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Bioactive Compounds from By-Products and Food Wastes: Recent Developments in their Health Benefits

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Abstract

Background: Agro-waste and by-products pose social, economic, and environmental problems, hence they are a growing source of concern. Due to the potential for these materials to be used as sources for useful product development and the rising demand for natural bioactive compounds, the conversion of food waste and by-products is garnering more and more attention. Agricultural production and the food supply chain are the main sources of food wastes, which are discarded and used as animal feed. These by-products contain bioactive compounds with great nutritional, functional properties associated with health-related benefits.
Scope and approach: This review describes the current scientific studies regarding bioactive compounds present in food wastes and by-products of the agro-food supply chain, as well as their health benefits. These findings intend to contribute for future research concerning novel functional food, nutraceutical and pharmaceutical product development based on food wastes & by-products.
Key findings and conclusion: Polyphenols, Terpenoids, Alkaloids, and other nitrogen-containing constituents, are examples of bioactive compounds that exhibit a variety of positive effects due to their anti-inflammatory and antioxidant properties. These compounds are present in a variety of fruits, vegetables, spices, grains, and their derived foods and beverages including fruit juices, tea, chocolates, essential oils, beer, wine, etc. Moreover, these by-products also present therapeutic properties including anti-diabetic, antioxidant, antihypertensive, anti-inflammatory, antiulcer, antitumor, hypocholesterolemic, hepato-, nephron- and neuro-protective effects and antibacterial properties fully justified by the presence of bioactive compounds. Therefore, these food wastes and by-products can be considered good candidates for the development of functional foods, nutraceutical and cosmeceutical, contributing to promote sustainability across food chain and achieving zero waste generation. Nevertheless, more research is needed on their clinical studies to fully support the development of functional foods, nutraceutical and pharmaceutical applications.

Keywords: *bioactive compounds; by-products; food wastes; health benefits; natural extracts*

Introduction

Functional foods, plant-derived nutraceuticals, and dietary supplements have recently embodied health-promoting ingredients that can improve human well-being. Functional foods, dietary supplements and nutraceuticals contain, beyond the nutritional components, bioactive compounds with health benefits (Sachdeva et al., 2020; Gul et al., 2016; Granado-Lorencio and Hernández-Alvarez 2016; Santos-Buelga et al., 2019; Granato 2020). The majority of so-called bioactive compounds are phenolic compounds (PCs), which include terpenoids (carotenoids and phytosterols), polyphenols, alkaloids, and other nitrogen-containing constituents (glucosinolates). These compounds can be found in vegetables, fruits, grains, spices, and their derived foods and beverages, including fruit juices, tea, chocolate, essential oils, wine, beer, etc. (Dillard and German 2000). The largest group of non-nutrient dietary PCs are secondary metabolites synthesized by plants under normal and stress conditions (Cheynier et al., 2013). PCs include polyphenols which, based on their structural characteristics, are subdivided into three major classes: flavonoids, non-flavonoids and phenolic acids (Zhang and Tsao 2016).
Due to their antioxidant and anti-inflammatory properties, polyphenol compounds exert numerous beneficial effects (Shahidi and Ambigaipalan 2015). In addition to acting as metal (Fe^{2+}) chelators, polyphenol compounds also act as chain breakers of lipid peroxidation reactions, which inhibit oxidant enzymes (e.g. xanthine oxidase) and modulate cellular signaling processes that interfere with protein and lipid kinase pathways (Tsao 2010). In addition, polyphenols enable the restoration of the endogenous antioxidant pool (including catalase, glutathione, peroxidase and superoxide dismutase), which is reduced due to a high rate of elimination (Uttara et al., 2009). Adequate amounts of antioxidants must be supplied by the diet or dietary supplements to maintain redox homeostasis (Liu 2003). According to several epidemiological studies, a diet rich in antioxidant polyphenol compounds (primarily flavonoids, phenolic acids, lignans, stilbenes, tannins and anthocyanins) or the intake of polyphenol-rich derivatives, appears to favor a delay in the onset of degenerative diseases such as brain dysfunctions, cancers, cardiovascular injuries, and metabolic disorders, in which oxidative stress plays a

