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Citrus wastes: A valuable raw material for biological applications

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ABSTRACT

Agricultural wastes have become a worrying concern worldwide due to the increasing demand for more food items brought about by the ever increasing population growth in recent times. In the quest toward maintaining a sustainable food production process and combating the issues of food security challenges, the accompanying agricultural waste has become a significant environmental concern to life. About 130 million tons of agricultural waste are generated by India and China alone yearly, which is a worrying amount by just two nations, most of which are not adequately managed and disposed of, posing severe threats to the environment and humans. Citrus is a prominent example of these agricultural wastes that have contributed substantially over the years. This is because citrus accounts for nearly a fifth of the total cultivars industrially processed into food materials, leading to a significant agricultural waste of about 120 million tons worldwide. The industrialization of citrus production due to their continuous usage as different dietary materials and nutritional benefits has led to this massive waste because only 45% of the total fruit weight is being harnessed. Nevertheless, these waste materials, such as peels, leaves, and seeds, have different phytochemicals such as naringin and hesperidin, which is indicative of their usefulness as biological agents for pharmaceutical, cosmeceutical, nanobiotechnology, food, and agricultural applications. Hence, this report briefly highlights the progress made in using citrus waste materials as biological agents by identifying some significant bioactive materials that have been found useful for various biological functions.

INTRODUCTION

The amount of agricultural waste generated worldwide has surged astronomically in recent years due to the fast-growing population, resulting in the increasing demand for food [1]. This should not come as a surprise, seeing that the world population has grown from 3.7 billion recorded in 1970 to 7.9 billion in 2021, which implies an increasing demand for food and the dire need for food security if everyone is to survive [1,2]. Thus, to ensure the sustenance of life, the demand for food and to meet the ever growing human population, there has been a significant increase in crop and livestock production, leading to a continuous rise in agricultural wastes [1,3]. In the quest toward maintaining a sustainable food production process and combating the issues of food security challenges, the accompanying agricultural waste has become a significant environmental concern to life. For instance, India and China, with about 3 billion population, account for solid waste (predominantly agricultural waste) of about 350–990 million and about 130 million tons per year, respectively [4]. This is a worrying amount of waste by just two nations, most of which are not properly managed and disposed of. Most of these agricultural wastes are usually disposed of by burning, resulting in the generation of harmful chemicals that pose severe threats to the environment and humans, such as greenhouse gases which include CO_2, CH_4, and N_2O [5]. Thus, the improper and limited management of these agricultural wastes require urgent attention for agricultural sustainability and human food and health security [1]. Although culturally, some of these wastes

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have been repurposed as a roofing material, soil mulching, compositing, animal fodder, combustion material, and in paper production, the vast majority are usually managed by burning or burying in soil, which causes soil, air, and water pollution and ultimately causes global warming [1]. Therefore, repurposing these materials to generate value-added products that can provide job opportunities and improve the farmer's livelihood while maintaining a sustainable environmental practice is in dire need [6,7].

There are different agricultural waste sources, and the primary sources of significant concern include [8–10]:

- Livestock: waste feed, urine, wash water, dung, and residual milk.
- Crop-residues: husks, stalks, weeds, leaf litter, seed pods, peels, stems, and straws.
- Aquaculture: fecal waste and uneaten feed.
- Agro-industrial waste: peels, molasses, bagasse, pulps, and oil-seed cakes.

Among the listed waste sources, agro-industrial waste, mainly from food processing industries, has been a significant source of agricultural waste. For instance, about 180.73 million metric tons of bagasse from sugarcane are produced yearly worldwide, and it has been forecasted to increase to 221 million metric tons by 2024 [11,12]. The material found as waste in this class includes bagasse and molasses from sugarcane, fruit skin and pomace from fruits (such as apple, mango, amla, orange, guava, litchi, tomato, cabbage, lettuce, and so on), rice husk, vegetable, starch residue, eggshells, poultry, and farm animal skin and meat from respective industries. Also, horticultural wastes belong to this class. They have been reported to contribute a significant amount of waste to agro-industrial waste and are usually produced during the preparation and processing of food items such as fruit juice, cider, jams, ketchup, jellies, sauces, and pickles [1]. Examples of these wastes include fruit seeds, peel, and pomace (mango, citrus, litchi, watermelon, pawpaw, musk melon, banana, apple, pineapple, and so on). Citrus fruits have received the most attention in this class due to their abundance and unique taste [13]. They have become a stable dietary component of most food consumed due to their enormous health benefits and their anti-infective, anti-inflammatory, antioxidative, anticancer, and neuroprotective properties [14]. The industrial processing of citrus into different dietary materials has led to the enormous generation of waste materials from almost every part of the plant. It has been reported that citrus accounts for nearly a fifth of the total cultivars industrially processed into food materials, leading to a significant agricultural waste of about 120 million tons per year worldwide [14–16]. Nevertheless, only 45% of the total fruit weight is being harnessed in this process which leads to the production of waste materials such as peel (flavedo; 27%), pulp (albedo and endocarp; 26%), and seeds (2%) [17]. Even though some of the citrus bye-products amassed from the industrial processing plants have been reused or repurposed, a significant amount of these materials is released into the environment, causing environmental concerns. Nevertheless, these byproducts have been identified as an excellent economical and renewable source of valuable compounds, which can be used in pharmaceutical, nutraceutical, food, and cosmetic industries [18].

Citrus peels are useful in providing low-cost, high-energy cattle feed [18]. The oil from citrus peels is known for its pleasant odor, used to flavor confectionaries and beverages, and as a fragrance in cosmetic and perfumery industries. They are a good source of many bio-resource materials, which have been useful as reducing agents in synthesizing many nanoparticles [18]. This review thus seeks to identify the possible usage of citrus waste materials as potential agents for various biological applications, such as their usage as anti-inflammatory, antimicrobial, antioxidant, and anticancer agents.

MATERIALS AND METHODS

The study was conducted by an extensive literature search for published articles, using relevant scientific databases, such as Google Scholar, Mendeley, PubMed, ScienceDirect, Scopus, and Web of Science. Searches were made for relevant publications on the subject matter in the last 25 years (1999–2023). The major search keywords included "citrus wastes," "citrus raw materials," and "biological applications of citrus wastes." The inclusion criteria for the literature search included "citrus plants," "orange plants," "citrus fruits," "citrus peels," "citrus leaves," "citrus seeds," "phytochemical contents of citrus peels, leaves, and seeds," "chemistry of citrus leaves, peels, and seeds," "antioxidant properties of citrus," "anti-inflammatory properties of citrus," "antimicrobial properties of citrus," "prebiotic activity of citrus," "cytotoxic properties of citrus," "insecticidal properties of citrus," "antidiabetic properties of citrus," and "usefulness of citrus wastes." Exclusion criteria included "phytochemical contents of citrus juice," biological applications of citrus juice" and "biological applications of plant waste other than those from citrus." The molecular structures of compounds identified in citrus peels, leaves, and seeds were drawn with the ChemDraw Ultra® 7.0 software package, CambridgeSoft Corporation (Cambridge, MA). Figure illustrations and pie charts were drawn with Microsoft 365 Publisher and Microsoft 365 Excel (Microsoft Corporation, Redmond, DC), respectively.

