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Citrus Peels as a Source of Bioactive Compounds with Industrial and Therapeutic Applications

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Abstract

Agriculture wastes are considered a good starting point to discover for new drugs all over the world. In this context, Agriculture wastes contain millions of compounds to be screened to find bioactive compounds responsible for the activity to be used in drugs. Citrus agriculture is one of the most important commercial and industrial agricultural activities in the world. The peel waste of Citrus species is a rich source of bioactive compounds such as essential oils, flavones, polyphenols, and pigment. Citrus peel has been widely used in the medicine industry. The waste peel of citrus consider a rich source of pharmacologically active metabolites with antioxidant activities.

Keywords: Citrus waste, Phenolic compounds, Liminoids, Antioxidant activity, Therapeutic Activity, Industrial uses

1. Introduction

Agriculture crops, fruits, vegetables, cereals, bean crops produce large amount of wastes or by-products. These huge amounts of wastes could be of significant value if properly utilized. They could be more valuable than the main products and hence an added value will maximize these wastes. The main uses of these wastes are as animal feed or as compost used in enhancing soil fertility and used instead of chemical fertilization. Some products wastes such as banana stem waste can be used as an fiber for hand made paper and several grades of recycled papers. Beet waste can produce natural colors. Papaya is used as medicine (papain), toothpaste and meat tenderizers. Pine apple core for natural sweetener, grape pomace is a source of tartaric acid and polyphenols a natural antioxidants. Resveratrol a compound found in grape pomace known for its beneficial cardiovascular effects. Citrus peel includes cellulose, hemicellulose, lignin, pectin (galacturonic acid), chlorophyll pigments and other low molecular weight compounds (eg limonene) [1]. Polyphenol from grape seeds is used for management of Alzheimer disease [2]. Imitation vanilla is a liquid concentrate comes from treated wood pulp by –products.

In Egypt the major cultivated fruit trees are citrus, which came after mango and grapes in its cultivated area. Citrus has been cultivated in Egypt since ancient times,

and there are some types grown in different regions such as Baladi orange, sweet (sugar) orange, and blood orange mandarin, lime, lemon, grapefruit, sour orange, kumquat, shadouk, pummelo and citron. At present, the area of citrus cultivation has increased rapidly, as this area reached 204,095 hectares, representing about 29% of the total fruit area (700,854 hectares), while the total productive area reached about 175734 hectares, producing approximately 4.27 million metric tons [3]. In Egypt these wastes were a main sources of agricultural cultural waste. The main use of these wastes are as animal feed or as compost. However higher amounts of these wastes were burned in the field or thrown in water canals, causing hazards and environmental pollution [4]. Recycling of such residues is one suitable technology adopted in industrial and developed countries, because these wastes are high value product and their recovery may be economically attractive. Citrus juice production generates 15 million tons of waste annually in the world, including peels, seeds, and fruit pulp [5].

Recently there is increase in the use of plant byproducts. The availability, potentiality, no side effect and no cost of byproducts in comparison to modern therapeutic drugs for the treatment of dangerous diseases such as cancer, and Alzheimer makes them more attractive [2, 6, 7]. Citrus fruits are the biggest fruit sector production all over the world, at the same context, waste the dominant byproduct of Citrus processing industries [8]. These citrus fruit residues, which are generally discarded as waste in the environment, can act as potential nutraceutical resources. Due to their low cost and easy availability such wastes are capable of offering significant low-cost nutritional dietary supplements. The utilization of these bioactive rich citrus residues can provide an efficient, inexpensive, and environment friendly platform for the production of novel nutraceuticals or for the improvement of older ones.

