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Functional attributes and bio-prospects of fruit peel waste

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Abstract:
The fruit processing industry generates a considerable amount of waste, which leads to significant nutritional and economic losses. The most common waste materials include pomace, peels, rind, and seeds. They contain valuable natural bioactive compounds, such as carotenoids, polysaccharides, dietary fibers, enzymes, polyphenols, oils, and vitamins. These compounds can be recovered by using suitable conventional or non-conventional methods. Conventional methods include Soxhlet extraction, hydro-distillation, and maceration. Non-conventional methods include enzyme-assisted, ultrasound-assisted, microwave-assisted, solid-liquid, and solvent extractions, as well as pulsed electric field. Fruit peels can be used to synthesize metallic nanoparticles, edible packaging, single-cell proteins, biosorbents, biochar, carbon dots, and biofertilizers. Furthermore, their bioactive compounds have a significant pharmacological potential. In particular, they can be utilized as antioxidant, anti-inflammatory, antimicrobial, antiviral, and anti-neoplastic agents.

Fruit peels are also a cost-effective solution that can mitigate various environmental problems and aid in reducing nutritional loss. In this article, we reviewed different extraction techniques employed to retrieve bioactive compounds from fruit peel waste, along with their industrial, biotechnological, and pharmacological applications.

Keywords: Bioactive compounds, nanoparticles, carbon dots, biochar, biofertilizers, edible packaging, single-cell protein, biosorbents

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INTRODUCTION

Around the world, 931 million metric tons of fruit and vegetable waste is produced each year, with China producing the most at 91.65 million tons, followed by Nigeria and India at 68.76 and 37.94 million tons, respectively [1]. Fruit and vegetable processing generates a significant amount of by-products, such as pulp, seeds, peels, and stones, with waste peels accounting for approximately 25–30% [2]. Fruit peels contain essential bioactive functional constituents, such as polyphenols, vitamins, enzymes, dietary fibers, oils, carotenoids, polysaccharides, and other beneficial compounds. These bioactive compounds exhibit antibacterial, antioxidant, anti-carcinogenic, anti-phlogistic, and antidiabetic properties [3, 4].

Bioactive compounds can be recovered and recycled by suitable techniques, such as solvent extraction, mechanical expelling, supercritical extraction, and microwave extraction. Conventional extraction has time limitations, low extraction efficiency, low yield, and solvent requirements. Ultrasound-assisted extraction (UAE), by contrast, is an efficient extraction technique that can recover bioactive components from plants with less energy and solvent. It extracts valuable components, such as polyphenols, carotenoids, aromas, and polysaccharides, from both plants and their by-products at low temperatures while retaining their functionality. To optimize the UAE process, a number of variables need to be understood and optimized for each by-product, including frequency, power, duty cycle, temperature, time, solvent type, and liquid-solid ratio [5].

In recent years, there has been a notable shift in the perspective towards fruit and vegetable by-products. Studies have indicated that these by-products can exhibit higher concentrations of bioactive compounds in comparison to the edible portions of the fruit. For instance, the peels of lemons, grapes, and oranges, as well as the seeds of avocado, jackfruit, and mangoes, have been shown to contain 15% more phenolic compounds than the pulpy parts of the fruits. These findings suggest that fruit and vegetable by-products may possess greater health benefits than previously thought and warrant further investigation [6]. Using fruit peels to recover and recycle bioactive compounds has emerged as a cost-effective and eco-friendly solution to environmental challenges while also providing numerous health benefits [7].

Studies of fruit waste have uncovered such bioactive compounds as polyphenols, dietary fiber, enzymes, polysaccharides, proteins, and olfactory components. These beneficial nutrients are responsible for a number of health benefits. The use of fruit peels in nutrient supplementation depends on their chemical composition. Studies have shown that *Punica granatum* L. peels, typically inedible, contain such essential phytochemical constituents as gallic acid, ellagic acid, punicalins, and punicalagin. These compounds have multiple pharmacological properties, such as immune modulation, humectancy, as well as antibacterial, antioxidant, and anti-atherosclerotic effects [8]. Similarly, the phytochemical profile of *Mangifera indica* L. peels reveals that they contain phenols (14.85–127.6 mg/g dry weight), ascorbic acid, fibers (26–78 g/100g dry weight), as well as tocopherols and carotenoids (0.1–51 mg/g dry weight) [9]. Previous research has identified a group of phenolic compounds (*p*-coumaric, caffeic, ferulic, and sinapic acids), polyethoxylated flavones (tangeretin and nobiletin), and flavanones (hesperidin and naringin) responsible for certain peels' antioxidative properties [10]. The peels of *Ananas comosus* L. were found to contain ferulic acid (19.50 mg/100 g), catechin (58.51 mg/100 g dry extracts), gallic acid (31.76 mg/100 g), and epicatechin (50.00 mg/100 g) [11]. *Musa sapientum* L. peels contain crude fat (5.93 ± 0.13%), crude proteins (1.95 ± 0.14%), and saccharides (11.82 ± 2.17%), as well as phosphorus, iron, calcium, magnesium, and sodium. They also have low concentrations of copper, zinc, potassium, and manganese [12]. Further, a comparative analysis of various fruit peels has shown that orange peels have the highest DPPH radical scavenging activity, total anthocyanin composition, and total phenol content, compared to kiwi, pineapple, apple, and banana peels.

The fruit peels, often discarded as waste, not only pose significant environmental issues but also represent an enormous loss of nutrients with high bioactive properties. These bioactive compounds have been recently shown to exhibit multiple pharmacological properties, such as antidiabetic, anticancerous, anti-glycemic, neuroprotective, antimutagenic, antibacterial, and anti-inflammatory effects [13]. In addition, these compounds can be used directly as nutraceuticals due to their potential health benefits or can be utilized as raw materials by various industries, including pharmaceuticals, cosmetics, and food industries. This idea has captured the interest of developing nations that seek to optimize eco-friendly methods and ensure food security [14]. Bioactive compounds derived from fruit peels are also being explored for their biotechnological properties which can be used in the production of biodegradable plastics and biofuels.

Our study aimed to suggest a way of minimizing fruit peel waste. We explored a possibility of using selected fruit peel wastes for therapeutic purposes to combat a wide range of multidrug-resistant microorganisms. We also sought to review various innovative approaches to extracting bioactive compounds from fruit peels. The study explored their diverse applications, including synthesizing metallic nanoparticles, edible packaging, carbon dots, biofertilizers, biochar, and more. Additionally, we briefly discussed the diverse pharmacological activities that fruit peels exhibit, underscoring the need for further research in this area.