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significant role (Liu 2003; Tressera-Rimbau et al., 2017). According to several studies, eating foods high in flavanones (naringenin) and flavonols (quercetin), such as apples, onions, oranges, and grapefruit, lowers the risk of cardiovascular disease and tumor growth (Somerset and Johannot 2008; Benavente-García and Castillo 2008; Mahmoud et al., 2019; Sánchez Macarro et al., 2020; Tajaldini et al., 2020; Asgharian et al., 2022). Specifically, a number of active systems have been developed recently using the flavonoid quercetin, primarily utilizing its antioxidant properties to stop oxidation processes in food products (Montone et al., 2022). In addition to its well-known antioxidant activity, some authors suggest that this flavonoid has antimicrobial activity against Gram-positive and Gram-negative bacteria *in vitro* and through a shelf-life study on food products (Malvano et al., 2022; Malvano et al., 2021). Additionally, studies on flavonoids' anti-inflammatory activity, particularly those of quercetin glycoside compounds, were conducted. When quercetin is more exposed on the surface of nanoparticles, Montone et al. (2021) observed a significant decrease in cytokine production during infection of the human macrophage cell line U93, particularly IL8. Indeed, these components play a key role in the prevention of non-communicable diseases, like type 2 diabetes, certain cancers, and neurodegenerative diseases as well as cardiovascular diseases. (Koch 2019). Therefore, the intake of phenolic compounds is part of a healthy diet. Today, many people follow a vegetarian lifestyle and consume more fruits, vegetables, and agricultural products as a result of the knowledge of the beneficial effects of bioactive compounds on health. However, the production of food and the food supply chain are significant sources of waste biomass. A large amount of agro-industry wastes and by-products, such as leaves, peels, seeds, stems, shells, and skins, are produced throughout the entire food life cycle, from the cultivation, through industrial manufacturing to market (Helkar et al., 2016).

Because of this, it has been predicted that vegetable and fruit wastes would increase in the near future, posing an unavoidable environmental burden. Therefore, efficient waste disposal is required to prevent unfavorable and severe environmental effects (Mahawar et al., 2020). But, since proper wastes disposal embodies a cost to the circular economy, a model of economy has been proposed by Romani et al., (2019) as a solution to minimize raw material input and waste production, where by-products are not waste but resources to be valorized and reused. Agri-food processing residues are recognized as materials of high biorefinery potential, due to their unique composition, offering a range of opportunities for the sustainable production of food, feed, chemicals and energy (Makris and Sahin).

The aim of this review is to highlight current research demonstrating various potential uses of wastes and by-products of the agro-food supply chain, which can have various applications such development of novel functional foods, nutraceuticals, pharmaceuticals, and cosmeceuticals. Extracts derived from fruit and vegetable wastes have recently attracted the attention of researchers because they offer a means of utilizing waste production for the development of novel formulations that can have a substantial positive impact on human health (Sorrenti et al. 2023; Bhandari et al., 2013; Karam et al., 2016; Neacsu et al., 2015; Sharma et al., 2017; Cook et al., 2022).

In this review, we focus on the main bioactive compounds present in the most popular fruits eaten worldwide such as Citrus fruits, Mango, Avocado, Watermelon and Papaya.

Bioactive Compounds Obtained from Wastes and Innovative Applications

The following paragraphs discussed the main bioactive compounds present in the most popular fruits eaten worldwide.

Health Benefits of Citrus Fruit Waste and Its Utilization

Citrus fruits, like oranges, lemons, grapefruits, limes, tangerines and mandarins, are among the most popular fruits grown globally (FAOSTAT 2021). The Citrus genus belongs to the *Rutaceae* family, subfamily *Aurantioideae*, and it has long been known for its beneficial effects on health. These plant groups contain many beneficial nutrients and bioactive compounds, which could lower the risk of various chronic diseases (e.g., cardiovascular diseases and metabolic disorders) (Yamada et al., 2011; Deng et al., 2022; Siti et al., 2022). Citrus fruits have numerous biological functions including antimicrobial, anticancer, antidiabetic, antiplatelet aggregation, and anti-inflammatory activities, which have been highlighted in numerous studies (Sharma et al., 2017). Furthermore, Abdelghffar et al., (2021) recently reported the chemopreventive effect of orange peel extract against cyclophosphamide-induced organ toxicity in an *in vivo* model.

Citrus fruits are primarily grown in tropical and subtropical areas because of the soil and climate there, which are ideal for their growth. Due to a rise in citrus fruit output each year, there is also an increase in the waste produced during processing. Only 45% of the weight of the total citrus fruit is used, with the peel, pulp, and seeds being thrown away, while about a fifth of all citrus cultivars are subjected to industrial processes (Mahato et al., 2019). Also, tree pruning is used to enhance the fruit's quality, which results in a lot of leaves being produced as a by-product, adding to the already considerable amount of citrus waste (Leporini et al., 2021; Russo et al., 2021).