THE GENUS *CITRUS*: PRODUCTION AND ECONOMIC ANALYSIS OF CITRUS

The genus of citrus has been identified as one of the most widely grown subunits of the family Rutaceae worldwide [19]. This is due to their enormous nutritional and pharmaceutical properties, making them highly valuable to man [20]. In addition, citrus fruits have been reported to be a rich source of minerals, vitamins, and dietary fibers, which are responsible for the general well-being of the human body [21]. Although citrus has been reported to originate from Northern India, Northern Myanmar, Southern China, and Southeast Asia [22], their cultivation has spread to other parts of the world due to their enormous economic value, making them one of the most sought-after fruits in the world [23]. The citrus genus has been found to possess about 1,400 genera and 1,300 species. Notable examples are the *Citrus aurantifolia* (Limes), *Citrus sinensis* (Orange), *Citrus reticulata* (Mandarin), *Citrus paradisi* (Grapefruit), *Citrus limon* (Lemon), *Citrus junos* (Yuzu), *Citrus bergamia* (Bergamot), and *Citrus japonica* (Kumquat) [24]. *Citrus sinensis* (sweet orange) accounts for about 70% of this genus's total production and consumption [19]. These evergreen plants usually occur as a shrub or a tree with a height that ranges between 3 and 15 m, with elliptical-shaped leathery leaves and stemmy spikes, which produce flowers that grow individually in the axils of the leaves [20]. The various types and their respective byproducts are presented in Figure 1.

The fruits of citrus are rich in a wide range of phytochemicals and bioactive compounds, which possess several health properties. These chemicals include folic acid, vitamin C, pectin, and potassium [25]. The interest in this group of crops has continued to increase over the years because of its high polyphenols, mainly flavonoids, and antioxidant potential. For instance, in the peels and tissues of citrus fruit, different phytochemicals like flavones such as naringin and hesperidin have been found, which indicates their therapeutic potential as anti-inflammatory, antioxidative, and anti-carcinogenic agents [26]. The ever rising interest in their fruit is due to their fragrance, appealing taste, and nutritional benefits [27]. Generally, all species of citrus have similar anatomical features, as shown in Figure 2 [27].

In the past, the various varieties of their fruit were only used and traded as fresh fruits, even in places that did not support their growth due to extraordinary post-harvest stability, promoting global trade [27]. Their constant demand has encouraged the industrialization of citrus fruits because they are not only consumed unprocessed but have been used in the production of various items such as jams, jellies, marmalades, and essential oils (EOs) [23,27]. About 18% of these fruits are utilized in the industries, mainly for juice production [28]. Citrus fruits have been reported to account for about 98% of the total industrialized crops, and oranges have been said to account for 82% of the whole citrus fruits produced [29,30]. In 2020, about 158.49 million metric tons were produced globally [27]. Among these, Asia, Africa, America, Europe, and Oceania accounted for 47.7%, 43.7%, 8.1%, 0.4%, and 0.1% of the total citrus fruit production, respectively [27]. China alone is responsible for about 28.16% of the world's citrus fruit production in 2020, approximately 44.63 million metric tons of global citrus fruit production. Other major producing nations that account for over 5% include India, Brazil, and Mexico. Furthermore, it has been reported that about 10.07 million hectares of land, mainly in nations such as China, India, Nigeria, Brazil, and Mexico, are currently being used to produce citrus fruits [27]. Thus, the geographical production distribution of the major types has been concisely presented in Figure 3, according to Sharma *et al.* [19].

The continued interest in citrus production has, in turn, resulted in the continued generation of waste which has become a severe environmental burden [27]. The unhygienic disposal of citrus waste has been termed dangerous if not treated before disposal [31]. The citrus wastes include peels (which account for about 50%–55% of the total fruit mass), seeds (which account for 20%–40% of total fruit mass, pomace), and wastewater (from spoiled fruit, seeds, pulp, and peels) [27]. Yearly, about 10 million citrus wastes are reported globally, just from the fruits alone, causing a severe ecological issue [16]. The genuine concern is that citrus waste is problematic because it contains 80% water, thus inviting microbes, flies, and mold. Therefore, they rot quickly and produce harmful mycotoxins [32]. Hence, their proper disposal and management are vital, as their indiscriminate disposal can lead to water and soil pollution and destroy the aquatic ecosystem [16].

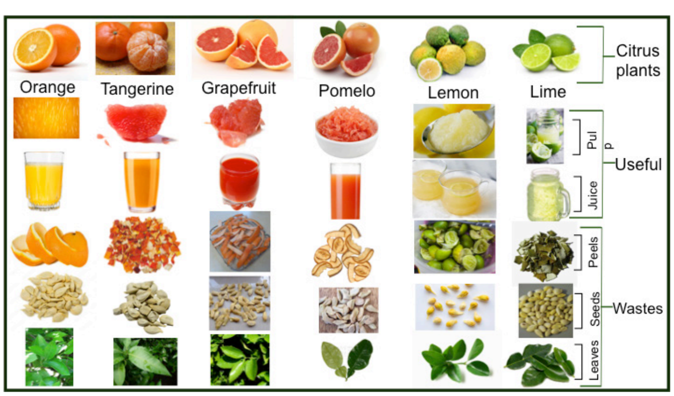


Figure 1. Some types of citrus fruits and their wastes [19].

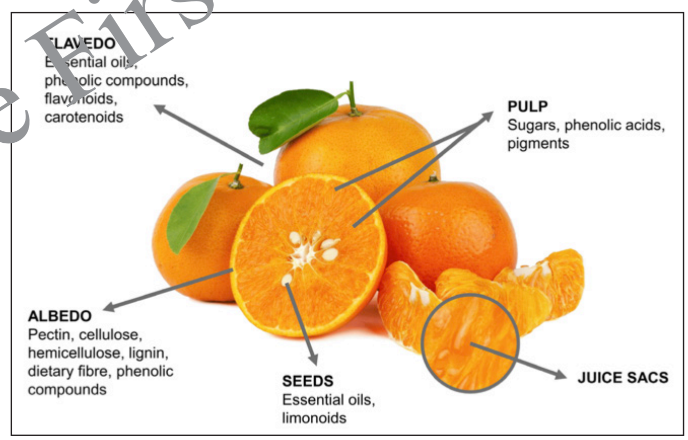


Figure 2. The general anatomical characteristics of citrus fruits [27].

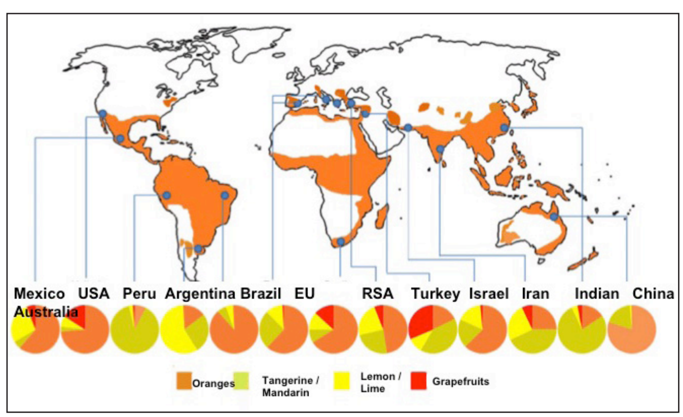


Figure 3. Map showing the geographical distribution of the major types of citrus fruits production from 2007–2016 across the globe [19].

Nevertheless, citrus leaves, seeds, fruit peels, and pomace, have been identified as a powerhouse for many bioresource materials that have found application as biological agents due to the enormous health properties of the available bioactive compounds found in these materials [27]. They have already been used in food industries as baking additives and as a source of flavoring, colorant, and pectin. Furthermore, many applications have been found for these materials in the pharmaceutical industries and research areas, such as biofuel, bio-absorbent, biofertilizer, activated charcoal, and packaging materials [19]. A large volume of EOs within these waste materials has led to their use as fragrances in cosmetic products [27].