METHODS FOR EXTRACTING BIOACTIVE COMPOUNDS

The methods for extracting bioactive compounds can be classified as conventional and unconventional techniques (Fig. 1). Some of the conventional methods are Soxhlet extraction, maceration, and hydro-distillation. Unconventional methods include ultrasound-assisted, supercritical fluid, pressurized liquid extraction, microwave-assisted extraction, and others.

1. Conventional methods

Conventional methods have been in use for a long time and are known as traditional approaches. These methods rely on the solvent extraction capacity or energy delivered, or both [5].

1.1. Soxhlet extraction

Soxhlet extraction is a conventional technique used to extract bioactive compounds from plants. This method involves a continuous cycle of boiling and condensation

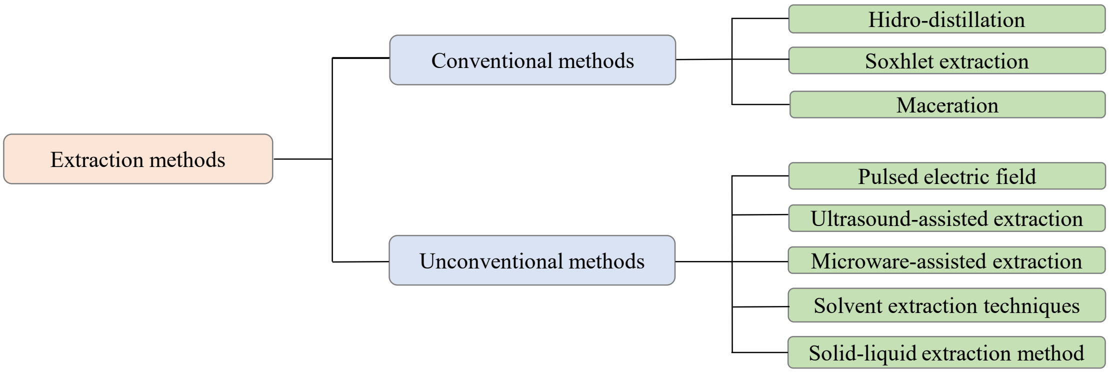

Figure 1 Methods for extracting bioactive compounds from plant sources [15, 16]

that enables efficient extraction of desired components. A small dry material is placed in a thimble, and a beaker is filled with a preferred solvent. The solvent is repeatedly added to the plant material while the extracted solute remains in a distillation flask [15]. For example, Rezvankhah *et al.* [17] effectively extracted fatty acids from hemp seeds at 70°C for eight hours and phenolic compounds from hemp leaves for two hours using 60% ethanol.

1.2. Hydro-distillation

Hydro-distillation is an approved method used to extract essential oil. Fragrant plant material is boiled with water in a still or added to live steam to release oil glands. Oil is separated from distillate water in a separator [18]. Azmat *et al.* [19] compared supercritical fluid extraction with hydro-distillation used to extract essential oil constituents from pomegranate peel. They found that supercritical extraction provided a higher yield (1.18%, v/w) compared to hydro-distillation (0.21%, v/w).

1.3. Maceration

Maceration is a standard method for extracting medicinal herbs typically used in galenical medicines. The fundamental principles and procedures involved in maceration, percolation, and infusion for obtaining crude drug extracts are similar to those used in leaching, which involves extracting soluble elements from solid substances using a solvent. The extraction process is influenced by such factors as the speed at which the solvent enters the mass, the rate at which the soluble elements dissolve in the solvent, and the rate at which the solution exits the insoluble material. Low efficiency and long duration are the major disadvantages of this extraction method [15]. A number of studies used maceration to extract flavonoids from turmeric rhizomes (non-ionic surfactant Triton X-100, neutral pH, 35°C), from *Arbutus unedo* L. fruits (79.6°C, 3.7% diluted ethanol), and from the leaves of *Ficus carica* and *Euphorbia neriifolia* (75% concentrated ethanol, room temperature) [20–22].

2. Unconventional methods

Various novel methods that can extract bioactive substances from agricultural waste include enzyme-assisted extraction, solvent extraction, solid-liquid extraction, pulsed electric field, microwave-assisted extraction, subcritical water extraction, ultrasound-assisted extraction, and supercritical fluid extraction.

2.1. Solid-liquid extraction and solvent extraction techniques

Phenolic compounds can be extracted from agri-food residues using organic solvents, but they can be expensive, time-consuming, and environmentally harmful. On the other hand, water seems an ideal solvent for polar and hydrophilic compounds [23]. Deep eutectic solvent extraction is an eco-friendly and cost-effective method that can recover phenolic compounds [24]. The Naviglio extractor is a new solid-liquid extractor that can extract bioactive compounds by depleting the solid matrix [25]. Its benefits include performing extractions at room temperature, reducing thermal stress, and improving extraction accuracy [15].

Previous studies have reported that potato phenolic compounds extracted using solid CO_2 cryomaceration and solid-liquid extraction with 10% ethanol/water showed efficient antioxidant activity, which could help maintain the quality of fresh-cut apples. The studies also highlighted the potential use of natural deep eutectic solvents (NADES) to avoid the use of chemicals in food applications [26, 27].

Solvent extraction is an effective way to extract complex soluble components and extra flavorings from raw materials. The choice of a solvent impacts the effectiveness of extraction. Smaller particles improve the solvent's ability to penetrate, but the filtering procedure becomes challenging if they are too small. Commonly used solvents are alcohols, acetone, and acetonitrile. However, with hazardous solvents, this approach needs an evaporation/concentration phase for retrieval, enormous volumes of solvent, as well as a lengthy time frame. Other technologies, such as ultrasonic, microwave-assisted, Soxhlet, or supercritical fluid extractions, have increased solvent extraction yields [15].

2.2. Enzyme-assisted extraction

Enzymes can extract bioactive substances from food waste by breaking down plant cell wall polysaccharides such as pectin, hemicellulose, and cellulose. This allows associated compounds to be released. Enzyme-aided extraction is an eco-friendly method that uses water instead of organic solvents. Based on the enzymes' ability to catalyze interactions in aqueous media under moderate process conditions, it can replace traditional solvent extraction methods [28]. Enzyme-assisted extraction is highly effective for extracting phenolic compounds from citrus peels at 20–60°C [29].

