphenol-rich chlorogenic acid can be useful for its antioxidant and antimicrobial activities.

9.3.11 Buckwheat

Buckwheat (*Fagopyrum esculentum Möench*), typically grown for its black triangular seeds, is a traditional crop originated from Asia and Eastern Europe. It is not a true cereal and belongs to the Polygonaceae family (Sun and Ho 2005; Wijngaard and Arendt 2006; Christa and Soral-Śmietana 2008). Usually, buckwheat grown as a companion crop and has great capability to grow well in harsh climates and soil condition (Mazza and Oomah 2005). Among a variety of buckwheat species, the most cultivated species include *Fagopyrum esculentum* known as common buckwheat and tartary buckwheat (*Fagopyrum tataricum*) (Zhu 2016; Krkošková and Mrázová 2005; Mazza and Oomah 2005).

Generally, common buckwheat is grown all over the world except few places where tartary buckwheat were grown such as Sichuan, China and some parts in India and Nepal. Common buckwheat divided into two groups; the first group has tall, late maturing and photoperiod sensitive varieties found in India and Nepal while the second group is small, early maturing and rather insensitive to photoperiod which grown in Sichuan, China. Meanwhile, tartary buckwheat produce greenish seeds which is bitter in taste and has high number of flavonoids in the kernels. Recent interest on production of buckwheat due to demands of health food leads to accumulation of by-product; buckwheat hull (Li et al. 2016a, 2016b).

Buckwheat hull consists of numerous phytochemicals such as flavonoids (rutin, quercetin, orientin, vitexin, isovitexin and isoorientin) and phenolic compounds such as caffeic acid, p-coumaric acid, ferulic acid and gallic acid (Terpinc et al. 2016; Liu et al. 2019). Previous antioxidant study done by Mukoda et al. 2001 using buckwheat hull extract in an animal experiment and vitro studies. Buckwheat hull extract scavenged super oxide anion by reducing about 80% of nitroblue tetrazolium generated from xanthine oxidase at 45 mg phenolic compound per millilitre and strongly inhibited autoxidation of linoleic acid. They also found positive antioxidant reactions in animal experiment where Deutschland, Denken, and Yoken (ddY) mice were fed a standard diet supplemented with 0.75% buckwheat hull extract. In blood, liver and brain, thiobarbituric acid reactive substances and fluorescent substance concentration were significantly decreased compared with those of non-treated mice (Mukoda et al. 2001).

The claim of antioxidant properties of buckwheat hull supported by another study by Kabir et al. 2015 reported that high level of antioxidants detected in buckwheat hull and it has exhibited scavenging efficiency with half maximal effective concentration at 37.6 ± 6.7 microgram per millilitre by using with 2,2-diphenyl-1-picrylhydrazyl free radicals system (Kabir et al. 2015). Apart from that, Li et al. 2016a, b demonstrated that buckwheat hull has antiproliferative capabilities where free phenolic fraction of buckwheat hull inhibited the growth of human hepatoma (HepG2) cell line with an approximate inhibition rate of 61%. (Li et al. 2016a, b).

In conclusion, buckwheat hull is useful for antioxidant and antiproliferative activities since it has numerous phytochemicals such as flavonoids (rutin, quercetin, orientin, vitexin, isovitexin and isoorientin) and phenolic compounds such as caffeic acid, p-coumaric acid, ferulic acid and gallic acid.

9.4 By Product and Waste of Nuts

Nuts are healthy snack option due to the greater content of minerals, vitamins, unsaturated fat, protein and fibre. Nuts skins are especially rich in polyphenols and fibre, but the skin is often regarded as waste materials. Many studies investigating association between nut consumption and risk of cardiovascular diseases, cancer, type 2 diabetes mellitus and even mortality have reported positive findings (de Souza et al. 2017). By-products of nuts such as its husk, leaves, roots, skin or stem have been considered as environmental pollutants. However, these by-products have high levels of phenolic compounds which contributed to its excellent antioxidant property.