BIOLOGICAL APPLICATIONS OF CITRUS WASTES

The application of plant byproducts for health needs has increased tremendously in the last few decades due to their availability, biological potentials, minimal side effects, and low cost of sourcing byproducts, unlike what is obtainable in the production of modern therapeutic drugs and other healthcare products [33]. Citrus wastes are among such popular plant byproducts, which can act as medicinal raw materials because of their bioactive phytochemicals, which include volatile (EOs and limonoids) and nonvolatile (phenolics and flavonoids) compounds [34]. Their peels and leaves are implicated along with many aromatic plants in aromatherapy—an alternative or supportive therapy that uses EO-bearing plants and their oils for disease management [35]. Citrus wastes have found medicinal applications across many cultures. For instance, in traditional Chinese medicine, dried lemon peel oils and extracts are used as remedies for coughs and to reduce phlegm in the upper respiratory tract [36]. The Xhosa tribe of Amathole District from Eastern Cape, South Africa, also uses lemon peels to manage respiratory and skin diseases [37]. The fiber portion of citrus peels is involved in improving intestinal and physiological functions. It is often associated with a lower risk of life-threatening chronic diseases such as diabetes, cardiovascular disease, obesity, and cancer [38].

Over the years, some ethnomedicinal claims have been validated to be effective, with reports of considerable inhibitory effects of the extracts and EOs of citrus peels on inducible nitric oxide synthase (iNOS), a pro-inflammatory enzyme involved in many respiratory tract diseases [39]. This unique biological property of citrus wastes (peels) has been linked to their rich flavonoid contents, especially nobiletin, and tangeretin, which are reported to inhibit the deoxyribonucleic acid (DNA)-binding activity of pro-inflammatory cytokines, nuclear factor kappa B (NF-κB) and reactive oxygen species production in lipopolysaccharide (LPS)-activated RAW 264.7 macrophages [40]. Extracts and oils from citrus wastes (leaves and seeds) have also been shown to exhibit free radical scavenging, antiperoxidase, and antipolyphenol oxidase activities [41,42]. Also, the waste material from *C. junos* is implicated in the Asian traditional medicine for treating asthma, coughs, and chronic inflammatory diseases, while coumarin compounds, notably isogosferol, are reported to be responsible for the anti-inflammatory properties observed in the seed shell extract [43]. Isogosferol potently attenuated the production of nitric oxide (NO) in LPS-induced RAW 264.7 cells and inhibited the expression of iNOS and cyclooxygenase-2 (COX-2) in LPS-stimulated macrophages; thus, suggesting it as a drug candidate for the treatment of inflammatory diseases [43].

In recent times, the limonene content of citrus wastes (peels and leaves) is extracted for use in household products as a sweetener in drugs and foods, and as an antiseptic and odorant in the cosmetics industry, to produce sanitizers, soaps, body creams, and perfumes [44]. The pectin-rich dry peels of citrus have gelation and emulsion stabilization properties, making them useful in manufacturing drugs, cosmetics, and food products [45]. The fragrance and biological properties of EOs from citrus wastes make them a valuable raw material in cosmetic products [46]. *Citrus reticulata* peel extracts have shown anti-collagenase and anti-elastase activities, and this byproduct is a potential anti-aging agent in cosmetic products [47]. Also, the EO component of the peels has been reported to show strong antibacterial and anti-inflammatory activities [48].

The peels of *Citrus medica*, *C. sinensis, C. limon, C. reticulata*, and *C. maxima* are now known to be important cancer preventive food additives based on their remarkable cytotoxic and cancer preventive properties, which are attributed to their volatile (EOs and limonoids) and nonvolatile (polymethoxy flavones) components [49]. Dry citrus peels are rich in cellulose, hemicellulose, and pectin, which can be utilized as fermentation substrates and processed into cattle feeds and molasses [50]. They are also used as sources of fiber for food enrichment [38] and as natural antioxidants such as polyphenols in processed foods and beverages [51]. Citrus wastes are also processed for their limonene content to produce solvents and resins, as a wetting and dispersing agent, and in insect control [44].

Citrus limon peels can be hydrolyzed by enzymes into sugars, which can be successively fermented to produce bioethanol and used as fuel for industrial processing plants [52]. Citrus wastes can also be used as substrates in the industrial production of biofertilizers, biofuel, and biosorbents [19]. They can also serve as natural biosorbents for removing dyes and other contaminants in water and wastewater treatments [45]. They have also found usefulness in the production of polystyrene, a common thermoplastic polymer used in the production of packaging materials and household and consumer goods [33].

Most recently, citrus wastes, like many natural product wastes, are utilized in nanoparticle synthesis as alternative, eco-friendly, and biocompatible waste-derived nanoformulations for many applications [53]. The citrus waste material can act as a capping and reducing agent to control the aggregation of the nanoparticles [54]. Nowadays, the waste material (peels) from *C. sinensis, C. limon,* and *Citrus limetta* can serve as a bio-reductant in the biogenic synthesis of metal or metal-oxide nanoparticles for optimal biological functions, such as antioxidant, antimicrobial, and cytotoxic activities, to name a few [55]. Evidence has emerged on the utilization of citrus wastes as part of nanomaterials used for the preparation of nano-insecticides (nano-emulsions) for food pest control, citrus EO nano-emulsion for disease vector mosquito control, nano-formulated bio-insecticides, aerosol and fumigant for home use, and as antimicrobial EO nano-formulations [56]. The cellulosic component of citrus waste can also be formulated into nano-cellulose for water and waste treatments, thus, offering an alternative to zeolites and activated carbon, which are conventional adsorbents [57,58]. Based on the above evidence, it may not be far-fetched to describe citrus wastes as a valuable raw material for biological applications, such as in pharmaceutical, cosmeceutical, food, industrial, and agricultural productions (Fig. 4).

Antioxidant activity

Antioxidants are chemical substances, that when present at low concentrations compared to those of an oxidizable substrate significantly delay or prevent oxidation of that substrate [59]. There has been increasing scientific evidence of the considerable antioxidant properties of citrus fruits and their waste materials [60,61]. This biological function has been attributed to their rich phenolic and polyphenolic contents, such as phenolic acids, flavonoids, and their derivatives [62]. The peel EO of citrus fruits such as *C. reticulata* and *C. sinensis* has been reported to be of considerable antioxidant potentials, while that of *Citrus aurantium*, *C. limon,* and *Citrus paradisii* showed remarkable free radical scavenging activities [63–66]. The leaf EO of *Citrus limettioides* and *Citrus pseudolimon* of Nainital District showed considerable antioxidant properties, while the leaf methanolic and aqueous extracts of *Citrus clementina* and *C. limon* showed remarkable antioxidant activities owing to their high phenolic and flavonoid contents [42,67]. The antioxidant constituents of citrus play an important role in delaying or inhibiting the process leading to inflammation, microbial infections, cancer, diabetes, chronic respiratory diseases, and cardiovascular diseases among others [62,68].