2.3. Pulsed electric field

Pulsed electric field is a new method to obtain valuable molecules from fruit leftovers. It uses high-voltage microsecond pulses on a material sandwiched between two electrodes. Pulsed electric field improves recovery rates of chemicals without affecting the grade of retrieved substances. It is a non-thermal method that improves recovery when used as a pre-treatment over heat-based pre-treatment. The critical process variables are the electric field strength and processing time. The energy needed is modest and does not affect the general architecture of the cell [30, 31]. Pulsed electric field serves as an effective method for valorizing by-products, e.g., for extracting phenolic compounds from plum, grapes, and citrus peels [23].

2.4. Microwave-assisted extraction

Microwave-assisted extraction generates heat within the material to rupture cell walls and extract bioactive compounds. This method allows for shorter extraction and has been used to recover various bioactive substances. Different processes occur during microwave-assisted extraction, including solvent penetration, component solubility or dissolution, and transfer of solubilized chemicals. Microwave-assisted extraction can be carried out in sealed or exposed vessels. Recently, devices operating in a vacuum or nitrogen atmosphere have been developed [32]. Several studies have reported that oil from curcuma can decompose during traditional Soxhlet extraction. However, it was successfully extracted using microwave-assisted extraction under the best conditions of 29.99 minutes extraction time, 160 watts power, and a curcuma powder-to-ethanol ratio of 1:20 (w/v), resulting in an optimal yield of 10.32% [33]. Thus, microwave-assisted extraction is a highly versatile and user-friendly technique that enables extraction of volatile compounds in significantly reduced time frames [34].

2.5. Ultrasound-assisted extraction

Ultrasound-assisted extraction uses ultrasound energy and solvents to extract target compounds from plant matrices. It uses high-frequency mechanical waves that induce cavitation bubbles, which grow and collapse, creating hot spots and extreme local conditions. The collapsing cavitation bubbles generate shockwaves and accelerate inter-particle collision, causing fragmentation in cellular structures and leading to the solubilization of bioactive components in the solvent. Ultrasound-assisted extraction also induces erosion, sonoporation, and shear force, resulting in the release of bioactive compounds. This method increases the plant tissue matrix's water absorption and swelling indexes, which helps in the desorption and diffusion of solutes, resulting in increased extraction. Ultrasound-assisted extraction can be performed in an ultrasonic bath or a probe-based system. While both systems are economical and easy to handle, probe-based systems are commonly preferred due to higher ultrasonic intensity and efficient cavitation effect [5]. Several studies have reported extraction of polyphenols from *Punica granatum* L. peels at 50–60°C and 37 kHz [35].

INDUSTRIAL APPLICATIONS OF FRUIT PEELS

1. Edible coatings

Edible coatings are thin coats that are applied to prolong the shelf life of food products. It is a cost-effective method to maintain the properties, quality, functions, and effects of the food material [36]. Edible coatings have the potential to prevent the damage resulting from microbial attacks. Several studies have reported the use of edible coatings as a carrier matrix for specific antimicrobial agents [37]. Packaging materials can incorporate natural bioactive compounds such as essential oils, α-tocopherol, and polyphenols, which can replace chemical preservatives and increase food longevity [38].

According to previous studies, pomegranate peel waste is rich in functional bioactive constituents and natural antioxidants which can be used to prepare edible films based on biopolymers to enhance their bio-functionality. However, its bitter taste is a limitation that can be addressed by using encapsulation strategies, such as biopolymers/edible matrices. Encapsulated forms of pomegranate peel extracts can have customizable wall thickness to mask their bitter taste and determine their release effect over time. Incorporating pomegranate peel extract in an edible matrix can improve the interaction between the matrix and the particles. This can result in enhanced mechanical, biochemical, and structural features such as phenolic composition, as well as antioxidant and antimicrobial potential.

Pomegranate peel extract can also prevent lipid oxidation, natural pigment retardation, and microbial contamination, thereby enhancing the shelf life of food products [39]. Additionally, an edible coating based on a combination of mango kernel seed starch and lemongrass essential oil can extend the storage life of guava fruit. It can also maintain its physiochemical characteristics, including acidity, total soluble solids, textural properties, and phenolic contents [40]. To prepare edible biofilms, several other fruit peels are employed (Table 1).

2. Fruit peel-derived metallic nanoparticles

Bioactive functional components in fruit peels, such as polyphenols, enzymes, amino acids, proteins, alkaloids, tannins, carbohydrates, saponins, and vitamins, can act as reducing agents during the synthesis of metallic nanoparticles [45]. Some of these components can also serve as capping agents preventing nanoparticle agglomeration, while others can act as modeling agents allowing particles to grow in a specific direction [46]. Different fruit peel extracts with high efficacy have been utilized to develop metallic nanoparticles, such as silver, gold, iron, palladium, titanium, and zinc oxide. Silver and gold nanoparticles have shown promising antimicrobial action against a wide range of pathogenic microbes. These nanoparticles can be synthesized through hydrothermal, electrochemical, microwave, and green chemistry methods [47, 48]. For example, polyphenolic-rich *Punica granatum* waste has been utilized to synthesize silver nanoparticles with antiviral, antioxidant, anticancerous, and antimicrobial activities. The antioxidant and antimicrobial potential of pomegranate silver nanoparticles allows citrus fruit to be stored in the cold for a long period [49]. Nano-bacterial cellulose has been made from citrus waste such as pomace and peel, using *Komagataeibacter xylinus*, which has distinct physicochemical characteristics and potential applications in various pharmacological and biomedicine sectors [50].

Using fruit peels to synthesize metallic nanoparticles is an eco-friendly and non-toxic alternative to toxic solvents, which benefits the environment and human health. This green method reduces the use of hazardous organic solvents, toxic reagents, or non-biodegradable stabilizing agents. In addition, it does not need expensive instruments to control the chemical reduction process, which results in a more environmentally-friendly process. Researchers have evaluated various plants and plant-based materials as substrates for synthesizing metallic oxide nanoparticles due to their reduction potentiality and simple scale-up process [49]. Several other fruit peels can be utilized to synthesize nanoparticles (Table 2).