9.4.1 Almond

Almond is one of the most commonly consumed tree nuts worldwide. It is either consumed whole, peeled, roasted, flour, baked goods or as non-dairy beverages. Almond tree belongs to the family of *Rosaceae* and share genus *Prunus* similar to peach, plum, apricot and cherry. Almond can be found in the shell, with or without peel (Mushtaq et al. 2015).

Almond skin is removed via hot water blanching and is regarded as waste product. During blanching process, more than 4% of almond skin waste will be produced and is often used in agricultural settings for feeding livestock and compost. However, almond skin has potential health benefits to human health due to its high fibre and polyphenol content which can be utilized as functional food, food additives and nutraceuticals (Varzakas et al. 2016).

High concentrations of polyphenols are also found as phytoalexins in seed coats and skin which prevent oxidation of seed kernel and microbial activities until germination. Currently, with the advancement of technology, the almond blanching process has used more steam and less water, thus reducing the loss of polyphenols (Chen et al. 2019).

Almond has 575 kilocalories, 21.22 gram protein, 12.20 gram of dietary fibre, 264 milligram of calcium, and 3.720 gram of iron per 100 gram and almost 50% fat. The predominant fat in almond is monounsaturated fatty acids (62%) and has the lowest saturated fat content, almost 3.7 gram per 100 g almonds which makes almond a heart-healthy food. Almond can improve endothelial function, lower cholesterol, reduce risk of sudden cardiac death. The high fibre content of almond contributed to the structural integrity of their cell wall is associated with proper blood glucose control, enhancing feeling of satiety, improving gut heath as natural prebiotic, and thus slower rate of digestion and absorption (Bolling 2017).

An 8-week randomized, controlled, parallel-arm trial involving 71 college freshmen who were randomized into the intervention group receiving 57 gram per day whole, dry roasted almond with skin and control group which consumed five sheets of graham crackers (contributed the same calorie as 57 gram almond) demonstrated declining levels of pathogenic bacteria, *Bacteroides fragilis* by 48%. High polyphenol content in almond improves gut microbiota and protects gut against gastrointestinal inflammation. In the same study, improved glucose tolerance and postprandial insulin sensitivity were also observed in the group receiving almond (Dhillon et al. 2019).

In addition, the health benefit of almond is closely associated with its high content of polyphenol, almost 312 milligram per hundred-gram almond which contribute to its colour, shelf-life, enhanced anti-microbial and anti-oxidative properties (Bolling 2017). Almond skin is removed from the kernel via hot water blanching and comprise about 4% of the total almond weight. Almond polyphenols are mostly concentrated in the almond skin and the most represented components are hydroxybenzoic acid, aldehydes, hydroxycinnaminc acids, catechin, epicatechin, kaempferol, isorhamnetin, 3-O-rutinoside or 3-O-glucoside. High polyphenol content in almond skin has various health benefits such as inhibiting low density lipoprotein oxidation and deoxyribonucleic acid damage in vitro, 2,2,-diphenyl-1-picryhydrazyl radical scavenging activity, as well as antimicrobial and antiviral activities (Musarra-Pizzo et al. 2019).

Almond skin is regarded as a potential functional food due to its high antioxidant polyphenol, prebiotic fibres and probiotic index (Chen et al. 2019). It can be used as additives in food industries to lower lipid peroxidation as well as functional ingredient in dietary supplements (Garrido et al. 2008).

Almond skins have been proven to have prebiotic effect by contributing to the growth of beneficial gut microbiota. Almond skin consists of 50% dietary fibre as compared to only 12% in whole almond. In a randomized controlled trial involving three groups (commercial fructooligosaccharides group, almond skin powder group, and whole almond group) of healthy adults demonstrated significant increase in the population of faecal *Bifidobacterium* spp. and *Lactobacillus* spp. in the groups receiving almond and almond skin, while the growth of pathogenic bacteria, *Clostridum perfringens* was inhibited (Liu et al. 2014). Furthermore, the polyphenols in almond skin have anti-microbial properties against a variety of food-borne pathogens such as *Staphylococcus aureus*, *Listeria monocytogenes*, and *Salmonella enterica* (Mandalari et al. 2010).