Anti-inflammatory activity

Inflammation sets in when the biological system is immune compromised, a scenario triggered by damaged cells, toxic compounds and materials, pathogenic microorganisms, and a host of other factors [69]. The inflammatory process sets off oxidative stress and lowers cellular antioxidant capacity to prevent microbial infections, cancer, and a variety of age-related diseases, including arthritis, diabetes, cardiovascular, and autoimmune diseases [70]. Therefore, anti-inflammatory agents are biologically active substances that can interfere in the pathophysiological process of inflammation to inhibit the release of chemicals and migrating cells, such as bradykinin, histamine, leukotrienes, prostaglandins, phospholipase, COX-2, lipoxygenase (LOX), cytokines, interleukin-1β (IL-1β), interferon-γ, tumor-necrosis factor-α (TNF-α), NF-κB, and platelet-activating factor [71]. There have been several reports alluding to the considerable anti-inflammatory potential of citrus fruits and their waste products, which include peels, leaves, and seeds. The EOs obtained from the peels of four *Citrus* species, *C. limon, C. latifolia, C. aurantifolia,* and *C. limonia* exhibited significant anti-inflammatory properties at a dose range of 10–100 mg/kg, p.o. in mice by reducing cell migration, cytokine production, and protein extravasation caused by carrageenan [72]. The EO obtained from the fresh blossom (leaves and flowers) of *C. aurantium* showed considerable anti-inflammatory activity at a dose of 40 mg/kg, by significantly reducing carrageenan-induced paw edema in rats, and when compared to 50 mg/kg of diclofenac sodium (standard drug), they exhibited a comparable activity [73]. The aqueous leaf extract of *C. reticulata* exhibited a dose-dependent *in vivo* anti-inflammatory activity between 100 and 500 mg/kg b.w. by a significant dose-dependent ear section weight reduction in mice [74], while the leaf EOs of *C. limon* var Meyer and *C. aurantifolia* var Sans epines showed considerable *in vitro* anti-inflammatory properties by exhibiting inhibitory effects against the oxidation of linoleic acid in an LPS-treated cell at IC_{50} values of 46.5 and 49.35 ppm, respectively [75]. Methanolic extract from the young fruit peel of *Citrus unshiu* showed considerable anti-inflammatory activity by inhibiting iNOS in rat primary astrocytes [76], while the extract from the peel of *C. reticulata peel* acted as an *in vivo* anti-inflammatory agent by suppressing NO production and inhibiting NF-κB in macrophage RAW 264.7 cells [74]. Also, the crude methanolic extract of *C. aurantium* peel demonstrated considerable anti-inflammatory properties by modulating the expression of COX-2 iNOS protein, TNF-α, and COX-2 messenger ribonucleic acid (mRNA), in LPS-stimulated macrophage RAW 264.7 cells via the NF-κB pathway in a dose-dependent manner [77], as illustrated in Figure 5.

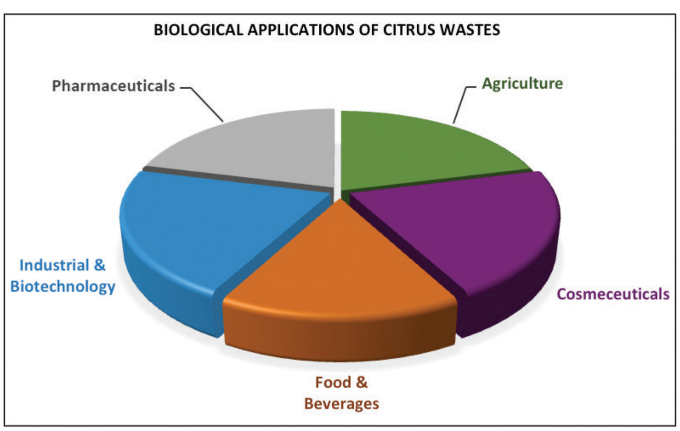


Figure 4. Biological applications of citrus wastes.

Prebiotic activity

Prebiotics are nondigestible food ingredient that favorably affects the host by particularly stimulating the growth and activity of one or a limited number of bacteria in the colon, to improve host health [78]. They are mostly nondigestible dietary fibers that resist digestion in the small intestine until they reach the colon to get fermented by the gut microorganisms, producing short-chain fatty acids, which help to improve digestion, immune function, metabolic health, and other health benefits [79]. Prebiotic substances include fructan, galacto-oligosaccharide, starch and glucose-derived oligosaccharide, and pectin [78,80]. Some natural sources of prebiotic foods are apples, asparagus, bananas, barley, chicory root, citrus peels,

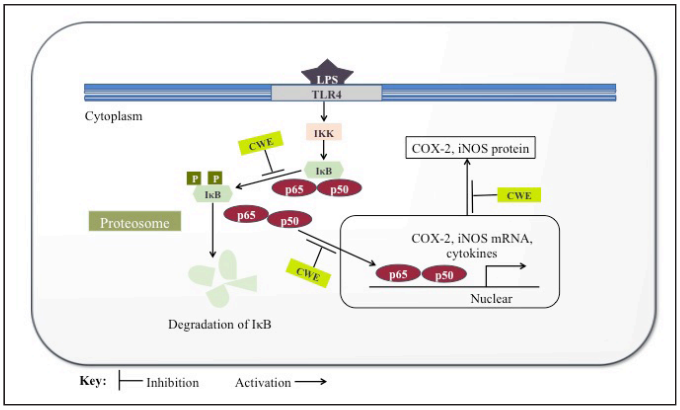


Figure 5. Anti-inflammatory response of citrus waste extract (CWE) by its inhibitory effects on LOX, LPS-induced inflammation. An illustration of CWE blocking NF-κB signaling pathway via inhibition of (i) IκB phosphorylation, (ii) subunits (p65/p50) of NF-κB translocation in nuclear, and (iii) proinflammatory mediators (COX-2, iNOS) transcription. Black arrows indicate the NF-κB signal pathway and target gene that DNA binding site of NF-κB. CWE: Citrus waste extract (methanol extract of *C. aurantium* peel); IKK: IκB kinase; IκB: Inhibitor of κB in the cytoplasm; p50/p65: subunits of NF-κB; COX-2: cyclooxygenase-2; iNOS: inducible nitric oxide synthase. The figure was redrawn according to Kim *et al.* [77], with copyright permission from ©Hindawi Publishing Corporation.

cocoa, dandelion greens, flaxseeds, garlic, jerusalem artichoke, leek, oats, onions, and seaweeds [81,82].

Citrus peel wastes are an important source of prebiotic dietary fibers, such as pectins, which are known to play a significant role as nutraceuticals [83]. Structurally, pectins are heteropolysaccharides that contain galacturonic acid units, linked at positions 1 and 4 [84]. Pectins as prebiotics can promote anti-inflammatory commensal bacteria in the colon, such as *Eubacterium eligens* and *Faecalibacterium prausnitzii*, to produce anti-inflammatory cytokines and modulate chronic inflammation [85].

In a recent study, the pectins obtained from citrus peel wastes demonstrated greater prebiotic activity than other commercially available prebiotics, such as inulin and fructo-oligosaccharides [81]. In addition, those pectins obtained through enzymatic treatment and membrane separation processes were shown to be more effective as prebiotic and antimicrobial agents [81]. Pectic oligosaccharides (pectin derivatives) extracted from *C. limon* peel wastes have also been shown to exert considerable prebiotic properties, with the joint populations of bacteria in the genera bifidobacteria and lactobacilli increasing from 19% to 29% [86].

Furthermore, pectic oligosaccharides obtained through enzymatic depolymerization of citrus peel wastes were reported to cause high prebiotic activity in *Bifidobacterium infantis*, *Lactobacillus acidophilus, Clostridium perfringens,* and *Bacteroides fragilis*, with considerable antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli* as well as inhibitory activity against the invasion Caco-2 cells by *Campylobacter* species [87,88]. Pectin oligosaccharide obtained from citrus peel pectin by controlled chemical degradation showed a significantly high prebiotic score of 0.41 for *Lactobacillus paracasei* LPC-37 and 0.92 for *Bifidobacterium bifidum* ATCC 29521 [89]. Also, pectin-derived oligosaccharides obtained through an enzymatic fermentation process from lemon peel wastes resulted in similar shifts in the elderly microbiota compared to fructo-oligosaccharides, the standard prebiotic [90]. Thus, this result shows the potential of pectins as food ingredients for the improvement of the profiles and metabolic activities of gut microbiota in the elderly [90]. Based on the various prebiotic activities of pectins among other biological properties, they have been found useful in the pharmaceutical industry, for drug delivery, tissue engineering, and wound healing, while they are used as gelling, thickening, and stabilizing agents in the confectionery industry [84,91].