3. Fruit peel-derived carbon dots

"Carbon dots" are minute fluorescent carbon nanoparticles below 10 nm in size which exhibit photoluminescent behavior. Carbon dots are produced by two methods, namely bottom-up and top-down synthetic routes (Fig. 2). The top-down approach involves breaking down

Table 1 Fruit peels as a source of edible coatings

Common name	Scientific name	Matrix	Food item	Technique	Effects	References
Apple	*Malus domestica*	Carboxymethyl-cellulose	Fresh beef patties	Micro-fluidization	Totally reduced lipid oxidation and effectively inhibited microbial development on uncooked beef patties. No impact on the sensory qualities of beef patties, either raw or cooked	[41]
Pomegranate	*Punica granatum*	Chitosan/gelatine	n.d.	Film	Improved rheological, antioxidant, and antibacterial qualities	[39]
		Mung bean protein	n.s.	n.d.	Increased total phenolic content, antioxidant activity, and antibacterial capacity in pomegranate peel-enriched films compared to the control mung bean protein film	[44]
		20% glycerol	Bread	Film as wrapping material	Substantially reduced microbial load and bread weight loss during storage	[39]
Orange	*Citrus sinensis*	Chitosan film	Deepwater pink shrimp	Casting	The shelf life of fresh shrimp extended to 15 days by chitosan film with 2% orange peel essential oil	[42]
		Pectin coating	Fresh-cut orange	n.d.	The shelf life of orange slices extended by nanoemulsion-based edible coatings enriched with orange peel essential oil, with no adverse effects on sensory qualities	[43]

n.d. – not detected

n.s. – not specified

Table 2 Fruit peels as a source of nanoparticles

Common name	Scientific name	Type of nano-particle	Reaction time	Morphology	Size	Applications	References
Orange	*Citrus sinensis*	Silver	10 min	Sphere	47–53 nm	Photocatalytic activity against methylene blue	[51]
Cavendish banana	*Musa acuminata*	Silver	30 min	Sphere	55 nm	Antimicrobial activity against *S. aureus, E. coli, Bacillus subtilis* and *K. pneumoniae;* antioxidant activity (DPPH); 2,2’-azino-bis (3-ethylbenzothiazoline-6)	[52]
Banana	*Musa paradisiaca*	Silver	1 h	Sphere	23.7 nm	Antibacterial efficacy against *E. coli, S. aureus, P. aeruginosa,* and *Bacillus subtilis*; antifungal activity against *C. albicans*	[53]
Orange, banana	*Citrus sinensis*, *Musa*	Silver	1 h	Sphere	n.d.	Antibacterial activity against *Proteus vulgaris* and *Staphylococcus aureus*	[54]
Orange, banana, apple	*Citrus sinensis*, *Musa*, *Malus domestica*	Silver	2 min	Sphere	25 nm	Antibacterial activity against *Aeromonas hydrophila*, *Pseudomonas spc, E. coli*, and *Salmonella spc*; antifungal action against *Fuarium spc.*; antioxidant activity and cytotoxicity (DPPH) against human breast cancer cells MCF-7	[55]
Orange	*Citrus sinensis*	Zinc oxide	1 h	Hexagonal	12.55 nm	Photocatalytic activity against methylene blue	[56]
Grapefruit	*Citrus paradise*	Zinc oxide	1 h	Hexagonal	19.6 nm	Photocatalytic activity against methylene blue	[56]

n.d. – not detected

complex carbon structures using electrooxidation, acid-assisted chemical oxidation, or laser ablation. On the other hand, the bottom-up approach uses plants and their by-products instead of chemical substances. This method is more cost-effective, with cheaper precursors and simpler experimental setups [57]. In particular, it involves selecting suitable carbon precursors, such as carbohydrates, citrate, and polymer-silica nano-compo-

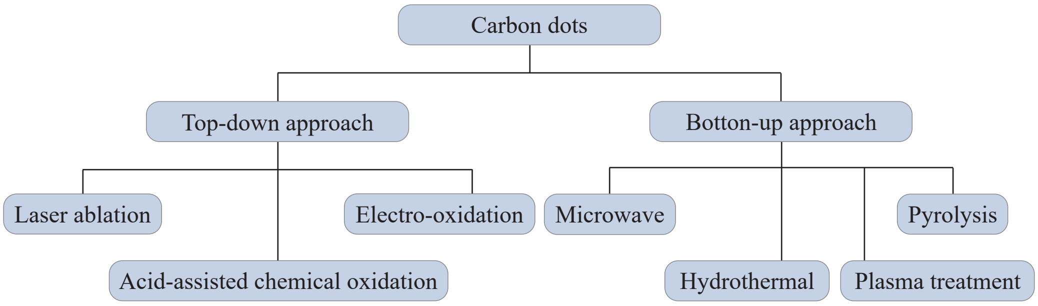

Figure 2 Approaches for synthesizing nanostructured materials (carbon dots) [57]

Table 3 Carbon dots derived from different fruit peels

Common name	Scientific name	Conditions	Heavy metals detection limit	Applications	References
Sweet lime	*Citrus limetta*	Hydrothermal/180°C/3 h	n.a.	Breast cancer detection, gene therapy	[61]
Grapefruit	*Citrus paradisi*	Hydrothermal/190°C/12 h	n.a.	Photoluminescence immunoassay	[62]
Pomelo	*Citrus maxima*	Hydrothermal/200°C/3 h	0.23 nM	Hg^{2+} sensing	[63]
Pomegranate	*Punica granatum*	Hydrothermal/180°C/36 h	n.a.	Recovering latent prints	[64]
Banana	*Musa acuminata*	Microwave-assisted/ 500 W/20 min	n.a.	Determination of colitoxin DNA	[65]
Mango	*Mangifera indica*	Hydrothermal/300°C/2 h	1.2 µM	Detection of iron ions (Fe^{2+}) using cellular labelling	[66]
Watermelon	*Citrullus lanatus*	Hydrothermal/220°C/2 h	n.a.	Imaging probe	[67]

n.a. – not assessed

sites. These precursors are then carbonized and purified to remove any impurities. The resulting nanoscale carbon structures are assembled through chemical processes. Carbon precursors with functional groups such as hydroxyl or carboxyl are suitable for this process. Carbon quantum dots (CQDs) can be synthesized through various methods, including microwave irradiation, thermal decomposition, hydrothermal treatment, template-based routes, and plasma treatment.

The use of green material as a carbon source for CQD synthesis (hydrothermal and microwave synthesis, carbonization) has attracted scientific interest due to its eco-friendliness. The raw materials and methods used for CQD synthesis affect the size, crystallinity, functional groups, colloidal stability, fluorescence properties, quantum yield, and compatibility of the resulting CQDs. Hydrothermal synthesis is the dominant method for synthesizing biomass-based CQDs compared to other chemical methods. Recently, many studies have focused on synthesizing environmentally friendly biomass-based CQDs from common biomasses using various hydrothermal synthesis conditions [58].