Citrus by-products is a major source of phenolic compounds; flavonoids, [9]. These flavonoids belong to six classes and have different biological activities i.e. antioxidant, anticancer, antiviral and antiinflammatory. Dimou et al. 2019 on their review concluded that by-product of fruits and vegetables have an important role to be used as functional activity in cosmetics, nutraceuticals and as functional foods either in their raw material for additive processes or as ingredients for a new products [10]. Citrus waste have limonoids and flavonoids as their anticancer constituents. The most abundant citrus flavonoids, generally known as the flavanones, include hesperidin, naringin, narirutin, and neohesperidin, and these compounds have been found to provide health benefits such as antioxidative, anticancer, antiinflammatory, and cardiovascular protective activities. Furthermore, the consumption of naringin and hesperidin reduced cholesterol levels in hamsters by 32 to 40% [11].

2. Materials and methods

The peel waste of citrus fruit after juice extraction was obtained from a local food processing company. Samples were extracted using a different polar solvent. Yield extract of peels by different solvent was determined phenol contents according to Singleton et al., [12] total flavonoid were assayed by method Zhishen et al. [13].

Extract Limonin from citrus pee were prepared and purified according to the procedures Tian et al., and Tian et al. [14, 15]. A kilogram of powder peels was extracted (Soxhlet) overnight with hexane at 25°C to remove the oil. The solvent was changed to acetone and methanol sequentially to extract the peels. The methanol fraction was evaporated by a rotary evaporator under vacuum at 60°C and the residue was partitioned with 1:1 methylene chloride-water using an ultrasonic sonicator. The

methylen chloride fraction and the previous acetone fraction were combined and evaporated to dryness or purification of the limonoid aglycones. Limonin was purified by repeated crystallization in methylen chloride and isopropanol.

Extraction of the essential oils.a kilogram of citrus peel were macerated in 1Lof distilled water during 24 h before extraction. Peels were then submitted to Clevenger hydrodistillation for 3 h. The obtained the essential oils were dried over anhydrous sodium sulfate and after filtration stored at 4C. The yield of extraction was isolated according to Williams and Lasunzi [16].

3. Useful materials and compounds isolated from citrus peels

3.1 Useful materials, e.g. dietary fibers

Dietary fiber which is often classified as soluble fiber and insoluble fiber consists of a mixture of vegetable carbohydrate polymers, both oligosaccharides and polysaccharides, eg. Inulin, pectin, gums, cellulose, and resistant starch (**Figure 1**) [17]. Fewer sources of fiber. Apart from helping to avoid digestion, and absorption in the small intestine, fiber has one of the following functions, increases colon fermentation, lowers cholesterol levels and maintains insulin levels [17]. Healthy people prefer natural supplements for fear that synthetic ingredients could be a source of poisoning. A high fiber by-product that is high in fiber and bioactive constituents is a treat for food processors. Dietary fiber supplements can produce more economical diet with many health benefits. The average daily fiber requirement is 25 g per day for women and 38 g per day for men [18]. Most nutritionists suggest that 30% of our daily fiber intake should come from soluble fiber. Apart from health benefits, dietary fiber has several functional properties such as increased shelf life, water retention capacity, emulsion stability, oil retention capacity, viscosity or gelling, bile acid and binding capacity.

The wastes of whole grains, and fruits that are produced in large quantities every day can be used as value-added products. They provide fiber as well as bioactive constituents such as polyphenols and EOs and offer economic benefits to both producers and consumers. A typical example is the residue from the citrus waste treatment industry [19]. Garcia et al. reported that the addition of grain or fruit fiber,