The heaviest by-product from the almond processing is the almond hull which contributed 35 to 62% of the total fresh weight of almond. Almond hull which is often considered as having low economic value and waste product, can be used to as medicine to lower cholesterol levels (Esfahlan et al. 2010). Study by Meshkini 2016 demonstrated that almond hull contains potent antioxidant polyphenols such as chlorogenic acid, cryptochlorogenic acid and neochlorogenic acid. Chlorogenic acid is the most abundant phenolic acid present in the almond hull which has high antioxidant property (Kahlaoui et al. 2019). Almond hull powder administered to male Wistar rats fed with high cholesterol diet showed lower cholesterol levels. The almond hull powder exhibited excellent antioxidant capacity by improving the levels of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. In the same study, rats being fed with almond hull powder showed decrease in plasma low density lipoprotein due to the high fibre content in the almond hull (Safarian et al. 2016). These findings provide insight to the production of medicines or supplements using almond hull for treating various oxidative associated diseases.

In conclusion, almond by products such as skin and hull have numerous types of polyphenols which can be useful for antioxidant activities, exhibit anti-microbial and anti-viral effects.

9.4.2 Walnuts

Walnut is a commonly eaten tree nut which is widely cultivated for its kernel. Its shell and husk are often discarded during harvesting and processing. Walnut belongs to the Juglandaceae family which has about 60 species distributed in the Northern Hemisphere. Walnut is the seed of the Juglans plant from the *Juglandaceae* family. Walnut is a healthy snack considering the high levels of unsaturated fatty acid, protein, tocotrienols, sterols, folate, melatonin, tannins, polyphenols and dietary fibre (Tapia et al. 2013). Studies done on various types of nuts demonstrated that walnut has the highest antioxidant compounds particularly tocopherols and polyphenols. The high antioxidant activity of walnut is associated with reduced risk of cancer, cardiovascular diseases, diabetes, and degenerative diseases. Usually the edible portion of the walnut is its kernel. The by-products of walnuts such as the green husk, hard shell (endocarp), dividing membrane of the kernel (pellicle), flower, root, trunk (bark and wood), branch and leaf have medicinal properties to human health. The walnut leaves can be used to treat minor inflammatory skin disorders (Tsasi et al. 2016).

The walnut husk which is the outer green thick layer has ascorbic acid, alpha tocopherol, flavonoid such as catechin, epicatechin, myricetin, quercetin, sudachitin, and cirsilineol. During walnut fruit processing, the walnut husk will be burned to be used as fuel and this contributed to environmental pollution (Jahanban-Esfahlan et al. 2019). Walnut husk is a cheap source of phytochemical which is used as food additives especially for meat. Sausages added with walnut husk had less colour deterioration during storage, reduced springiness and chewiness, better smell as well as reduced risk of microorganism growth (Salejda et al. 2016). Moreover, walnut green husk is a natural antioxidant which can replace synthetic antioxidant especially for protecting oils and food against oxidation. Besides possessing antioxidant properties, the walnut husk is an effective inhibitor of gram positive bacteria such as *B.cereus, B.subtilis, S. epidermis* and *S.aureus* (Fernández-Agulló et al. 2013).

On the other hand, the walnut shell which surrounds the kernel has outstanding durability, elastic and is environmentally friendly. The shell consists of cellulose (17.74%), hemicellulose (36.06%) and lignin (36.90%) (Altun and Pehlivan 2012). In industrial setting, the walnut shell is used as a scrub in soap and cosmetics, as abrasive for polishing jewellery, gun casings, and metal materials, used as filtration medium in hydration systems, extender for adhesives materials, for development of commercially biodegradable packaging films as well as medium for crude oil separation from water (Jahanban-Esfahlan et al. 2020).