Researchers are looking into various carbon sources, including agricultural by-products, biomass, and food waste, to establish environmentally friendly and low-cost routes to produce CQDs. These carbon sources are plentiful, renewable, and less expensive, which makes them appealing alternatives to traditional sources. CQDs have the potential to be used in a variety of fields, including bioimaging, optoelectronics, and sensing. Heavy metals, including iron, chromium, copper, and aluminum, are nutritionally essential elements needed by various organisms to sustain their lives. These elements have a higher density than water and are the most common toxic and non-biodegradable contaminants. Their increased employment in various fields has led to an increase in environmental pollution. Eco-friendly, feasible, and efficient sensors are required to identify the presence of heavy metals and prevent their negative consequences [58].

Several studies have employed the peels of *Mangifera indica* and *Ananas comosus*. They are highly effective for developing carbon dots due to a variety of functional bioactive constituents, such as dietary fibers, gallic acid, polyphenols, and flavonoids [59]. Additionally, *Citrus maxima* can detect 0.23 nM heavy metals and Hg^{2+}, while *Citrus sinensis* can be used for sensing ferric ions and tartrazine, as well as for cell imaging. Fruit peels serve as a potential source of carbon dots due to low toxicity, photostability, biocompatibility, and innocuousness [60] (Table 3).

BIOTECHNOLOGICAL APPLICATIONS OF FRUIT PEELS

1. Fruit peel-derived biosorbents

Rapid industrialization and population increase have resulted in serious environmental challenges such as heavy metal poisoning of wastewater, which harms people's health. The primary sources of water pollution include the discharge of untreated sanitary and toxic industrial wastes, dumping of industrial effluent, and runoff from agricultural fields. In recent years, various toxic chemicals (e.g., micropollutants, personal care products, endocrine-disrupting compounds, pesticides, inorganic anions, etc.) have been detected at dangerous amounts in drinking waters in many parts of the world [68]. Various health risks due to water pollution have been reported in the literature. These heavy metals are commonly classified as hazardous and non-destructible pollutants. When agglomerated in living tissues, they cause various infectious diseases and disorders via food chain biomagnification [69]. In view of severe problems for human health caused by elevated concentrations of toxic pollutants, there is an urgent need to develop robust, economically feasible, and environmentally friendly processes to remove them from water and safeguard the health of affected populations.

Various treatment technologies are available, with varying degrees of success, to control or minimize water pollution. However, the shortcomings of most of these methods are high operational and maintenance costs, generation of toxic sludge, and complicated procedures involved in the treatment. Comparatively, the adsorption process is considered a better alternative to water treatment because of its convenience, ease of operation, and simplicity of design. Further, this process has a broader applicability in water pollution control since it can remove or minimize different types of pollutants.

Activated carbon is undoubtedly considered a universal adsorbent for effluent treatment and is commonly used to remove various pollutants from water. However, its widespread use in wastewater treatment is sometimes restricted due to its higher cost. A large variety of low-cost adsorbents have been examined for their ability to remove various types of pollutants from water and wastewater. Generally, an adsorbent can be assumed to be "low cost" if it requires little processing, is abundant in nature, or is a by-product or waste material from the industry. Various low-cost adsorbents of different origin have been found to show little or poor adsorption potential for the removal of aquatic pollutants, as compared to commercial activated carbon.

Recently, numerous approaches have been studied to develop cheaper and more effective adsorbents containing natural biopolymers. These biopolymers are an attractive alternative as adsorbents because of their particular structure, physicochemical characteristics, chemical stability, high reactivity, and excellent selectivity toward aromatic compounds and metals. This results from the presence of chemically reactive groups (hydroxyl, acetamido, or amino functions) in polymer chains.

Various bio-based/biopolymer materials have been examined for the removal of diverse types of pollutants from water. Agricultural waste materials are economical and eco-friendly due to their unique chemical composition. Their abundance, renewable nature, and low cost make them viable options for remediating aquatic pollutants [70]. There are numerous methods to remove heavy metals, one of which is using fruit peels as a natural sorbent. They are of low cost and have good absorbent properties attributed to various organic acids, tannins, lignin, protein, and mineral constituents [71]. Diverse functional groups associated with the biosorbent surface, such as sulfhydryl, carbonyl, hydroxyl, amine, amide, phenolic, phosphate, and sulfonate groups, are responsible for attracting and sequestering pollutants [72]. As renewable agro-industrial waste, fruit peels are a promising resource for environmental technology if applied in water and wastewater treatment [73]. Several studies have focused on the use of *Hylocereus undatus* L. and *Malus domestica* L. fruit peels to remove methylene blue dye from aqueous solutions [60]. These fruit peels can be used as a raw material for synthesizing biosorbent, biochar, nanoparticles, etc. (Fig. 3).

2. Fruit peel-derived single-cell protein

Single-cell proteins, also known as microbial proteins, are dead, dry microbial cells or complete proteins that are separated from a pure microbial cell culture and are created utilizing a variety of microorganisms such as bacteria, fungi, and algae [75]. Citrus waste, which has wide applications in various functional foods, can also be used to produce single-cell proteins. These single-cell proteins are regarded as the bulk of dried cells produced through the action of microbes, yeast, bacteria, fungi, etc. They are referred to as bio-proteins, microbial proteins, or biomass [76]. Single-cell proteins can be an excellent alternative to vegetable protein sources since they do not have high land or water requirements for production [77]. The cost of their production can be reduced by selecting cheap substrates or biodegradable agricultural and food industry waste as a nutrient source for microorganisms to grow and yield large amounts of protein. Various substrates have been used for this purpose. Some of the most common substrates are orange peels, apple pomace, yam pulp, citrus pulp, potato pulp, pineapple waste, papaya waste, and more [78].

Several studies have investigated the production of single-cell proteins using fruit waste [79]. For example, single-cell proteins have been synthesized from orange and cucumber peels by submerged fermentation using *Saccharomyces cerevisiae*. According to the results, the products obtained from biotransformation of agricultural waste are cost-effective and rich in protein [76].

The fruit peels are an excellent starting material for synthesizing single-cell proteins. For their production, a unique chemical technique converts the cellulose component into more easily accessible sugar [77]. Single-cell proteins can be produced from orange peels using *Aspergillus niger* and *S. cerevisiae* [80]. Several studies have looked into developing fungal single-cell proteins by using *Rhizopus oligosporus* on fruit waste [77]. Another study synthesized single-cell proteins from pineapple peels by using *S. cerevisiae* NCDC 364 [81].