Antimicrobial activity

Citrus is an important fruit that has been widely known across many cultures to be used for the management of microbial-related infections such as cholera, dysentery, diarrhea, wound infections, chronic inflammatory diseases, and urinary tract infections [62,92]. *Citrus sinensis* peel and leaf EOs are known to demonstrate considerable inhibitory activities against the growth of several pathogenic bacteria, including *S. aureus*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Salmonella typhimurium*, *E. coli*, and *Pseudomonas aeruginosa* [93]. The peel and leaf EOs of *C. reticulata* inhibited the growth of several bacteria including *E. coli, B. subtilis, P. aeruginosa,* and *S. aureus* [94]. *Citrus paradisii* EO has also been reported to inhibit the growth of wild food-borne spoilage and pathogenic bacterial strains [95]. The EO of *C. unshiu* peel demonstrated antibacterial activity against *Bacillus cereus*, *B. subtilis,* and *S. aureus* [96]. The ethanolic extract of *C. sinensis* peels demonstrated antibacterial activity against *E. coli* and *S. aureus*, while the EO of *C. limon* peel demonstrated both minimum inhibitory concentration (MIC) and minimum bactericidal concentration, which were the antibacterial activities of 1.25 and 5.0 mg/ml against *S. aureus* typed strain that has been implicated in food poisoning [97]. The EOs of *C. limon* and *C. aurantium* remarkably inhibited the mycelial growths of *Aspergillus niger* and *Geotrichum candidum* at the MIC values of 5 and 10 ppm, respectively [98]. The aqueous seed extract of *C. paradisii* has also been reported to exhibit higher antifungal activities against *A. niger*, *Candida albicans*, *Cladosporium cucumerinum*, *Penicillium digitatum*, *Penicillium italicum,* and *Penicillium chrysogenum* than its ethanol extract, thus, making it to be a suitable raw material to produce natural disinfectants or antiseptics [99].

Antidiabetic activity

Diabetes, also known as diabetes mellitus (is a chronic heterogenous metabolic disease that is characterized by unsuitably elevated blood glucose levels (BGLs) because of defects in insulin secretion, insulin action, or both [100,101]. Antidiabetic agents can act by stimulating insulin secretion, reducing hepatic glucose production, improving insulin action, or delaying digestion and absorption of starch hydrolyzing enzymes such as α-glucosidase and α-amylase inhibitors [102]. For decades, citrus plants have been used in traditional medicine and as an important dietary aromatic ingredient for the regulation of human BGL [103,104]. The extract of *C. sinensis* peel at a dose of 500 mg/kg b.w. showed the highest (61.36% ± 5.57%) *in vivo* antidiabetic and 55% antihypercholesterolemic activities [105]. It was found that the *n*-hexane extract of *C. limon* peel at a dose of 10 mg/kg b.w. in rats showed 44.57%, 75.96%, and 95.43% anti-hyperglycaemic effects after 24, 48, and 72 hours of drug administration, respectively, while the hydroethanolic extract of *C. reticulata* peel exhibited considerable antidiabetic activity [106,107]. The ethanol extract of *C. junos* Tanaka (Yuzu) peel exerted antidiabetic activity by increasing glucose uptake in C2C12 myotubes and by modulating the adenosine-5-monophosphate, AMP-activated protein kinase, and peroxisome proliferator-activated receptor gamma signaling pathways in a dose-dependent manner, thus, improving insulin resistance in mice that were fed a high-fat diet [108]. The methanol extract of *C. limetta* peels at 200 and 400 mg/kg b.w. demonstrated significant anti-hyperglycaemic effects over a 15-day period, which may be attributed to its remarkable antioxidant properties [109]. The aqueous extract of fresh *Citrus hystrix* leaf alone and in combination with two other extracts, *Eugenia polyantha* leaf and *Pandanus amaryllifolius* leaf showed considerable *in vitro* antidiabetic properties by their inhibitory effects on starch hydrolyzing enzymes, α-amylase and α-glucosidase, partly due to their rich phenolic composition and antioxidant properties [110]. The seed hydro-ethanolic extract of *Citrullus colocynthis* showed both *in vitro* and *in vivo* antidiabetic properties by α-glucosidase enzyme inhibition and by showing a marked time-dependent decrease in BGLs in streptozotocin-induced diabetic rat model, respectively [111]. Also, in an *in vivo* study, using a streptozotocin-induced diabetic rat model, the petroleum ether extract of *Citrus medica* seed (200 and 400 mg/kg, p.o.) induced a significant reduction in fasting blood glucose, serum cholesterol, serum triglycerides, high-density lipoprotein, low-density lipoprotein, and very-low-density lipoprotein in a dose-dependent manner [112].

Cytotoxic (anticancer) activity

Cancer can be described as a group of noncommunicable diseases characterized by uncontrolled or rapid growth and spread of abnormal cells, with a high propensity to cause death in affected individuals [113]. There is much to be desired about the potency and safety of cytotoxic agents and the currently available cancer drugs to date. Nevertheless, considerable experimental studies have shown the bio-functionality of many dietary natural products including citrus fruits and their by-products to inhibit or delay the development and progression of cancer [114].

The EOs obtained from the peel of *C. limon* grown in four different geographical locations have been reported to demonstrate 80% colorectal cancer cells (LIM1863) reduction, with an IC_{50} ranging between 5.75 and 7.92 µg/ml, while doxorubicin (standard drug) caused a 92% reduction in the cancer cell viability [115]. Likewise, an investigation of the Iranian *C. limon* peel EO revealed considerable levels of cytotoxic against the human breast (MCF-7) and cervical (HeLa) cancer cell lines at IC_{50} values of 10 and 17 µg/ml, respectively [116]. The EOs of four *Citrus* species, *C. limon, C. reticulata,* and *C. paradisii* were reported for their anticancer property, by showing their cytotoxicity against lung cancer cell lines (BV2) microglial cells at an IC_{50} ranging between 321.37 and 1,558.87 µg/ml [117]. The cytotoxicity was shown to be by an induction of a G0/G1 cell cycle arrest [117]. At 200 and 400 mg/kg b.w. the methanolic extract of *C. limetta* peel showed a considerable *in vivo* antitumor property [118]. The EO of *C. aurantifolia* peel showed 78% inhibition against human colon cancer cell lines (SW-480) at 100 µg/ml within a 48-hour period *in vitro*, while the aqueous extract of *C. aurantifolia* has been reported for its cytoprotective action against aflatoxin B1 induced liver injury *in vivo* [119]. The peel powders obtained from *C. sinensis, C. reticulata,* and *C. limon* have been shown in a recent study, to exhibit considerable cytotoxicity against the human colon carcinoma cell line (HCT116) [120]. The *n*-hexane extract of *C. hystrix* leaf has been reported to show considerable cytotoxicity against triple-negative breast cancer cells (MDA-MB-231), with an IC_{50} value of 317.63 ± 2.00 µg/ml [121], while the hydro-methanol extract of *C. limon* seed demonstrated 29.1% inhibition against human breast adenocarcinoma (MCF-7) at 100 µg/ml within 48 and 72 hours via apoptosis [122].

Insecticidal activity

According to the United States Environmental Protection Agency, insecticides are chemicals used for the control of insects and/or insect pests by killing them or preventing them from engaging in undesirable or destructive activities [123]. Insecticides are produced to help minimize disease burden or at best eradicate them, with the ultimate goals of attaining good health and wellbeing, food security, and economic stability [123]. Commercially available synthetic insecticides, such as organophosphates, carbamates, dinitrophenols, and some of the older, less costly ones can remain for years in soil and water thereby constituting a lot of hazards to the ecosystem [124]. Although many of these chemicals have been banned from agricultural use in developed countries, they are still used in many developing countries [125]. Thus, there is a need to exploit medicinal plants for natural insecticides, which are known to be easily biodegradable, biocompatible, eco-friendly, and less toxic [126].