In addition, the walnut leaves have medicinal properties especially in treating diabetes mellitus due to the high content of polyphenol such asgallic acid and caffeoylquinic acid. A two-arm randomized controlled trial conducted among 62 diabetic patients found that group consuming walnut leaves extract tablet twice per day had improvement in glycemia especially in lowering fasting blood glucose, glycated haemoglobin, and increased insulin level. The mechanism underlying the glucose lowering property of the walnut leaf are regenerating beta cells, restore insulin sensitivity, interference with glucose absorption in the small intestine as well as improving the peripheral tissue use of glucose by activating insulin dependent glucose transporter (Del Rio et al. 2013). Besides that, walnut leaves are used for the treatment of hypoglycaemia, sedative, antifungal, haemorrhoid, antidiarrheal, hypotension, anthelmintics and anti-scrofulous (Jahanban-Esfahlan et al. 2019).

Walnut seed is covered by skin which serves to protect the walnut kernel from oxidation and microbial contamination. Walnut skin has 20-fold higher content of phenol which has antioxidant and antiatherogenic properties as compared to walnut kernel. The three highest phenolic compound in the walnut skin are juglone, syringic and ellagic acid. Removal of the skin will reduce the antioxidant activity by 90% (Arcan and Yemenicioğlu 2009).

Meanwhile, studies have proven that the walnut tree shoot, bark and root have beneficial phenolic compound used for various purposes. For example, the walnut bark can be dried and used as tooth cleaner and the decoction of walnut leaves and bark has anticancer, anti-inflammatory, laxative, diuretic, antifungal, antibacterial and blood purifying properties.

Walnut bark has therapeutically active compounds such as beta sitosterol, ascorbic acid, juglone, folic acid, gallic acid, regiolone, and quercetin-3-alpha-L-arabinoside (Zakavi et al. 2013; Jahanban-Esfahlan 2019). Besides that, walnut root is also a potent antifungal and antibacterial agent due to the presence of phytochemicals such as alkanoids, phenols, flavonoids, steroids, terpenoids, tannins and saponins (Raja et al. 2017).

Every part of walnut has excellent benefit to human health considering the presence of high phenolic compounds. Hence, the by-product of walnut which is often regarded as agricultural waste can be utilized by the pharmaceutical or nutraceutical industries for producing health products.

In conclusion, walnuts by products such as green husk, hard shell (endocarp), dividing membrane of the kernel (pellicle), flower, root, trunk (bark and wood), branch and leaf are consists of variety of phytochemicals such as folate, melatonin, tannins and polyphenols which are useful for antioxidant activities, decreased risk of cancer, cardiovascular disease and diabetes intervention treatments.

9.4.3 Pistachio

Pistachio is an ancient nut native to the Middle East which is regarded as a royal food. In early 1930s, pistachio trees plantation has started in California and by 1970s, its cultivation expanded. As a member of the *Anacardiaceae* family, pistachios have high levels of potassium, alpha-tocopherol, vitamin K, phytosterol, carotenoids and antioxidant polyphenols. The lipid in pistachio is predominantly monounsaturated fatty acid which is heart healthy. Analysis have proven that pistachio skin has higher levels of phenolic compound as compared to the kernel, but often the skin is removed and become waste or environmental pollutants (Grace et al. 2016). High-performance liquid chromatography analysis have shown that pistachio skin has 10 times higher phenols as compared to the seed, with cyanidin 3-*O*-galactoside and cyanidin 3-*O*-glucoside being the most abundant phenolic compound. Epicatechin, aglycones quercetin, naringenin, luteolin and kaempferol were also among the compounds identified in the pistachio skin (Martorana et al. 2013).