Waste from citrus fruit includes the fruit's seeds, peels, pomace, membrane remnants, secondary juice (obtained by pressing the pulp that was left over after the primary juice was extracted), and leaves. It has significant economic

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worth; in fact, a number of alternate uses for controlling citrus fruit waste have been suggested. In the food, pharmaceutical, and cosmetic industries, all of these wastes can be used as sources of bioactive compounds, to preserve food, and as a renewable energy source (Osorio et al., 2021; Chavan et al., 2018; Muscat et al., 2021).

Citrus peel can have a phenolic content of up to 5000 mg/g, which is more than the fruit's edible portion (Matsuo et al., 2019). Terpenoids and phenolics are the major subclasses of bioactive compounds found in citrus fruits. The main examples of the terpenoids are carotenoids and limonoids, whereas the main examples of phenolic compounds present in citrus fruits and in their wastes are flavonoids (hesperidin, naringenin, quercetin, naringin and rutin), phenolic acids and coumarins (Zou et al., 2016; Mahato et al., 2018; Sorrenti et al. 2023)

Two classes of carotenoids can be distinguished: carotenes, like β–carotene and lycopene and xanthophylls, which are oxygenated carotenoids like lutein and violaxanthin, (Saini et al., 2018; Sharma et al., 2021). They are precursors of vitamin A, which promotes the proper functioning of vision, strengthening of the immune system and is involved in epithelial tissue growth (Widjaja-Adhi et al., 2018; Cirmi et al., 2016). Hydroxybenzoic (gallic, vanillic and syringic acids) and hydroxycinnamic acids (caffeic, ferulic, p-coumaric and sinapic acids), classified as phenolic acids, are also present, which are known to possess high levels of free-radical-scavenging activity (Kim and Kim 2016; Kumar and Goel 2019).

The Citrus fruit plants contain essential oils, which are plant secondary metabolites and comprise a mixture of volatile compounds, usually found in the oil sacs of citrus peels and cuticles (El Asbahani et al., 2015). Essential oils have been used as bio-preservatives in all types of food with the purpose of extending their shelf-life due to their antioxidant, antimicrobial and insecticidal properties (Fernández-López and Viuda-Martos 2018).

Additionally, it has been demonstrated that aqueous orange peel extract has a variety of food applications including supplementing in minced beef to suppress lipid oxidation (Nupur et al., 2022) and milk to increase the antioxidant activity and total polyphenol content to decrease the total microbial count (Jalilzadeh-Afshari et al., 2021). Interestingly, citrus peel infusions were found to strongly suppress MAO activity, suggesting that they may be effective dietary approaches for the management and prevention of neurodegenerative diseases (Ademosun and Oboh 2014; Ayokunle 2022).

These essential oils can be used in sustainable green chemistry to replace chemical additives because the US Food and Drug Administration (FDA) considers them generally recognized as safe (GRAS) products (Fernández-López and Viuda-Martos 2018). The lipid components of citrus contain more than 200 different components, most of which are aldehydes, ketones, esters, acids, terpenes, and alcohols (Saini et al., 2022). The antimicrobial ability of these essential oils and major components against bacteria and yeasts showed that these are more effective on Gram-positive bacteria, Gram-negative bacteria and yeasts (Barraquer 1989).

Citrus fruit wastes are widely used in the cosmetic industry both due to their high content of bioactive compounds natural oils. Nowadays agro-industrial waste is also utilized as an active ingredient to obtain skincare products due to it being a rich source of bioactive compounds, antioxidants, vitamins (vitamin C and E) and polyphenolic compounds (Pinto et al., 2021). Citrus peel contains antioxidants that delay the aging process of the skin, reduce oxidative damage, and help with other skin-related problems including acne, wrinkles, dark spots, etc. Sebghatollahi et al., 2022. A research conducted by Wuttisin et al. 2017 confirmed that orange peel extract can be useful in the cosmetic industry for increasing the value of orange peel waste. The research focused on checking the anti-tyrosinase activity of orange (Citrus sinesis L.) peel extract, with the aim of formulating whitening cream that aids in preventing the production and accumulation of melanin pigment. Orange peel-based cream was discovered to have a 17.33% reduction in melanin pigment. Due to their richness in natural oils, citrus seeds are also utilized in the cosmetic industry to make soaps, body lotions, body sprays and other cosmetic products (Rosa et al., 2019). Citrus seed oil was used to make a soap by Atolani et al. that had exceptional anti-microbial, anti-fungal, anti-parasitic, and antioxidant properties. Moreover, using citrus seed oils to make cosmetic products might avert exposure to synthetic chemicals. Citrus pomace is another citrus waste that can be used as a pectin source (Zannini et al., 2021). Citrus residues have a high pectin content which has been used in the field of nanotechnology as an encapsulating agent for improving the stability, as well as the efficiency, of encapsulation (Panwar et al., 2021). For example, using a hydro-soluble component of citrus waste (pectin), citric acid, Ca^{2+} ion and ascorbic acid, citrus peel waste-based oil emulsion was fabricated. The prepared emulsion was stable and had a reduced droplet size, according to the study (Ren et al., 2020).