The limonene-rich citrus waste (peel) is one such natural raw material that is now being repurposed as natural insecticides for preservation against food pests [127]. EOs from the peel of *C. reticulata* have been reported to have contact and fumigant toxicities on various insects that attack stored food products [128]. The peel EO extracted from *C. reticulata* has been reported to show remarkable insecticidal and growth inhibition activities against two strains of *Rhyzopertha dominica* (Fabricius) found in wheat [129]. The *C. limon* peel EO has been reported to possess fumigant activity, with dose-response relationship and repellent activity against *Sitophilus granaries* and *Sitophilus oryzae* [130,131]. The C. *aurantifolia* peel EO has shown a considerable level of insecticidal activity (contact, fumigation, and feeding deterrent activities) against the maize weevil, *Sitophilus zeamais* [132]. Also, *C. sinensis* EO has shown significant insecticidal activity against *Tribolium confusum*, *Callosobruchus maculatus,* and *S. oryzae* [133]. The EO of *C. paradisii* peel has also been reported to show insecticidal activity against *Ceratitis capitata*, while the petroleum ether extract of *C. aurantium* peel showed

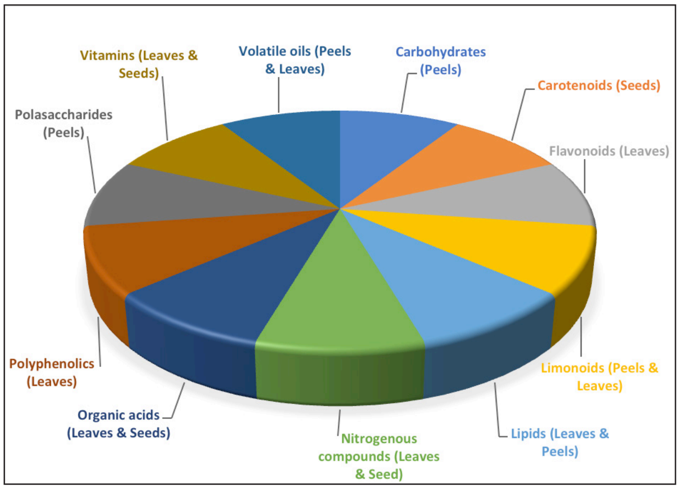


Figure 6. Class of compounds found in citrus wastes (peels, leaves, and seeds), according to Sharma *et al.* [19].

insecticidal activities against the males and females of olive fruit fly, *Bactrocera oleae* (Gmelin) and medfly, *C. capitata* (Wiedemann) adults at LD_{50} values of 44.8 and 40.1 µg/insect against the former and 38.8 and 67.8 µg/insect, respectively, against the latter insect [134].

PHYTOCHEMICAL OUTLOOK OF CITRUS WASTES

Source of bioactive compounds

Phytochemicals are chemical substances stored in grains, vegetables, fruits, and other food products for desirable health benefits beyond basic nutritional needs, including reducing the risk of major cardiovascular and chronic inflammatory diseases [135]. They are primarily secondary metabolites, such as flavonoids, alkaloids, terpenoids, steroids, saponins, and phenolic compounds, with unique chemical structures and demonstrable biological properties [136]. These bioactive compounds are known to be present in both the edible

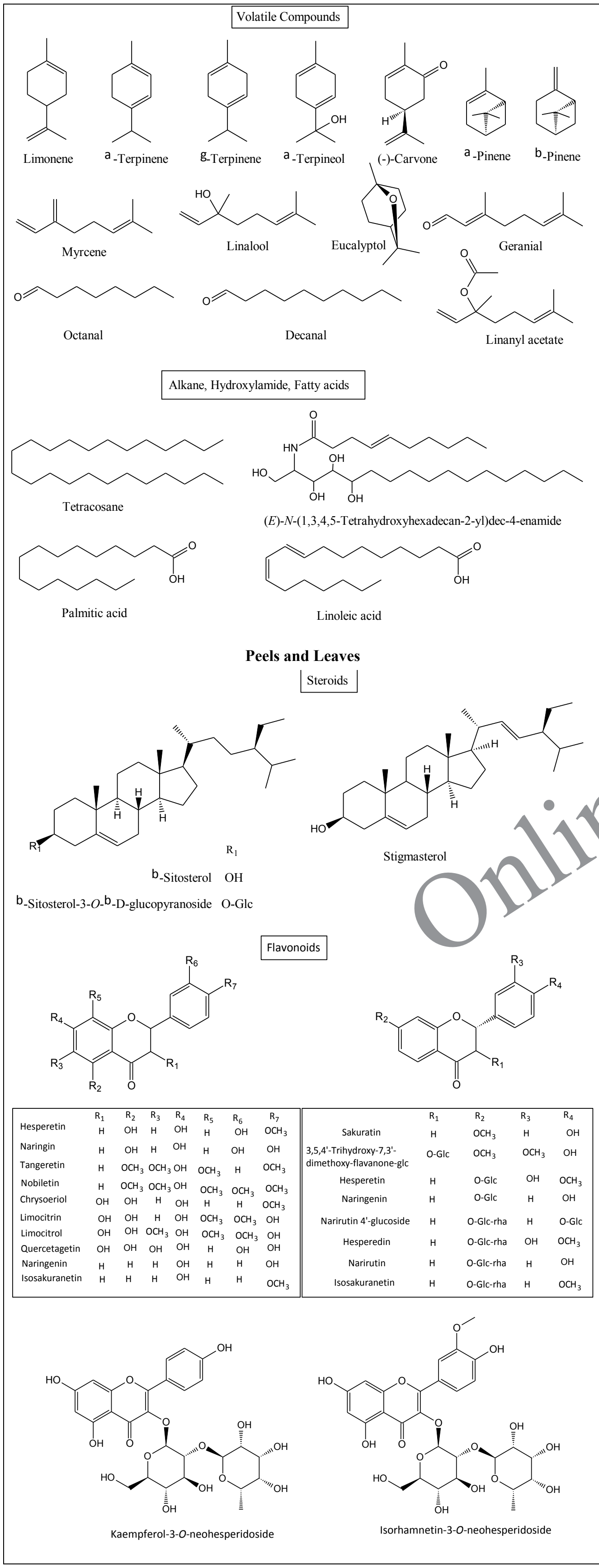
Table 1. Reported phytochemical contents and biological activities of some citrus wastes.