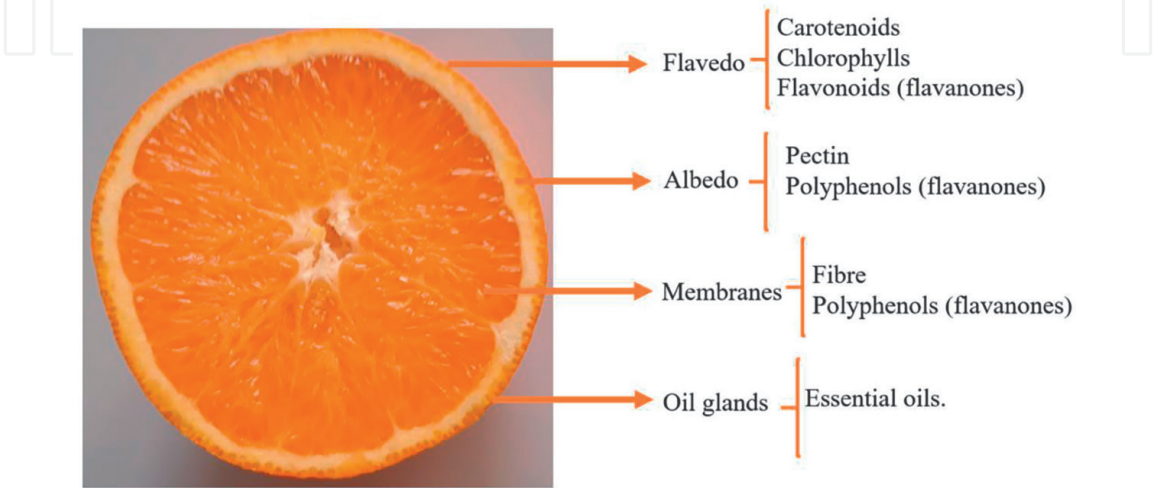


Figure 1.
Structure of peel from citrus sp.

especially citrus fiber, can be used as a fat substitute in dry fermented sausages [20]. Citrus fiber, which has a bioactive function due to the presence of components such as polyphenols, can be used as an effective inhibitor of lipid oxidation in meat products, thereby increasing oxidation stability and extending its shelf life [21].

Citrus fiber can also be used to reduce residual nitrite levels [22]. Citrus waste can be seen as a potential source of pectin [23]. Fiber consumption is often associated with a lower risk of life-threatening chronic diseases such as gastrointestinal disease, intestinal disease, diabetes, cardiovascular disease, obesity, cancer and improved physiological functions including lowering blood cholesterol, weight loss due to glucose [24]. The effectiveness of citrus waste on low plasma liver cholesterol, serum triglyceride levels, total serum cholesterol, total liver lipids and liver cholesterol [23] has been proven by many epidemiologists. The waste fiber extracted from citrus fruits is involved in improving intestinal function and health [25]. Waste, cellulose and waste fiber from *C. hystrix* and *C. maxima* can be used as potential food fiber sources for food fortification due to their high physicochemical properties.

3.2 Phenolic compounds, e.g. flavonoids

Total phenolics from orange, mandarin, and lemon were 178.90, 169.54, and 61.22 mg GAE /100 peel, respectively [26] and flavonoid was 80.94 to 87.71 mg/ rutin/100 g [27]. The main bioactive constituents known for their health benefits are phytochemicals, especially phenolic constituents found in vegetables and fruits. Studies report that phenols are not only present in edible parts of plants, but their presence has also been reported in inedible parts of plants with various biological effects. The mechanisms behind the contribution of phenolic constituents to improved health and prevention of related diseases include carcinogen inactivation, cell differentiation, maintenance of DNA repair, changes in estrogen metabolism and inhibition of N-nitrosamine formation. The main mechanisms for the antioxidant effects of phenolics in functional foods include metal chelating activity and free radical scavenging activity. It has been shown that reactive oxygen species such as superoxide radicals support human pathogenesis [28]. Phenols provide an effective way to prevent and treat free radical-mediated diseases such as cancer, neurodegenerative diseases, diabetes [29–31], the aging process [32] and cardiovascular dysfunction due to free radical scavenging and cooling ROS [33]. In addition, many of the antioxidants found in plants exhibit a variety of biological effects, including antiviral, antiallergic, anti-inflammatory, antibacterial, and antithrombotic effects [34].