Additionally, in vitro research revealed that encapsulated resveratrol had a higher bioavailability than free resveratrol. In addition, it was shown that resveratrol's antioxidant properties were improved (Huang et al., 2019). So it stands to reason that citrus by-products might be used as encapsulants.

Avocado Fruit Wastes: Utilization of By-Products

Avocado (*Persea americana* Mill.) is a subtropical/tropical fruit indigenous to Mexico and Central America. It is cultivated and consumed widely all over the world. The avocado fruit is a drupe constituting an epicarp (peel), mesocarp (pulp) and endocarp (seed), the size, shape, color and phytochemical content of which are determined

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by the genotype. It belongs to the *Lauraceae* family and the genus *Persea*, of which there are more than 150 known species (Araújo et al., 2020; Sorrenti et al. 2023).

As reported by the FAO, over six million tons of avocado are produced annually around the world (FAO 2020). Avocado wastes are thought to be a cause of environmental contamination and comprise the peel, seed, and defatted paste. However, as previously said, wastes can be utilized because of their abundance of protein, fibre, and numerous bioactive compounds (Dalle Mulle Santos et al., 2016; Salazar-López et al., 2020).

As described by Yahia and Woolf, 2011, avocado pulp is a good source of vitamins (e.g. vit. C, E and K, choline, niacin and pantothenic acid) and minerals, protein, carbohydrates and dietary fibers. Nevertheless, the avocado fruit is well recognized for its high lipid content (about 12–24% of the whole fruit). Monounsaturated fatty acids such as oleic acid (62.14%), palmitic (17.2%), linoleic (11.11%) and palmitoleic (7.34%) and polar lipids, such as glycolipids and phospholipids, which are crucial, especially for cell membranes, make up the majority of the lipids present. The avocado's peel and seed, which are by-products, are abundant sources of minerals (seed: 1.3–4.3%; peel: 1.5–6.0%), proteins (seed: 0.14–9%; peel: 0.17–8%), lipids (seed: 3–15%; peel: 2–9%), fibers (seed: 2–4.2; peel: 1.3–55%), carbohydrates (seed: 42–81%; peel: 43–81%) and various other bioactive compounds (Araújo et al., 2020). According to Rodríguez-Carpena et al., (2011), Avocado fruit is rich in phenolic compounds, which are particularly abundant in its peel and seed. The most relevant types of phenolic compound present in avocado fruit are tannins phenolic acids and flavonoids (Indelicato et al., 2017; Tremocoldi et al., 2018). The lipid fraction of avocado fruit and its by-products contains polyhydroxylated fatty alcohol derivates (PFAs), which are more polar than fatty acids due to their hydroxyl groups. Two main avocado-derived PFAs: 1-ace-toxy-2,4-dihydroxy-heptadec-16-ene (PFA-A) and 1-acetoxy-2,4-dihydroxyheptadec-16-ene (PFA-B), with relative concentration percentages of 32% and 54% in the seeds, and 51% and 29% in the pulp, respectively was identified by Rosenblat et al. (2011). Acetogenins, a type of PFA whose chemical structure contains a long-chain fatty acid with a terminal -lactone, are characteristically found in avocado mesocarp and seed. The acetogenin profile and concentration have been shown to vary in avocado seed during early ripening, with no change in the mesocarp (Rodríguez-López et al., 2017).

Other minor ingredients found in avocado fruit and its by-products include carotenoids, alkaloids, phytosterols, and tocopherols, among others. Therefore, based on the available scientific evidence, avocado residue extracts (peel, seed coat, and seed extracts) may be employed as functional ingredients to be added to nutraceuticals or novel food products (Velderrain-Rodríguez et al., 2021; Figueroa et al., 2021; Cerda-Opazo et al., 2021).