3. Fruit peel-derived biochar

Biochar is a stable carbon-rich solid formed under high temperatures and anaerobic conditions as a result of thermo-chemical decomposition followed by pyrolysis of organic materials [82]. Biochar is utilized to remove heavy metals and impurities from contaminated water [83]. Biochar has garnered significant attention

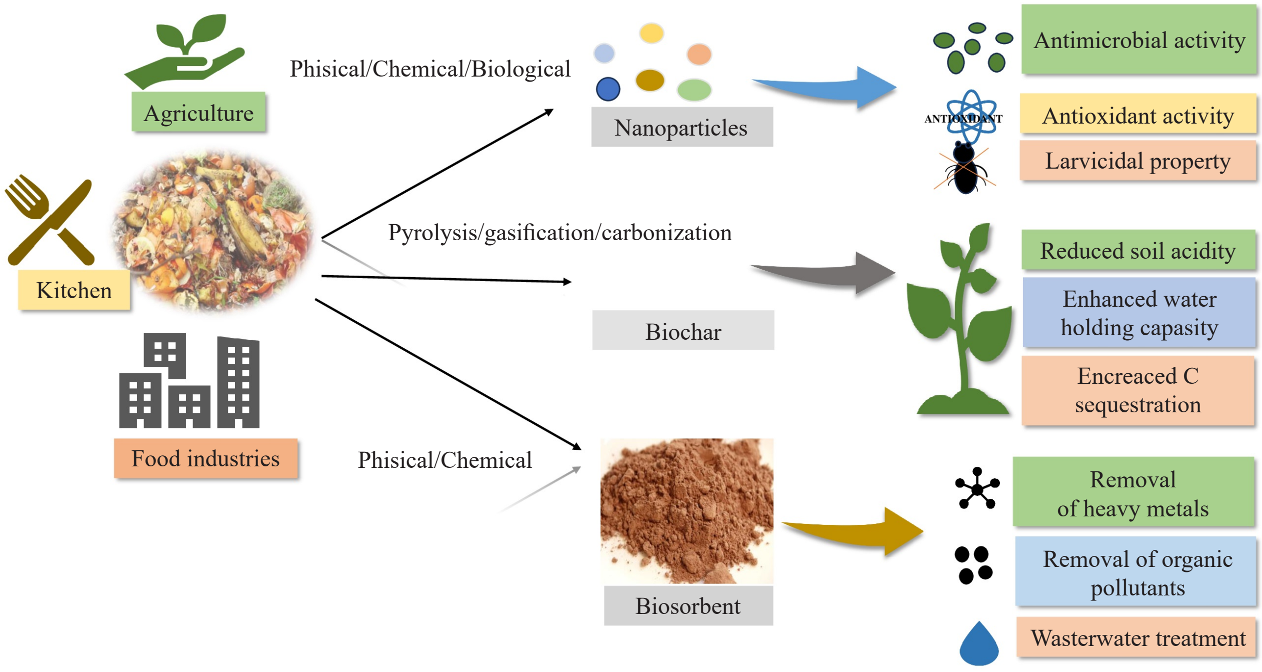

Figure 3 Extraction and application of fruit peels as valuable products [49, 55, 71–75]

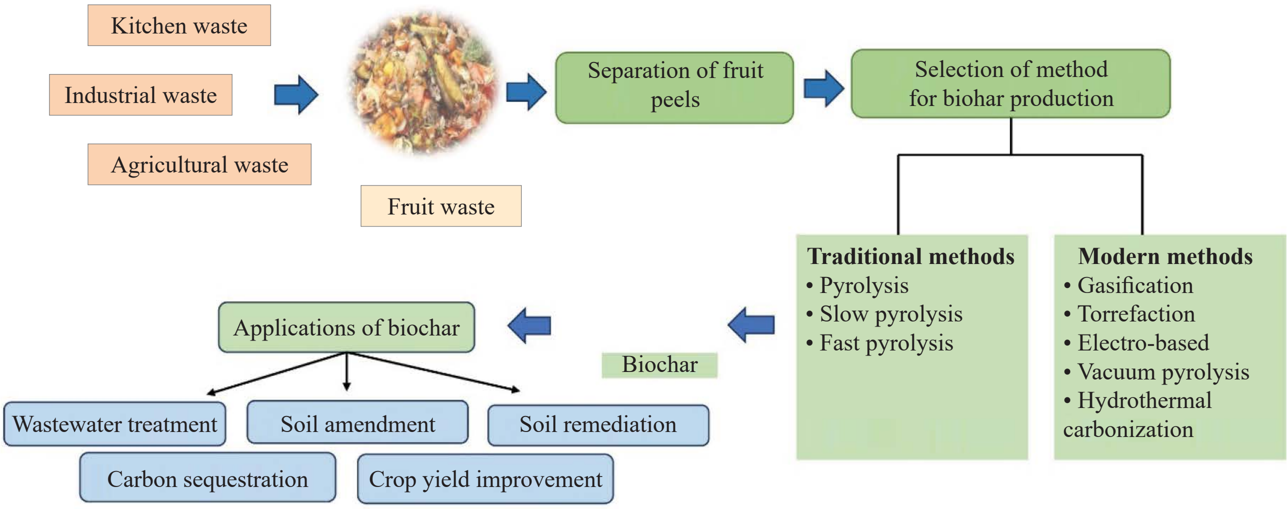

Figure 4 Fruit peel waste utilization for producing biochar and its applications [75, 84]

recently for its versatility in various agricultural and industrial applications.

The physicochemical characteristics of biochar play a crucial role in determining its suitability for different purposes. Recent studies have shown that the raw material and process parameters significantly affect biochar properties, including elemental ingredient concentrations, density, porosity, and pH [84].

Biochar is used in industrial waste treatment to eliminate organic and inorganic pollutants, dyes, and pigments from textiles. In agriculture, it helps improve the soil quality and nutrient retention. Additionally, biochar's high carbon content makes it a suitable fuel for power generation. The primary biomass sources for biochar production include agricultural and animal wastes, algae biomass, crop residues, activated sludge, energy crops, and digestate. Various physical, thermochemical, and biochemical methods can convert biomass into high-value products. Thermochemical conversion techniques, such as pyrolysis, gasification, torrefaction, and hydrothermal carbonization, produce biochar by heating carbonaceous biomass at temperatures ranging from 300 to 900°C in limited oxygen conditions. Biochar's physical, chemical, and mechanical characteristics vary depending on the raw material and pyrolysis conditions. Therefore, choosing an appropriate locally available feedstock is essential to minimize transportation costs and CO_2 emissions [85]. Furthermore, numerous fruit by-products are used to create these stabilized carbon-rich solid substances with diverse physiochemical properties (Fig.4) [86].