Citrus considered one of the most popular fruit plants in the world, contains many active constituents that can protect health. In addition, it contains enough folic acid, vitamin C, pectin and potassium. Citrus species from various origins have been evaluated for their phytochemical composition and contribution to improved health [35], and it has been recognized that citrus species have promising biological properties, including anti-inflammatory, antiatherogenic, anti-tumor activity, anticoagulant and antioxidant activity [36].

Citrus waste has been shown to be rich in healthy constituents, including vitamin C, carotenoids, and polyphenol antioxidants [37]. Benamrouchea and Madania confirm that *C. sinensis* L. and *C. aurantium* L. [38]. wastes are powerful antioxidants. In the last decade, Interesting phytochemicals such as 40-geranyloxyferulic acid and boropinic acid have been found to have valuable pharmacological effects such as chemoprophylactic, anti-inflammatory, neuroprotective and antipyloric agents. *C. sinensis* is richest sources of phytochemicals such as 40-geranyloxyferulic acid and boropinic acid [39].

Flavonoids are phenolic constituents with the structure of phenylbenzopyrone which are two benzene rings connected by a linear triangular carbon chain with a carbonyl group in position C. The prevention of serious chronic disease has attracted the attention of many researchers. Citrus flavonoids include one group of glycosides, namely naringin, and hesperidin [40]. Wang et al. mentioned that a 117 flavonoid were isolated from different *citrus species* by using LC–MS/MS. The flavonoids were identified as 39 polymethoxylated flavonoids (PMFs), 7 flavones, 10 C-O-glycosylflavonoids, 44 O-glycosylflavonoids, 10 C-glycosylflavonoids and 7 newly O-glycosylpolymethoxylated flavonoids, O-glycosylated flavonoids [41]. Citrus flavonoids have been shown to have health-related properties that include cancer-fighting, antiviral, and anti-inflammatory activities, reducing capillary fragility, and limiting human platelet aggregation [42]. The broad biochemical functions of flavonoids in citrus waste have recently been extensively studied. They increase the antioxidant capacity of serum against lipid peroxidation and reduce oxidative stress in the elderly [43]. These constituents have beneficial effects of anti-inflammatory, anti-tumor anti-diabetes, neuroprotective agent and anti-atherosclerosis [44–47]. HPLC analysis of citrus waste extract showed that hesperidin was present in all extracts in the highest concentrations [48]. The flavonoid glycosides naringin, didimine, pontsirin, narirutin [49]. Several reports highlighted the relationship between structure and antioxidant activity of the flavonoid subclass in citrus extracts. Johan found that bioactive compounds of flavonoids were extracted from orange peel. The compounds were polymethoxylated flavones, flavanone-O-trisaccharides, flavone-O-disaccharides, and, finally, flavone-C-glycosid. Flavonoids showed to have antioxidant properties [50].

Dry mandarin waste is used as a traditional Chinese medicine to cure various diseases including dyspepsia, bronchial asthma and cardiovascular disease [51]. Numerous scientific studies report that it is a rich source of many flavonoids, especially flavonoid glycosides, which play an important role in protecting against life-threatening diseases such as neurodegenerative disorders, atherogenesis and cancer [52–54].

3.3 Essential oils, e.g. limonoids

This citrus fruit is one of the most original oranges in Egypt. It is important to note that the citrus wastes variety offers an excellent EC yield. GC–MS analysis of citrus wastes essential oil EO identified many bioactive components. Terpenes form base-grade constituents and d-limonene. Interestingly, the resulting EO of orange waste showed remarkable antibacterial activity against *C. acnes*, which is a potential therapy for the treatment of acne. However, further research is needed to investigate the mechanism of their biological activity and its effect on *C. acnes* in order to exploit this EG on a commercial scale. Citrus EO is an important biologically active ingredient in orange wastes. It is collected intensively in the oil glands of orange wastes [55]. On average, it makes up about 1–3% of the skin weight of fresh orange wastes [56]. Citrus EO consists many different constituents depending on the citrus variety [57]. The ingredients also differ significantly depending on the method of extraction [58]. Citrus EO is widely used in the chemical, medical and food due to its pleasant aroma, antimicrobial activity, and antioxidant properties. The nature of EO is very attractive. Previous research has shown that orange EO has a broad spectrum of antimicrobial activity against yeasts, fungi, and bacteria and that activity mainly depends on the EO constituents [59].