Nevertheless, due to their antioxidant, antiproliferative, and anti-inflammatory activities, consuming foods high in these phenolic compounds on a regular basis has been linked health-related benefits. According to certain studies, avocado residues may be used to obtain extracts high in phenolics that have antiproliferative properties and could be used to prevent or cure cancer. It has been suggested that avocado peel extracts may induce apoptosis in MDA-MB-231 cells as a result of increased activation of caspase 3 and caspase 3 target protein PARP. On the other hand, avocado seed extracts have shown anti-inflammatory and antiproliferative activities against the HCT-116 (colorectal carcinoma) and the HepG-2 (liver cancer) cell lines in a dose-dependent manner (Velderrain-Rodríguez et al., 2021). Avocado fruit is rich in lipid molecules such as PFAs which have received attention as useful cytotoxic molecules; indeed, certain studies have demonstrated their cytotoxic effects on various cell types, which have been linked mainly with apoptosis induction. More than 20 groups of bioactive compounds, including long-chain lipid molecules such as avocatins, pahuatins, persenins, have been associated with avocado's anti-cancer activities. Ethanolic extract of immature avocado fruit (which contained higher proportion of persin) demonstrated cytotoxic activity against different cell lines including lung carcinoma cells (A549), kidney cells (A498), pancreas (PaCa2), breast adenocarcinoma (MCF-7), colon (HT-29) and prostate (PC-3) (Ochoa-Zarzosa et al., 2021). Avocatin B, predominant in avocado seed and peel, had greater selectivity towards cancer cells (Lee et al., 2015; Sorrenti et al., 2023).

The photoprotective and anti-inflammatory potential of PFA derived from the seed of avocado fruit was described in another study. It examined the protective properties of PFA against UVB irradiation in cultured keratinocyte and in a human skin explant. In human skin explants, the photoprotective effect was demonstrated by higher cell viability and fewer number of sunburnt cells. Furthermore, improved DNA repair was demonstrated by measuring the removal of cyclobutane pyrimidine dimers (CPD), one of the most important characteristics of DNA damage and mutagenesis. The exposure of keratinocytes to 20 mJ/cm^2 UVB induced the formation of CPD, as was measured immediately after irradiation. CPD elimination for 24 hours was achieved in the PFA-treated cells (Rosenblat et al., 2011).

Mango Fruits: Health Benefits of Mango Waste Extracts

Mango is a tropical fruit belonging to the *Anacardiaceae* family. India, China, Thailand, Indonesia, the Philippines, Pakistan and Mexico are among the tropical and subtropical mango-producing countries (Sorrenti et al. 2023)

The plant's scientific name is *Mangifera indica*. The fruit is divided into three distinct parts: a large seed (or endocarp) surrounded by a yellow-orange pulp that makes up about 40–65% of the average weight, and the peel

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(or epicarp). The edible part of the fruit is the pulp, the remaining part is usually discarded (Mirza et al., 2021). The main consumable part of the mango is the mango pulp and it is the source of nutritional compounds including reducing sugars, amino acids, aromatic compounds and functional compounds, like vitamins, pectin, polyphenols and anthocyanins (Quintana et al., 2021). Mango intake has been recently reported to exert beneficial effects in slowing the progression and reducing the IBD severity (Kim et al., 2020).

Mango processing generates peels and kernels as wastes, which also contain functional compounds. Protocatechuic acids, mangiferin and β–carotene, which are found in mango peels, are known for their anti-diabetic, anti-inflammatory, anti-carcinogenic and antimicrobial properties (Mirza et al., 2021; Jahurul et al., 2015; Saleem et al., 2019; Donga et al., 2020).

Mango peels have a high content of polyphenols, enzymes and vitamins C and E. In particular, ethylgallate and penta-*O*-galloyl-glucose are two of the bioactive compounds that have been isolated in the peel. In addition to having important antioxidant activity (hydroxyl radical ($OH^{\bullet}$), superoxide anion ($^{\bullet}O_2^-$) and singlet oxygen ($^1O_2$)-scavenging activities), gallate derivatives (e.g., penta-*O*-galloyl-glucoside) have been the subject of several studies that have demonstrated their bioactivity, including anticancer (Lizárraga-Velázquez et al., 2020; Lizarraga et al., 2008), antioxidant (Hatano et al., 1989), anti-cardiovascular (Ignarro et al., 2007) and hepatoprotective effects (Eun-Jeon et al., 2008).

Kim et al., (2010) in this regard, tested the antioxidant and cytoprotective properties of a mango peel extract on H_2O_2-induced oxidative damage in a human hepatocarcinoma cell line (HepG2). Mango peel extract exhibited significant antiproliferative effect against the tested cancer cell lines in a dose-dependent manner. Compared to the mango pulp and peel, the mango kernel contains higher amounts of polyphenols and antioxidants. It is used for oil extraction and for preparing nutraceuticals by combining it with corn and wheat flour (Lebaka et al., 2021). Agro-industrial by-products are sources of bioactive compounds according to Silva et al., (2014) who revealed that mango by-products showed higher levels of β-carotene and lycopene, as well as anthocyanins and yellow flavonoids, when compared to the fruit pulps. The anti-cancer effect of *Mangifera indica* L. Peel extract (MPE) is associated with γH2AX-mediated apoptosis in colon cancer cells according to Lauricella et al., (2019) demonstrated that. The authors characterized the polyphenolic profile of MPE and proved, for the first time, the presence of lepidimoic acid, a pectic disaccharide, in mango peel. The findings obtained by Lauricella et al., (2019) provided a new insight into the potential anti-tumor benefits of mango peel as a supportive strategy for antineoplastic therapies.