Analysis from Tomaino et al. 2010 demonstrated that total flavonoids in pistachio skin is 70.27 ± 5.42 milligram while in seed is only 0.46 ± 0.03 milligram. The same study also found that proanthocyanidins which has free radical scavenging activities, is extensively higher in pistachio skin (27.56 ± 0.18 milligram per gram of fresh weight) as compared to the seed (1.03 ± 0.06 milligram per gram of fresh weight). Besides skin and nut, pistachio green hull, which is often recognized as waste product is also an excellent source of natural phenolic and antioxidant compounds. Study by Rajaei et al. 2010 demonstrated that the aqueous extract of the pistachio green hull has potential anti-microbial activity by inhibiting Gram positive bacteria such as *Bacillus cereus* and *Staphylococcus aureus*, as well as possessing good antioxidant and anti-mutagenic activity. Considering its potential health benefits, the pistachio green hull has gained attention from the food industry to be used as food stabilizer for increasing shelf life of processed food. Longer storage time of the processed food such as chicken burger patty will affect its flavour and nutritional quality due to exposure to lipid oxidation and microbial growth (Bali et al. 2011).

Hence, antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene have been used as food preservative to prevent fat from becoming rancid and retaining the aroma, smell colour and taste. However, the long-term effect of synthetic food antioxidant on human health have been great concern among nutritionist and toxicologist (Bali et al. 2011). Use of pistachio hull as natural food antioxidant has been proven to increase the antioxidant activity of the burger, decreased lipid rancidity, better cooking time and improved quality of burger even after storage of 10 days. In the same study, the chicken burger added with pistachio hull extract had lower thiobarbituric acid reactive substances value as compared to the control burger due to the enhanced free radical scavenging effect of the pistachio hull extract which lowered the lipid peroxidation indicator value (Al-Juhaimi et al. 2017).

In addition, pistachio hull extract has been studied for its cytotoxic and apoptotic potential towards cancer cells. Anticancer drugs are tumour specific entities which induced apoptosis in targeted cancer cells. In a study investigating the apoptotic potential of pistachio hull extract using human hepatoma HepG2 cell line, demonstrated that the extract had the ability to reduce cell viability, induce apoptosis and interfere with gene expression related to apoptosis (Fathalizadeh et al. 2015). Pharmaceutical industries producing anti-cancer drugs may further explore the pharmacological properties of pistachio hull towards different types of cancer cells. The polyphenol-rich, hull acts as natural antioxidant, anti-inflammatory agent as well inducer of apoptosis.

In conclusion, pistachio by products such as skin and hull are full of numerous phytochemicals such as phenolic epicatechin, aglycones quercetin, naringenin, luteolin and kaempferol which are useful for antioxidant and anti-inflammatory activities.

9.4.4 Cashew Nut

Cashew nut from the family *Anacaedium occidentale* L, is one of the widely consumed nuts worldwide. Being the largest producer and exporter of cashew nut, India managed to conquer approximately 50% of the world export of cashew (Prakash et al. 2018). Cashew nut is the preferred nut to be investigated in many randomized controlled trials for its health benefits. A two-arm randomized controlled trials involving 300 adults with type 2 diabetes mellitus demonstrated lower systolic blood pressure and higher plasma high density lipoprotein cholesterol, in the intervention group consuming 30 gram cashew nut daily for 12 weeks (Mohan et al. 2018).

Similarly, another study involving 8 weeks consumption of cashew nut revealed improved baroreflex sensitivity, a key component for maintaining blood pressure (Schutte et al. 2006). Cashew consists of an outer shell (epicarp), a snugly fitted inner shell (endocarp) and an edible portion (kernel). Cashew nut kernel is widely exported while other components are discarded as agricultural waste. Cashew nutshell, which is one of the most versatile food waste, is a potent raw material for fuel production and chemical products for replacing fossil-based petroleum resources to be used in the manufacturing of chemicals, materials, polymers, energy and fuel (Mgaya et al. 2019).