Ananas comosus, Citrus limetta, and *Citrus maxima* peels are used to create biochar that eliminates hexavalent chromium from aqueous solutions [55]. Some authors have also shown that biochar is generated by using rambutan and pomegranate peel to remove copper (II) ions from soil and aquatic systems [87]. For instance, biochar derived from orange and banana peels through pyrolysis at 400–500°C yields approximately 30.7–47.7 wt%. Biochar is durable against various chemical reactions, including oxidation, and has a hard texture, no sulfur, and a volatile composition. As a result, pyrolysis is the preferred method for converting fruit peels into biochar, which acts as an excellent adsorbent [88]. Producing biochar from different fruit peels with suitable methods is illustrated in Table 4.

4. Fruit peel-derived biofertilizers

Fertilizers are a most vital input for enhancing the agricultural yield. Due to their immediate action and low cost, farmers employ higher dosages of chemical fertilizers than the recommended level to enhance crop production. As a result, they not only accelerate the soil acidification but also introduce contaminants in water and the environment. Thus, there is an urgent need for developing biofertilizers that satisfy both nutritional value and crop yield [94]. The synthesis of biofertilizers from fruit peels is illustrated in Fig. 5.

Citrus waste can be used as a biofertilizer to improve soil fertility as it contains such essential micronutrients as carbon, nitrogen, and potassium. This biofertilizer has antimicrobial properties because of its high pH and

Table 4 Fruit peels as a source of biochar

Common name	Scientific name	Conditions	Applications	References
Banana	*Musa*	Pyrolysis at 500°C for 10 min	Reducing biological and chemical oxygen demands, total suspended solids, and palm oil mill effluent to an acceptable level below the discharge	[88]
Pineapple	*Ananas comosus*	Pyrolysis at 750°C for 2 h	Adsorbing hexavalent chromium at 7.44 mg/g	[89]
Litchi	*Litchi chinensis*	Hydrothermal carbonization at 180°C for 12 h	Adsorbing malachite green and congo red at 2468 and 404.4 mg/g, respectively	[90]
Orange	*Citrus sinensis*	Pyrolysis at 500°C for 10 min	Reducing biological and chemical oxygen demands, total suspended solids, and palm oil mill effluent to an acceptable level below the discharge	[88]
Pomegranate	*Punica granatum*	Pyrolysis at 300°C for 2 h	Adsorbing Cu (II) at 52 mg/g	[91]
Rambutan	*Nephelium lappaceum*	Pyrolysis at 600°C for 3 h	Removing copper ion Cu(II) from aqueous solutions of 50 and 100 mg/L at 0.2 and 0.4 g/L adsorbent dosages, respectively	[92]
Pomelo	*Citrus maxima*	Pyrolysis at 450°C for 1 h	Adsorbing methyl orange dye (1 g of biochar adsorbing 150 mg/L of methyl orange dye)	[93]

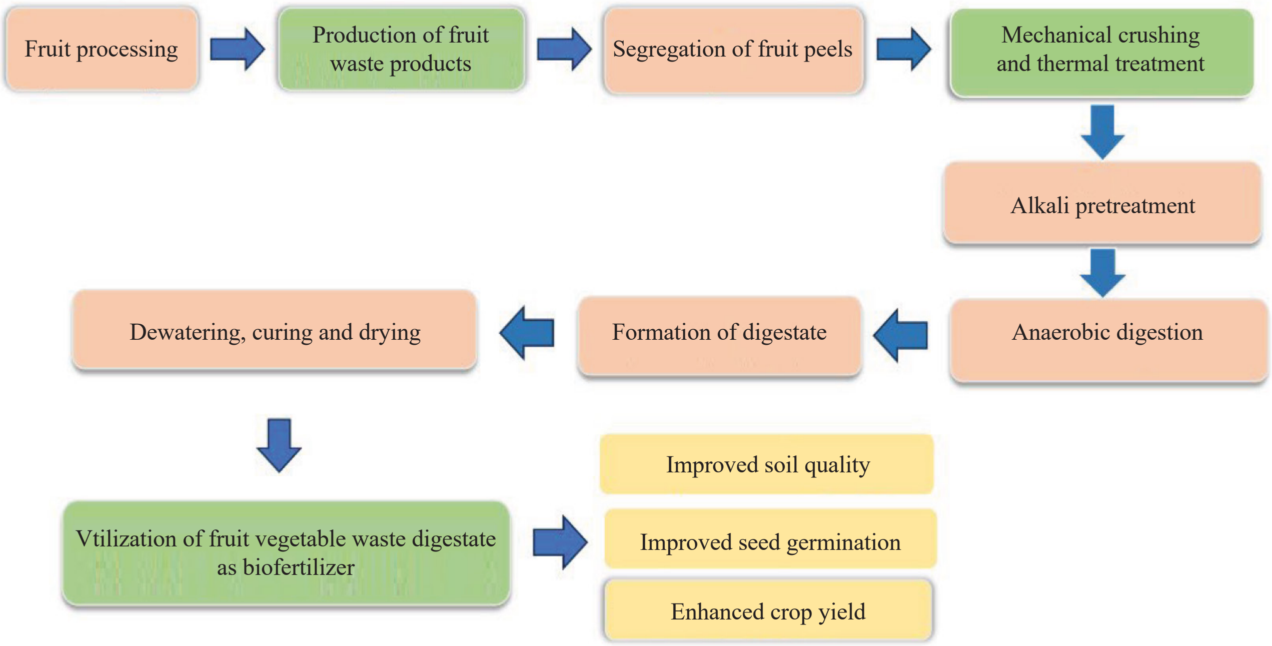

Figure 5 Fruit peel waste utilization for developing biofertilizers [93, 94]

lignocellulose, and it can remove toxic heavy metals from soil [96]. Citrus pulp waste can be used as a biofertilizer as well as to produce biogas [97]. A combination of maize silage, animal manure, and citrus pulp waste was found to be a better substrate for biogas development. The residual digestate, rich in antioxidants, can also be used as a biofertilizer. The peels of orange, sweet lime, and pomegranate can serve as a low-cost source of lactic acid bacteria, which makes them an excellent biofertilizer [98–99]. Several studies have looked into the synthesis of biofertilizers from papaya peels to enhance the nutritional value of crops [95]. Other researchers have identified beneficial bacteria such as *Azospirillum* in food waste which can enhance plant growth [100]. Thus, probiotic farming can be an alternative to chemical fertilizers for long-term benefits. Enriching the organic matter composition and soil morphology, fruit peel by-products can help maintain the soil's pH, nutritional content, seed germination, and fertility. By promoting the growth of soil microbiota, they can protect the plants from insects, fungi, and pathogenic attacks [101].