Citrus plant	Waste	Phytochemicals	Biological activities	Mechanism of action	Reference
C. limon (Lemon)	Peels	Catechin, rutin, naringin, quercetin, hesperidin, and pectin	Antioxidant, antibacterial and cardioprotective functions	Reduction of lactate dehydrogenase and malondialdehyde, increased in superoxide dismutase (SOD), catalase, and glutathione, downregulation of Bcl-2-associated X protein, caspase-3, nuclear factor erythroid 2-related factor 2 and heme oxygenase-1 expression, and upregulation of Bcl-2 expression	[138,139]
	Leaves	EOs (limonene, geranial) and fatty acids	Anti-spermatogenic and anti-fertility effects	Suppression of spermatogenesis may result from germ cell apoptosis because of decreased production of testosterone	[140]
	Seeds	Mineral nutrients (K, Ca, Na, Fe and Mg), vitamins (tocopherols, carotenoids), α-linolenic acid, simple phenolics and polyphenols	Antioxidant and cytotoxic activities	Induction of cancer cell death through apoptosis, autophagy and necroptosis	[141]
C. aurantifolia (Lime)	Peels, leaves	Fatty acids (palmitic acid, oleic acid, linoleic acid), ascorbic acid, flavonoids (apigenin, rutin, quercetin, kaempferol, and nobiletin), EOs (limonene, linalool, linanyl acetate	Antioxidant, anti-inflammatory and anticholinesterase properties	Phenolic (ascorbic) and polyphenol (flavonoids) exhibit redox properties Modulation of enzymatic (acetylcholinesterase and butyrylcholinesterase) activities, and the inhibition of cellular proliferation	[142]
	Seeds	Limonin, isolimonexic acid and L-limonexic acid, D-limonene, D-dihydrocarvone, verbena, β-linalool, α- terpinol, trans-α-bergamotene	Antibacterial activity	Terpenoidal skeleton ensures lipophilicity and bactericidal effects by penetration into bacteria cell wall	[143]
C. sinensis (Sweet orange)	Peels	Decanal, octanal, linalool, 1,8-cineole, limonene	Antioxidant, antibacterial	Increased lipophilicity and bactericidal effects by bacteria cell wall penetration	[144]
		Hydroxylated and nonhydroxylated polymethoxyflavones	Cytotoxicity against human lung cancer cells H441 and H460	Inhibition of cell proliferation and induction of cell apoptosis	
	Leaves	Terpineol, 1,8-cineole	Insecticidal activity	Volatile compounds bind to odorant receptor proteins on ciliated dendrites of specialized odor receptor neurons found on the antennae and maxillary palps of the insect	[145,146]
	Seeds	Dietary components such as protein, crude fibre, carbohydrate, vitamins A and D, fatty acids (linoleic acid, palmitic acid, isopropyl linoleate, pentadecanoic acid, stearic acid, butyl linoleate, glutaric acid), iron, phosphorus	Antifungal activity against white rot caused by a saprophytic mushroom, *Lentinus sajor-caju*	Synergistic inhibition of fungal growth by specific or selective inactivation of fungal enzymes involved in cell wall synthesis such as 1,3-β-glucan synthase	[147,148]

(Continued)

Citrus plant	Waste	Phytochemicals	Biological activities	Mechanism of action	Reference
C. clementina (Tangor)	Leaf	Tangerine, methoxyflavones, nobilletin, acridones, xanthyletin, suberosin, E-suberenol, E-methoxysuberenol, 6-formylumbelliferone, aurantiamide acetate, limonin, stigmasterol, β-sitosterol and β-sitosterol-3-O-β-D-glucoside	Antioxidant, anti-inflammatory, urease inhibition and anti-diabetic activities	Inhibition of free radical release, LOX and α-glucosidase enzymes	[149]
	Peels, leaves	Eriocitrin, hesperidin, neohesperidin, hesperetin, caffeic acid, didymin, poncirin, chlorogenic acid, limonene, linalool, myrcene, sabinene	Antioxidant and hypoglycaemic effects	Inactivation of free radicals, inhibition of lipid peroxidation and that of carbohydrate metabolizing enzymes, α-amylase and α-glucosidase	[150]
C. reticulata (Mandarin)	Peels	Hesperidin, neohesperidin, naringin, nobiletin, methoxylated flavones, tangeretin, sinesetin	Hypocholesterolemic and antidiabetic effects	Lowering of plasma and hepatic cholesterol and triacylglycerol by inhibiting the hepatic enzymes	[151]
	Seeds	Citriolide A (limonoid)	Cytotoxic properties	Inhibition of human lung (A-549) and leukaemia (P388) cancer cell lines	[152]
	Leaves, peels	Depcitrus A, atranorin, 5-hydroxy noracronycine, flavanone, isocoumarin, citracridones, citrusinol, citrusinine-I, citramine, scopoletin, limonin, 4-hydroxybenzoic	Antioxidant, antimicrobial and cytotoxic activities	Inhibition of free radicals, inactivation enzymes involved in cell wall synthesis. Anticancer (cytotoxicity) mechanisms of action such as DNA binding, inhibition of oxidative stress, cell cycle regulation and programmed cell death (apoptosis)	[153,154]
	Peels	Hesperidin, quercetin, naringin, and polymethoxylated flavones such as nobiletin and tangeretin	Anti-diabetic activity	A significant decrease in the elevated liver lipid peroxidation and an increase in the lowered glutathione content and glutathione peroxidase, glutathione-S-transferase, and SOD activities. mRNA expression of glucose transporter-4 and the insulin receptor β-subunit, while quercetin contributed to the significant increase in the expression of adiponectin in adipose tissue of diabetic rats.	[106]
C. deliciosa (Mediterranean Mandarin)	Peels	Phenolics, flavonoids, tannins	Antioxidant activity	Prevent the initiation of free radical-mediated chain reactions by stabilizing reactive species before they can participate in deleterious reactions	[155]
C. paradisi (Grapefruit)	Leaves, peels	Volatile compounds (β-myrcene, β-phellandrene, D-limonene, γ-terpinene, caryophyllene	Antioxidant and anti-inflammatory activities	Help in the fight against inflammation by free-radical damage in the body by preventing the initiation of free radical-mediated chain reactions	[156]
	Seeds	Alkaloids, flavonoids (naringin, hesperidin), cardiac glycosides, tannins and saponin	Antioxidant, antidiabetic, and antimicrobial properties	Prevent free radical release, lowering of BGL, and reduction of lipid content and the risk of cardiovascular diseases	[157–159]
C. aurantium (Bitter orange)	Seeds	Hesperidin, limonoids, fatty acids (linoleic acid, palmitic acid)	Neuroprotective effect	Prevention of progressive neurological damage associated with Alzheimer's disease	[33]
	Peels, leaves	Volatile oils (limonene, linalool, linalyl acetate), phenolic acids (ferulic acid, *p*-coumaric acid), flavonoids (naringin, hesperidin), limonoids (limonin and nomilin)	Antioxidant, neuroprotective, anticancer, antidiabetic, antiproliferative, hypolipidemic, and cardio-protective properties	Promote immune response by expression of interleukin 6 and TNFα. Also promote the production of iNOS, and IL-1β by stimulating their mRNA expression levels. Promote the phosphorylation of p65, p38, c-Jun N-terminal kinase, and the extracellular signal regulated kinase. Modulate insulin signalling cascade by preventing the phosphorylation of glycogen synthase kinase-3 beta and the activation of serine/threonine protein kinases	[160]