Another by-product from the cashew nutshell is the cashew nut shell liquid. Cashew nut shell liquid is obtained via extraction and is rich in naturally occurring polyphenols. Cashew nut shell liquid mainly consist of anacardic acid, cardanol and cardol. Cardanol from the cashew nut shell liquid is used as synthon in industries manufacturing polymers. Furthermore, cashew nut shell liquid is used as folk medicine due to its anti-inflammatory, antidiarrheal, anti-asthmatic, and depurative properties as well as for wounds and wart treatment (de Souza et al. 2018). Besides that, purified cashew nut shell liquid is able to stimulate migration of fibroblast cells for wound healing and promoting apoptotic cell death in cervix adenocarcinoma HeLa cells (Ashraf and Rathinasamy 2018).

In addition, every part of the cashew tree has various bioactive compounds which can be useful for drug discovery in the nutraceutical and medicinal field (Salehi et al. 2020). Cashew bark and leaves are high in tannins, a type of polyphenol possessing antioxidative and antimicrobial activities. Cashew leaves have also been used as traditional remedy for treating rheumatic disease and hypertension. Major flavonoid present in the cashew leaves are kaempferol 3-O-glucoside, kaempferol 3-O-arabinofuranoside, quercetin 3-O-glucoide and quercetin 3-O-galactoside (Tan and Chan 2014). Tan and Chan 2014 have demonstrated that blanched and microwave-treated cashew leaves had greater antibacterial activity against Gram-positive bacteria such as *M.luteus* and *S.cohnii* as well as Gram-negative bacteria such as *E.coli* and *P.aeruginosa.* In addition, cashew shoot is a natural antioxidant due to possessing excellent superoxide anion radical scavenging property (Razali et al. 2008). The pharmacological properties of the cashew tree are presented in Table 9.1 below.

9.4.5 Hazelnut

Hazelnut (Corylus spp.), is a widely grown nut in Turkey, European Union and United States. Hazelnut by-products produced during harvesting and processing are the green leafy cover, shell and skin (Xu et al. 2012). Disposal of these by-products causes severe environmental pollution. The most abundant by-product of hazelnut is the ligno-cellulose shell which is often used as a low-value heat source for mulching and furfural production in dye manufacturing as well as to produce methanol, hemicellulose sugars and reducing sugar (Yuan et al. 2018). Almost 50% of the total nut weight is contributed by its shell, while 2.5% of the weight is.

Hazelnut shell extract has excellent free-radical scavenging activities due to its high content of phenolic compounds such as catechin, epicatechin gallate, gallic

Table 9.1 Therapeutic use of each part of the cashew tree

Part of cashew plant	**Therapeutic use**
Bark	Anti-inflammatory effect for treating lower extremity pain, skin injury, diarrhoea, haemorrhoids, skin rashes, sores, toothache, sore gums, pellagra
Leaves	Anti-hypertensive, malaria, blisters, ulcers, wart, toothache, mouth ulcers, dysentery, eczema, bronchitis, cough, genital problem
Root	Diarrhoea, stomach pain, hypertension, malaria, cough
Apple	Scorpion or bee sting
Stalk	Teeth caries as toothpick

Modified from Salehi et al. (2020)

Future studies should be done to elucidate the potential health benefits of each part of the cashew trees which is often considered food waste acid, quercetin, protocatechuic acid, quercitrin and epicatechin. Findings from study by Esposito et al. 2017 revealed inhibitory effect of hazelnut shell extract on the growth of human cancer cell lines such as cellosaurus cell line (A375), skin malignant melanoma cells (SK-Mel-28) and cervix adenocarcinoma cells (HeLa). In addition, hazelnut skin is rich in dietary fiber and polyphenols which have antioxidative properties. Thus, hazelnut skin is widely known as `antioxidant dietary fibre`. Hazelnut especially its skin, has the highest content of condensed tannins (proanthocyanidins) as compared to walnut and almond. Tannins is 15 to 30 times more effective in scavenging peroxyl radicals as compared to simple phenolic and Trolox. Hence, hazelnut skin can be a good and cheap source of natural antioxidant (Alasalvar et al. 2009).