Limonoids are a unique class of highly oxygenated tetracyclic triterpenoids, Members of the class limonoids have wide health-promoting and disease-preventing activities, including anticancer, antibacterial, antioxidant, larvicidal, antimalarial

and antiviral activities, and thus has potential applications in nutraceuticals, pharmaceuticals and agriculture [60]. Kikuchi et al. mentioned that a new limonoids has been isolated from *Satsuma orange* and characterized as limonoids 1–5; 21,23-dihydro-21-hydroxy-23-oxonomilin (1), 21,23-dihydro-23-methoxy-21-oxonomilin (2), 21,23-dihydro-21-hydroxy-23-oxonomilinic acid methylester (3), 21,23-dihydro-23-methoxy-21-oxolimonin (4), and 21,23-dihydro-21-oxolimonin (5), along with known compounds (6–12) (**Figure 2**) [61]. The most important citrus fruits are mandarin (*C. reticulata*), bergamot (*C. bergamia*), bitter orange (*C. aurantium*), lime (*C. aurantifolia*), sweet orange (*C. sinensis*), and lemon (*C. limon*) [62]. The citrus limonoids are responsible for a wide variety of therapeutic properties such as antiviral, antifungal, antibacterial and antimalarial [63]. Senevirathne et al. and Miyake et al. reported on the occurrence of limonoid in large amount in citrus juice and citrus tissue as water soluble glycosides and found in seeds as water insoluble glycones [64, 65]. The latter is responsible for delaying the bitterness of citrus fruit. These limonoids are converted to the non bitter glycosides during maturation. These limonoids are similar to the limonoid found in Neem seeds and possess insecticidal activity.