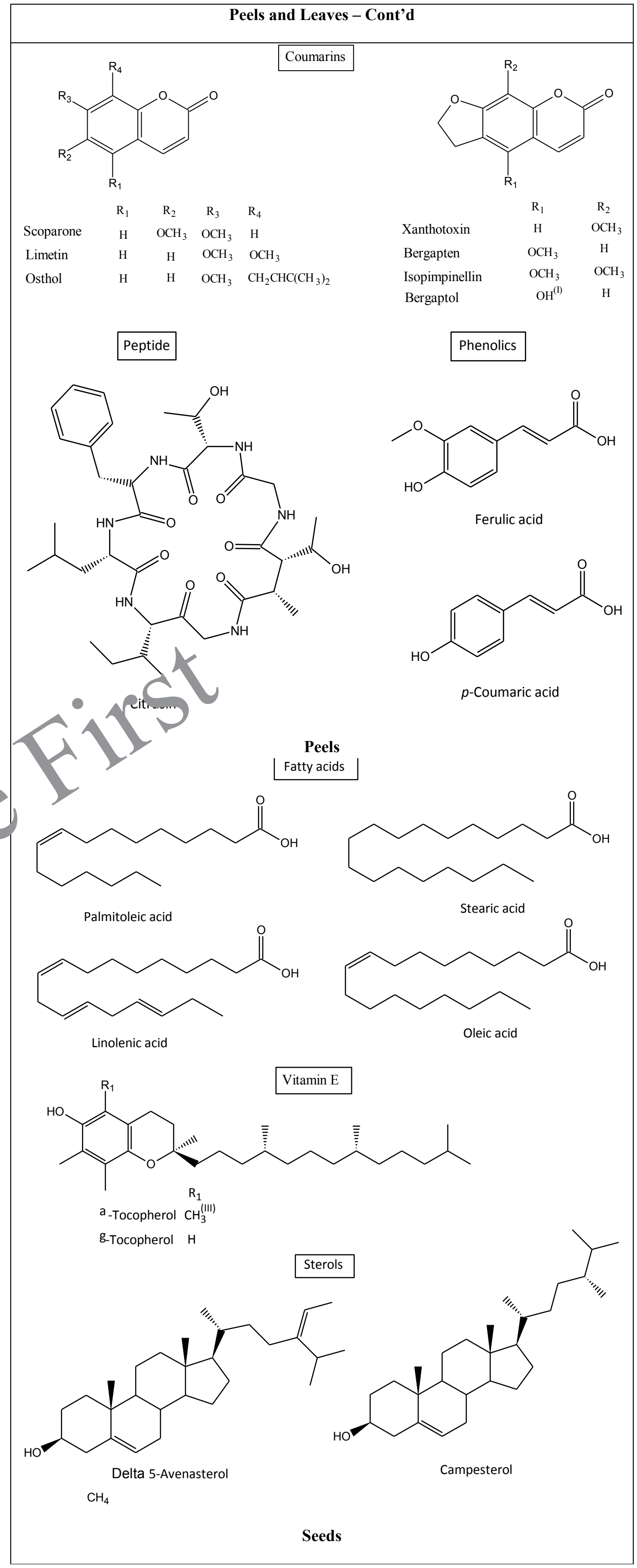
and nonedible parts of grains, vegetables, and fruits [137]. Most parts of the citrus plants generally possess rich phytochemical contents such as carbohydrates, carotenoids, flavonoids, limonoids, lipids, nitrogenous compounds, organic acids, polyphenolics, polysaccharides, vitamins, and volatile oils [19], which are highlighted in Figure 6. These useful phytochemicals are often not wholly expended after consumption but find their way as the constituent of citrus waste [103]. The biological activities and mechanisms of action of some compounds identified in citrus wastes are presented in Table 1. Furthermore, the chemical structures of some of the implicated compounds are shown in Figure 7.



	R_1
b-Sitosterol	OH
b-Sitosterol-3-O-b-D-glucopyranoside	O-Glc

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Hesperetin	H	OH	H	OH	H	OH	OCH_3
Naringin	H	OH	H	OH	H	OH	OH
Tangeretin	H	OCH_3	OCH_3	OH	OCH_3	H	OCH_3
Nobiletin	H	OCH_3	OCH_3	OH	OCH_3	OCH_3	OCH_3
Chrysoeriol	OH	OH	H	OH	H	H	OCH_3
Limocitrin	OH	OH	H	OH	OCH_3	OCH_3	OH
Limocitrol	OH	OH	OCH_3	OH	OCH_3	OCH_3	OH
Quercetagetin	OH	OH	OH	OH	H	OH	OH
Naringenin	H	H	H	OH	H	H	OH
Isosakuranetin	H	H	H	OH	H	H	OCH_3

	R_1	R_2	R_3	R_4
Sakuratin	H	OCH_3	H	OH
3,5,4'-Trihydroxy-7,3'-dimethoxy-flavanone-glc	O-Glc	OCH_3	OCH_3	OH
Hesperetin	H	O-Glc	OH	OCH_3
Naringenin	H	O-Glc	H	OH
Narirutin 4'-glucoside	H	O-Glc-rha	H	O-Glc
Hesperedin	H	O-Glc-rha	OH	OCH_3
Narirutin	H	O-Glc-rha	H	OH
Isosakuranetin	H	O-Glc-rha	H	OCH_3



	R_1	R_2	R_3	R_4
Scoparone	H	OCH_3	OCH_3	H
Limetin	H	H	OCH_3	OCH_3
Osthol	H	H	OCH_3	$CH_2CHC(CH_3)_2$

	R_1	R_2
Xanthotoxin	H	OCH_3
Bergapten	OCH_3	H
Isopimpinellin	OCH_3	OCH_3
Bergaptol	$OH^{(I)}$	H

	R_1
a-Tocopherol	$CH_3^{(III)}$
g-Tocopherol	H

CH_4

Figure 7. Some phytochemical constituents of citrus wastes (peels, leaves, and seeds).

CONCLUSION

This study has shown that citrus byproducts (peels, leaves, and seeds), though may portend serious environmental hazards if not well managed but can be repurposed as a useful raw material because of their unique chemical entities, with novel biological functions, such as antioxidants, anti-inflammatory, prebiotic, antimicrobials, cytotoxic, antidiabetic, and insecticidal activities. Flavonoids (hesperidin, nobiletin, quercetin, and tangeretin), coumarins (isogosferol and isocoumarin), volatile oils (limonene, linalool, myrcene, and sabinene), fatty acids (palmitoleic, linolenic, and stearic acid), phenolic acids (*p*-coumaric acid, ferulic acid, and chlorogenic acid), alkaloids (citracridones, citramine, and citrusinine), and pectins are among the bioactive compounds of citrus wastes highlighted in this report.

Many of these bioactive constituents from citrus wastes are now sourced as useful ingredients for pharmaceutical (antioxidants and antibiotics), cosmeceutical (body cream, perfumes, and soaps), agricultural (biofertilizers and pesticides), food and beverages (fibers, sweeteners, and food additives), and industrial (biofuel and biosorbent) productions. Citrus byproducts are fast becoming the biogenic raw materials of choice, as alternatives to conventional adsorbents (e.g., zeolites and activated carbon), and to produce nano-cellulose for water and waste treatments.

In light of the above-mentioned applications, it has become apparent that the useful applications of citrus wastes would help to mitigate possible environmental hazards that are associated with their indiscriminate disposal. It would also help to improve health and social status and promote food security and industrialization for sustainable development. Nevertheless, there is a need to further exploit citrus wastes for their pharmacological potentials, as most studies were done to evaluate their biological properties at the *in vitro* and *in vivo* preclinical level. Thus, the bioavailability and tangible benefits of these byproducts can be fully harnessed by obtaining relevant clinical data on them.

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LIST OF ABBREVIATIONS

BGL: blood glucose level; CWE: citrus waste extract; COX-2: cyclooxygenase-2; DNA: deoxyribonucleic acid; EO: essential oil; IC_{50}: concentration at 50% inhibition; IκB: IkappaB kinase or IKK; IL-1β: Interleukin-1beta; iNOS: inducible nitric oxide synthase; LD_{50}: lethal dose; LPS: lipopolysaccharide; MIC: minimum inhibitory concentration; mRNA: messenger ribonucleic acid; NF-κB: nuclear factor kappa B; NO: nitric oxide; p50/p65: NF-κB heterodimer; RAW 264.7: a semi-adherent macrophage-like cell line derived from BALB/c mice; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-alpha.

AUTHOR CONTRIBUTIONS

Conceptualization and design—AOO (Adebola O. Oyedeji), YSH, OOO, SKK, GMM, AOO (Ayodeji O. Oriola); manuscript draft—DT and AOO (Ayodeji O. Oriola); revision of manuscript—AOO (Adebola O. Oyedeji), YSH, OOO, SKK. All authors approved the final version of the manuscript to be published.

CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used AI-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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