Roasted hazelnut skin has higher antioxidant effect as compared to the roasted hazelnut itself and thus the skin is widely used in food industries (Contini et al. 2012; Anil 2007). Addition of 5% hazelnut skin in bread dough produced satisfactory sensory results and improved the rheological properties of the bread (Anil 2007). Study by Bertolino et al. 2015 found that 55% of hazelnut skin is composed of dietary fibre which is mostly from the insoluble source. Besides that, the same study also revealed that yogurt fortified with hazelnut skin had higher concentration of microbial starter strain such as *S.thermophilus* and *Lactobacillus bulgaricus*.

Another study has added hazelnut skin in egg pasta and findings indicated that pasta fortified with hazelnut skin had higher fiber and polyphenol content. The pasta fortified with 5% hazelnut skin had mean of 70.1 g insoluble dietary fibre as compared to 45.7 g in the control pasta having no hazelnut skin. Moreover, the total phenolic content, radical scavenging capacity, Trolox equivalent antioxidant capacity and oxygen radical absorbance capacity values of the fortified pasta are significantly higher than the control pasta (Zeppa et al. 2015). Hazelnut skin has also been widely used in food industry producing processed meat such as chicken burger patty since processed meat are susceptible to lipid peroxidation and the skin may act as natural antioxidant. Chicken burger fortified with 2% and 3% of hazelnut skin had higher antioxidant capacity than the control burger (Longato et al. 2019).

Another hazelnut waste is its leaves which has good antimicrobial properties against bacteria responsible for human gastrointestinal and respiratory tract infection such as *B.cereus, B.subtilis, S.aureus, E.coli, K.Pneumoniae,* and *C.neoformans*. Moreover, low concentration of the leaf extract has excellent antioxidant activity (Oliveira et al. 2007). Alasalvar et al. 2006 have demonstrated that the green leafy cover of hazelnut had greater antioxidant and antiradical properties as compared to the hazelnut kernel itself. Significant differences have been observed between the kernel and hazelnut green leafy cover in the content of total phenolic, condensed tannins and total antioxidant activity. Green leafy cover had better 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity as compared to the hazelnut kernel (Alasalvar et al. 2006). Extracts from the hazelnut bark, shells and leaves can be used as anti-cancer medication since have compounds such as taxol and taxanes, having anti-mitotic efficiency on tumour cells (Gallego et al. 2017). Each part of hazelnut plant as highlighted in Fig. 9.2 has various therapeutic potential which can be utilized by industries for producing fortified food products or medications.

Fig. 9.2 Hazelnut kernel (Corylus avellana L.) and its green leafy cover possessing high antioxidant properties. (Modified from Alasalvar et al. 2006)

In conclusion, hazelnut wastes such as skin and leaves are full of variety of phenolic compounds such as catechin, epicatechin gallate, gallic acid, quercetin, protocatechuic acid, quercitrin and epicatechin which are good chemopreventive agents for antioxidant, anti-cancer and anti-microbial effect.

9.4.6 Peanut

Peanut (*Arachis hypogaea*) is a widely grown and consumed crop worldwide, especially for its seed and oil. Peanut shell, skin, leaves, and root have bioactive compounds which have antioxidant properties. Groundnut shells will often be discarded during processing. The shells are pollutants as they have very low biodegradable rate under natural condition (Zheng et al. 2013; Duc et al. 2019). Previously, groundnut shell has been used for feeding cattle, and production of pulp, feedstock for bioethanol, carbon nano-sheet, building material, enzymes, biodiesel, and hydrogen. Upendra et al. 2018 have reported the usefulness of groundnut shell for producing good quality paper using kraft's pulping method. The shells were compressed and exposed to kraft's pulping and soda pulping using various chemicals.