Watermelon Fruits: Health Benefits of Watermelon Waste Extracts

Watermelon (*Citrullus lanatus*) is a fruit vegetable, belongs to the genus *Citrullus* and the family Cucurbitaceae native to tropical areas of Africa near Kalahari Desert. (Naz et al. 2014; Kyriacou et al. 2018; Renner et al. 2017; Maoto et al., 2019). It is known as a “pepo” by Botanists, which is a fruit having a thick rind and fleshy center (Mehra et al., 2015). Because of its ability to refresh, appealing color, delicate flavor, and high water content to quench summer thirst, it is widely consumed as a refreshing fruit in the summer (Romdhane et al., 2017). Lycopene and β-carotene are carotenoids responsible for the red and orange colors of the watermelon, respectively. The watermelon sweetness is primarily due to a combination of sucrose, glucose, and fructose. In a ripe watermelon, sucrose and glucose account for 20–40% and fructose for 30–50% of total sugars (Bianchi et al., 2018). Watermelon contains nutrients and phytochemicals reported to be beneficial to human health (Choudhary et al., 2015; Elumalai et al., 2013; DeWeese et al., 2017; Ijah et al., . 2015Maoto et al., 2019). It is a good source of vitamins B, C, and E as well as minerals such as phosphorus, magnesium, calcium, and iron (Romdhane et al., 2017). Epidemiological studies have shown that it possesses antioxidants with anti-inflammatory, antihypertensive properties as well as a protective effect against carbon tetrachloride-induced toxicity (Choudhary et al., 2015; Ijah et al., 2015).

The biomass of a watermelon may be divided into three primary parts: the flesh, the seed, and the rind. The watermelon's flesh makes up around 40% of its weight, while the rind and seeds make up about 60% of the entire fruit. This results in a significant amount of agricultural waste when compared to the peels of other fruits that are similar, such as melon (40%), pumpkin (45%), bitter apple (30%), musk melon (35%), and papaya (47%), etc. (Chakrabarty et al., 2020; Zamuz et al., 2021). Half of the watermelon fruit is edible while the other half goes to waste. Considering the production of watermelon in 2017–18, approximately 42 million tonnes of watermelon by-products (rind and seeds) was generated by various fruit juice processing industries, cottage fruit juice producers, and restaurants during production, preparation and consumption of watermelon. Despite being edible, these by-products are discarded indiscriminately into the environment and thereby constituting environmental problems (Esparza, et al. 2020). Watermelon rind (WMR) and watermelon seeds (WMSs) can represent a low-cost raw material (Hasanin, Hashem, Abd El-Sayed, & El-Saied, 2020; Zia et al. 2021), rich in potentially valuable components for other industries.

WMR is a thick white flesh between the outer green covering and inner red flesh, accounts for approximately one-third of the total fruit mass and is usually discarded, despite being edible; however, most times it is avoided due to its unappealing flavor. WMR structure generally comprises of a combination of hemicelluloses, celluloses,

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lignin and pectin with entrapped sugars, proteins, polyphenolics, citrulline, lycopene and carotenoids (Zia et al. 2021). Watermelon by-products have been the subject of several studies that have proved their bioactivity.

Owo & Beresford, (2020) reported that WMR exerts an anti-diabetic effect by attenuating the decreasing serum insulin level and increasing blood glucose level and might be recommended as a hypoglycaemic drug in the treatment of diabetes mellitus in alloxan-induced diabetic Wistar rats. It was proved from numerous investigations that WMR has hypoglycaemic effects on diabetes by improving the histological structure of the pancreas and/or by an increased level of insulin and improving glucose metabolism in experimental induced diabetic animal models (Abu-Hiamed, 2018; As'ari & Sugiyanta, 2020).

The antiproliferative activity of isolated polysaccharides from WMR was evaluated by Dammak et al. (2019) and results showed that these polysaccharides exhibit significant cytotoxic activity against human laryngeal carcinoma Hep-2 cells.