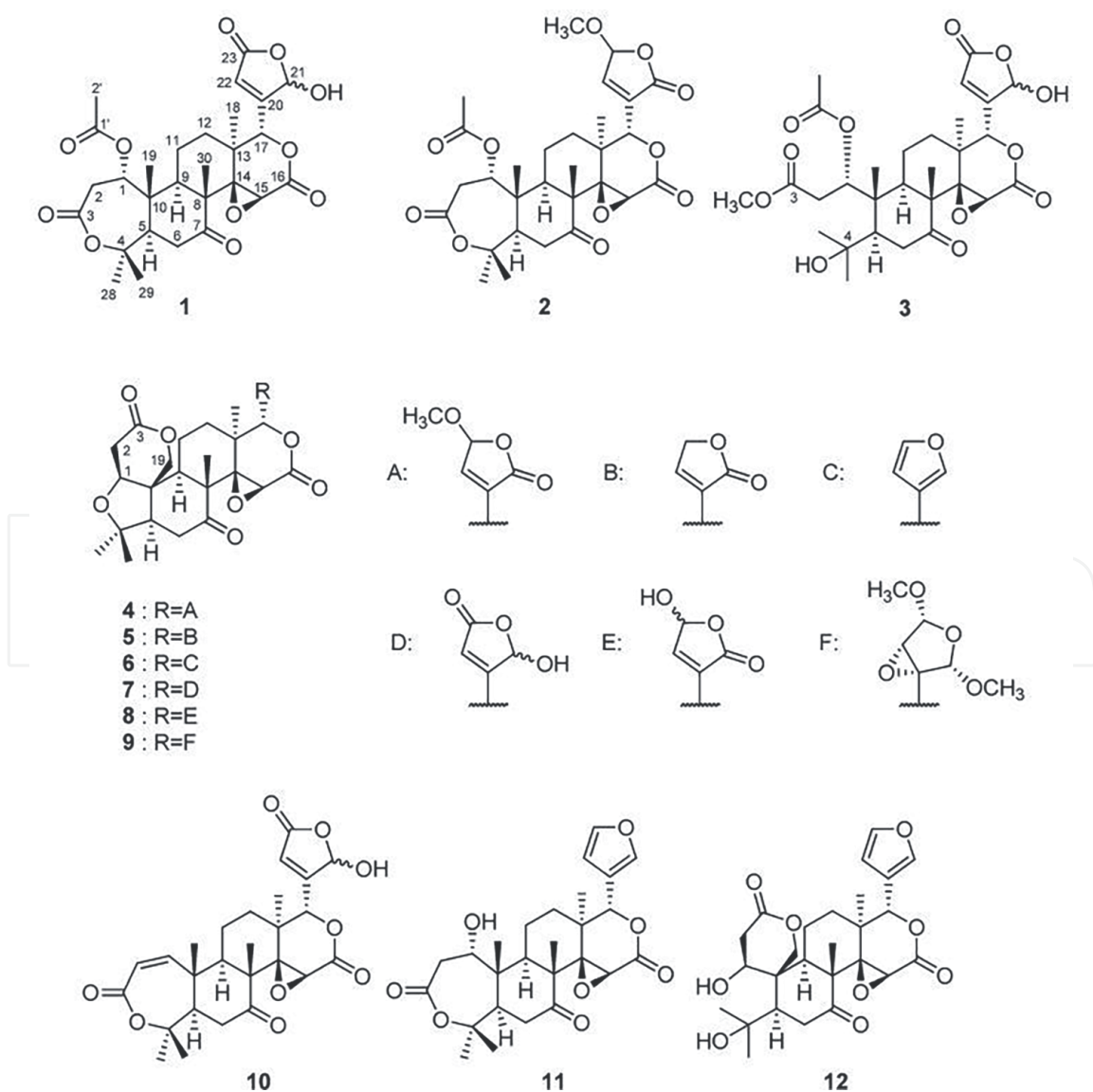


Figure 2.
New limonoids isolated from Satsuma orange.

The potential of citrus limonoids as anticancer agent was studied by Jacob et al. [66]. They concluded that limonin and nomilin topical application showed 60% reduction in tumor burden, however nomilin is less effective. Limonine glycoside and as aglycone administered in vitro to estrogen dependent and independent human breast cancer cell lines proved that the limonoids were equally potent like the standard drug tamoxifen for inhibiting the proliferation of estrogen dependant breast cancer cells, while more potent than tamoxifen for its activity against estrogen independent cancer cells.

4. Conclusions

Recent research on the functional properties of citrus wastes has added to our knowledge. Due to the low cost and availability of leftover fruit, which if not disposed of as environmental waste, should be seen as a potential source of nutrients capable of providing significant inexpensive nutritional supplements. Good use of citrus peels in the production of polystyrene. Polystyrene is one of the most common thermoplastic polymers used in the production of packaging materials and household and consumer goods. This unwanted manufacturing waste is rich in bioactive constituents and can be recycled as a value-added nutritional supplement that provides beneficial phenols, flavonoids, EOs, and fiber. They function as calorie-free fillers, enhance emulsions, increase water and oil retention, and can prevent a wide variety of ailments. Citrus waste extract holds promise as a source of bioactive constituents in the food industry. Some of the vital compounds extracted from citrus peels such as limonene, pectin, myrcene, and α -Pinene are used for flavor and good smell as safe food additives. Peels are a rich source of micro-nutrients and can be used as a source to improve the growth of agricultural crops and feed animals. According to literature, the biologically active compounds in the citrus peel can effectively prevent or inhibit diseases, enhance immune function, prevent cancer, and have antioxidant activity. In addition, the use of identified citrus waste will also help reduce pollution problems caused by poor residue disposal. Further research is needed to determine the bioavailability of this waste extract *in vivo*.

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Conflict of interest

The authors declare no conflict of interest.

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