Peanut shell has protein, fat, carbohydrate, sugars, minerals, hemicellulose, cellulose, lignin, as well as various bioactive and functional compounds (Prabhakar et al. 2015). Due to the presence of the bioactive compounds, peanut shell has been used for the therapeutic treatment of coughs, for lowering blood pressure and removing mucus from lungs (Adhikari et al. 2019). The major flavonoid present in peanut shells are eriodictyol, luteolin and 5,7-dihydroxychromone. The content of flavonoids varies according to its stage of development such as having highest concentration of eriodictyol during the immature stage. As the shell matures, concentration of luteolin possessing anti-oxidative ability increases (Francisco and Resurreccion 2008).

Peanut shell is also widely used in cosmetic industries due to the high content of amino acid. Analysis has proven that peanut shell has twenty-nine amino acid, of which eight are essential such as histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, and valine (Adhikari et al. 2019). Peanut shell has high content of luteolin as compared to other plants, and it has neuroprotective effect, able to inhibit the proliferation of human oesophageal cancer cells, increased the activity of superoxide dismutase and reduced the activity of reactive oxygen species (Liu et al. 2011). Luteolin is a type of flavonoid having various positive health benefits namely anti-inflammatory, anti-microbial, antioxidant and cancer chemopreventive activities. It can lower blood pressure, cholesterol and glucose levels, as well as decrease the production of beta-amyloid and histamine (Lopez-Lazaro 2009).

Peanut skin has polyphenols such as phenolic acids (chlorogenic acid, caffeic acid, and ferulic acid), flavonoids (epigallocatechin, epicatechin, catechin gallate, epicatechin gallate) and stilbenes (resveratrol), having peroxyl-radical scavenging activities and thus is used in food industries as natural antioxidant (Larrauri et al. 2016). One gram of peanut skin consists if 90–125 milligram of total phenolic compounds which is equivalent to the phenolic content of grape skin and grape seeds (Toomer 2020). Ground beef added with peanut skin extract had antimicrobial properties and inhibited lipid oxidation (Yu et al. 2010). Besides that, sheep patties added with peanut skin extract reduced lipid oxidation, reduced loss of red coloration and limited sensory changes during storage (Munekata et al. 2016). Findings from study by Peng et al. 2015 found that 0.5% concentration of peanut skin extract inhibited the growth of Listeria monocytogenes within 72 hours as well as hindered the growth of three commensal bacterial strains namely *Lactobacillus rhamnosus, Lactobacillus casei, and L.plantarum.*

Peanut vines consisted of its root, leaves, stem and flower. About 60 to 65% of the waste produced from peanut processing are the peanut vines (Zhao et al. 2012). Dean et al. (2008) have proven than peanut leaves, root and shell have phenolic compounds with antioxidant properties. Peanut root has resveratrol (3,5,4 trihydroxystilbene) which has chemo-preventive properties and this compound is also present in berries, grapes, and tomato skin (Medina-Bolivar et al. 2007).

In conclusion, peanut by products such as vines, skin and shell has plenty of phytochemicals which will be useful for antimicrobial, antioxidant and anti-proliferative activities.

9.5 Conclusion

Far from claiming a complete review encompassed all the plants and nuts available, this review discusses the potential of the important by-products of plant food processing in promoting better health. The transformation of by-products and wastes generated by agro-food companies serve as valuable sources of phenolic compounds such as phenolic acids, flavonoids, tannins, alkaloids and terpenoids. Although small portion of plant material is utilized directly for human consumption, substantial evidences suggest that by-products may provide one or more health beneficial effects such as antioxidants, free radical scavengers, anticarcinogens, cadiopreventatives, antimicrobials and antivirals. Therefore, importance of by-products and waste pf plants and nuts have been well recognized in playing a significant role in maintaining the health of humans and disease risk reduction.

Acknowledgement This work was supported by Short Term Research Grant, Universiti Sains Malaysia [Grants No: 304/PPSG/6315422 and 304/PPSK/6315418].

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A. Rana et al. (eds.), *Sustainable Agriculture Reviews 56*, Sustainable Agriculture Reviews 56, https://doi.org/10.1007/978-3-030-84405-9