According to Soliman, (2019) WMR extract mixed with polyvinyl alcohol (PVA) used to fabricate electrospun nanofibers showed 1.2 folds higher antimicrobial activity than that of WMR extract alone. The finding showed WMR/PVA nanofiber showed 83.5 ± 0.09% and 94 ± 0.8% area of inhibition of *E. coli* and *S. aureus*.

Oral administration of aqueous extract of WMSs (200, 400 and 600 mg/kg BW for 7 and 21 days) ameliorated alloxan-induced hepatic or nephrotoxicity in diabetic Wistar rats by significantly decreasing urea, creatinine and malondialdehyde (MDA) levels and liver enzyme activities (Ogbeifun, Peters, & Monanu, 2020). Antioxidant peptides purified from WMS protein hydrolysates showed a cytoprotective effect by protecting HepG2 cells from H2O2-induced oxidative damage by significantly enhancing the activities of antioxidative enzymes, inhibiting ROS and MDA level (Wen et al., 2020).

The pharmacokinetic behavior of bioactive compounds present in watermelon flesh, seeds and rind in human plasma was reported by Fan et al. (2020). L-citrulline and arginine (two major amino acids) are metabolized to nitric oxide, an important vasodilator, in the body which plays an important physiological role in the regulation of blood pressure and endothelial function by maintain the vascular health.

Karikpo, Bartimaeus, and Holy (2018) reported WMSs extract to possess substantial cardioprotective potential by ameliorating structural integrity of the cardiac muscles and significantly decreasing the levels of creatine kinase and lactate dehydrogenase (a marker of cardiac injury) in streptozotocin-induced diabetic albino rats.

The anti-hypertensive effect of WMSs in males and females rats by administrating 50 g daily for 40 days was assessed by Sajjad et al. (2020). The results show a significant decrease in systolic and diastolic blood pressure (13–16 mmHg; 8–10 mmHg) due to the presence of cations (K+, Ca+ and Mg+) and phytochemicals that give vasodilatory, antioxidant potential (Sajjad et al., 2020).

WMS extracts (aqueous and methanolic) at a dosage of 200 mg/kg and 400 mg/kg feed for 28 days had nephroprotective and healing effects on the physiological saline and acetaminophen-induced damaged kidney of female albino rats (Omotoso & Osadiaye, 2018).

The ameliorative effect of aqueous extracts of WMSs against hepato- and nephrotoxic in alloxan-induced diabetic Wistar rats at dosage up to 600 mg/kg BW was investigated by Ogbeifun et al. (2020). There's significant improvement in the electrolyte concentration, decrease in liver enzyme activities, urea, creatinine and MDA and healing/regeneration of liver and kidney tissues damaged due to alloxan.

WMSs ethanolic extract possesses excellent antimicrobial activity and can be utilized as an easily accessible source of natural antimicrobial agents (Hameed et al. 2020). Hassan et al. (2020) reported ethyl acetate WMSs extracts were found to exhibit potency on *Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella* sp. Aqueous and methanolic extract of WMSs powder can be served as a potential antibiotic against microbial infection caused by *Staphylococcus aureus, Pseudomonas aeruginosa, Pseudomonas fluorescence Escherichia coli, Salmonella typhi, Bacillus cerus* and *Bacillus subtilis* (Babaiwa et al. 2020; Osinubi et al. 2020).

Papaya: Health Benefits of Papaya Waste Extracts

Papaya (*Carica papaya* L.) is the most economically significant fruit in the *Caricaceae* family and cultivated all year round. The producing areas are largely tropical and subtropical countries, with India, Brazil, Indonesia, Nigeria, and Mexico as major producers of papaya (Pathak et al. 2018). In 2014, papayas were harvested on 418,604 ha, with global total production of 12,822,014 tonnes globally. The majority of products made from papaya include tutti frutti, powder, papaya chips, skin care products, papain, candy, jam, jelly, pickles, sauce, squash, etc. (FAOSTAT 2014; Medina et al., 2013). The antioxidant activities of the many bioactive compounds found in papaya, including carotenoids, phenolic compounds, vitamins A, C, and E, pantothenic acid, minerals (potassium and magnesium), folate, and fiber, have been linked to a number of positive health impacts on human bodies. In addition, papaya is a natural source of papain, a digestive enzyme that is used as an industrial ingredient to tenderize meat, pharmaceuticals, brewing industries and cosmetics. Thus, it is no surprise that using these fruits for the numerous reasons stated above produces a lot of waste and by-products, especially during the harvesting and post-harvesting processes. The two main by-products of papaya processing, papaya peel (PP) and papaya seeds (PSs), account for roughly 12 and 8.5% of the fruit weight, respectively. PP and PSs contain some bioactive compounds with added value which can be used as dietary additives; nutraceutical supplements new food and pharmaceutical products (Makaepea et al. 2019). PPs are traditionally used in animal feeds, cosmetics, and many

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home remedies. If not properly handled, PPs discarded into the environment can cause environmental pollution (Medina et al., 2013; Parniakov et al., 2014; Yogiraj et al., 2014); Aravind et al., 2013; Evans and Ballen 2015; Parniakov et al., 2015). However, PPs can be used as a good source of important compounds, food additives, or nutritional supplements. They can also be transformed into other products with added value (Pathak et al. 2018).
PP extracts exhibited anti-inflammatory and anticarcinogenic activity against AOM-induced cytotoxicity in rat colon due to presence of bioactive components (polyphenols and flavonoids) (Waly et al., 2014). Matsusaka and Kawabata (2010) noted that PP had a weak radical scavenging capacity but showed a strong ferrous ion-chelating capacity.
PP also exhibits antibacterial activity against some Gram-positive and Gram-negative microorganisms (*E. coli*, *Pseudomonas*, *P. vulgaris*, *S. typhi*, *S. pyogenes*, *E. faecalis*, *B. megaterium* ATCC9885, *B. subtilis* ATCC6633, *Corynebacterium rubrum* ATCC14898, *S. aureus* ATCC25923, *S. epidermidis* ATCC12228, *C. freundii* NCIM2489, *E. aerogenes* ATCC13048, *K. pneumoniae* NCIM2719, *P. mirabilis* NCIM2241, *S. typhimurium* ATCC23564) and fungal strains (*Candida albicans* NCIM3102, *Candida glabrata* NCIM3448, *Candida neoformans* NCIM3542, *Candida epicola* NCIM3367 *Aspergillus niger*, and *Trichophyton rubrum*) in various extracts (cold and hot water, ethanol, 1% HCl, acetone, petroleum ether, chloroform, benzene, tetracycline, methanol, ethanol, hexane, ethyl acetate, etc.). Ethanol and methanol were found to be the best solvents for extraction of natural products from PP to achieve maximum medicinal benefits, possibly due to the active components' better solubility in organic solvents, which may explain why the antimicrobial activity of PP is dependent on the solvent used for extraction (Asghar et al., 2016; Orhue and Momoh 2013; Prakash et al., 2013; Khan et al., 2012; Rakholiya et al., 2014; Roy, S., Lingampeta 2014).
PP is frequently utilized in a variety of home remedies and cosmetics. The vitamin A in PP aids in repairing and regenerating the skin's damaged tissues. PP can also be applied to the skin to lighten it. PP can hydrate the skin and alleviate irritation when applied to the skin with honey. When applied to the scalp 20 minutes prior to shampooing, vinegar made from PP and lemon juice can help combat dandruff. Bath water mixed with PP oil, vinegar, and essential oils like lavender, orange, and rosemary can be revitalizing, nourishing, calming, and helps ease pain and relax muscles. (Aravind et al., 2013; Yogiraj et al., 2014).

Conclusion and future directions

The purpose of this review is to highlight findings from recent studies that show how fruit wastes may be used as sources of bioactive compounds for treating or preventing chronic diseases, promoting wellbeing, or improving human health. Numerous scientific research support the idea that food and health are positively correlated. Food wastes can also be turned into resources because they are a rich source of bioactive compounds. The proposed review highlights the extra benefits of plant secondary metabolites, particularly as potential nutraceuticals for human health, and their ability to prevent a number of diseases linked to oxidative stress. Therefore, the agro-food industry generates a lot of by-products that may possess added-value compounds. In recent years, consumers' demand for healthier food and health products has increased, representing a challenge for the food and pharmaceutical industries.
However, the use of bioactive compounds is not just limited to the formulation of health-related products; they may also have other applications such as in the cosmetic industry (i.e., the prevention and treatment of skin-related issues) (Rodrigues et al., 2015) and in the food industry in order to develop functional food (Comunian et al., 2021), to extend shelf-life (Liu et al., 2022; Faustino et al., 2019) or to improve the quality of frying oil (Ahmed et al., 2022). Fruit wastes such as citrus, avocado, mango, watermelon and papaya wastes, being abundant and low-cost renewable resources, could be used to develop novel or functional food, nutraceutical and/or pharmaceutical, and cosmeceutical products, and may have a positive economic and environmental impact.
Despite the significant advancement in agro-food waste and by-product's research, studies on the effectiveness in animal models, mechanism of action, and safety profile were scarce. Further research is required to fill the gap in existing knowledge on the safety of food wastes and by-products as functional foods with health-related benefits.

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