PHARMACOLOGICAL APPLICATIONS OF FRUIT PEELS

1. Antidiabetic agent

Diabetes is a disease characterized by excessive blood glucose levels as a result of the body cells' improper reaction to insulin. Insulin is a hormone that allows human cells to receive and convert glucose into energy. If the body cannot absorb glucose, it builds up in the bloodstream (hyperglycemia), which causes a number of health problems. Diabetes mellitus can cause diverse organ failure, as well as typical symptoms such as polyuria, weight loss, blurred vision, and metabolic imbalance, which worsens with age and requires natural medication [102]. α-glucosidase facilitates the breakdown of starch and dietary carbohydrates into glucose, thereby elevating blood glucose levels. Its inhibition lowers postprandial hyperglycemia and delays absorption of glucose in diabetics.

An *in vitro* investigation has demonstrated that the ethanolic pomegranate peel extract contains phenolic compounds and flavonoids that suppress α-glucosidase [103]. Furthermore, *C. limetta* peel has been found to exhibit hypoglycemic activity (in vitro) and have a postprandial glycemic effect (in vivo), lowering blood sugar levels [104]. The peel of red dragon fruit (*Hylocereus polyrhizus*) can also be used as an antidiabetic medication. It is rich in flavonoids, polyphenolic, anthocyanins, isorhamnetin glucoside, rutin, quercetin hexoside, kaempferol glucorhamnoside, isorhamnetin, and galloylglucoside [105].

Another example includes the Citrus maxima peel extract, which effectively reduced blood glucose levels by 70.17% ($p = 0.05$). Further, the extract (600 mg) increased high-density lipoprotein cholesterol by 4.43%, while lowering total cholesterol (30.86%), triglycerides (10.58%), and low-density lipoprotein cholesterol (10.20%). The control groups' liver enzyme activity increased dramatically, whereas the treated groups exhibited no significant changes. Thus, fruit peels are associated with multiple pharmacological activities (Table 5).

2. Anti-microbial agent

Anti-microbials are substances that kill or inhibit the growth of microorganisms such as bacteria, fungi, and protozoa. Disinfectants are antibacterial compounds that are utilized on non-living items. Herbal medicines have a long history of being effectively used to treat infectious diseases. Most natural medicines are made from

Table 5 Pharmacological properties of different fruit peels

Common name	Fruit peels	Phytochemicals	Pharmacological applications	References
Apple	*Malus domestica*	Polyphenols, flavonoids, quercetin, procyanidin, chlorogenic acid, anthocyanins, and hydroxycinnamic acid	Antidiabetic, anti-inflammatory, anti-proliferative, and anti-hypertensive	[106]
Kiwi fruit	*Actinidia deliciosa*	Gallic acid, catechin, syringic acid, caffeic acid, chrysin acid, and quercetin	Anticancerous, antimicrobial, and antioxidant	[107]
Pineapple	*Ananas comosus*	Phenols, flavonoids, terpenoids, carotenoids, saponin, coumarins, lignin, ascorbic acid, myricetin, gallic acid, catechin, epicatechin, and ferulic acid	Antimicrobial, anti-inflammatory, antioxidative, anticarcinogenic, anti-hypertensive, and hypoglycaemic	[108]
Mango	*Mangifera indica*	Mangiferin, *p*-coumaric acid, epicatechin, ferulic acid, rutin, tannic acid, kaempferol, ellagic acid, quercetin, and homogentisic acid	Immunomodulatory, anti-inflammatory, antimicrobial, and antioxidant	[109]
Custard apple	*Annona squamosa*	Alkaloids, steroids, saponins, tannins, and polyphenols	Anti-thrombotic, anti-inflammatory, anthelmintic, anticarcinogenic, and antidiabetic	[110]
Banana	*Musa acuminata*	Carotenoids, biogenic amines, polyphenols, phytosterols, and antioxidants	Antioxidant, antimicrobial, anti-inflammatory, and anticancerous	[111]
Melon	*Cucumis melo*	Flavones, hydroxybenzoic and hydroxycinnamic acids, β-carotene, lutein, β-cryptoxanthin, and violaxanthin	Antimicrobial, anticancerous, antioxidant, and antidiabetic	[112]

plant materials, including leaves, flowers, fruits, and stems. These materials can be used to create new antimicrobial compounds with different chemical structures and mechanisms of action to fight against multidrug-resistant microorganisms. A previous study found that banana peel extracts had antimicrobial properties that were effective against *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus, Salmonella enteritidis*, and *Escherichia coli* [113]. Several studies have shown that *M. paradisiaca cv. Puttabale* and *M. acuminata cv. Grand naine* ethanol extracts have broad-spectrum antibacterial activity against *P. vulgaris* and *S. paratyphi*.

Bioactive compounds such as glycosides, flavonoids, terpenoids, and tannins were also discovered through phytochemical analysis. These derivatives may be used to treat clinical pathogenic bacteria. A study [114] showed that the *Musa acuminata* peel methanolic extract (300 mg/mL) has varying inhibitory activity against *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), *Lactobacillus casei, Bacillus spp., Pseudomonas aeruginosa,* and *Saccharomyces cerevisiae* [114]. Meanwhile, several other studies have reported that the oil from this methanolic peel extract (30 mg/mL) has high antibacterial potential against several bacterial species. This finding is attributed to 2-methyl-5-(1-methylethyl) phenol, a potent antimicrobial compound present in the peel. Tannins have also demonstrated antimicrobial activity against *E. coli, S. aureus, and P. aeruginosa* [114].

Punica granatum peel extracts are best against foodborne pathogens, including *E. coli, Fusarium sambucinum, Penicillium italicum*, and *B. subtilis.* These extracts also suppressed Gram-positive *S. aureus* and Gram-negative *Salmonella* growth in one of the tests [115]. Several studies have stated that the extraction procedures highly influence the antibacterial potential of pomegranate peels. Banana peels contain vitamin A, vitamin C, gallocatechin, dopamine, vitamin E, vitamin B6, â-sitosterol, malic acid, succinic acid, palmitic acid, magnesium, phosphorus, potassium, fiber, and iron as major constituents. Fatty acids found in banana peels are responsible for their antimicrobial action [116].

3. Anticancerous agent

Cancer is one of the primary causes of high mortality in humans. Drug development for cancer intervention has advanced significantly in recent decades, but the existing medications show many limitations in terms of their applicability and efficacy. They are sometimes associated with major side effects that can further degrade the patients' quality of life. Fruit peels are a rich source of bioactive chemicals which act as antioxidants and anticancerous agents in the treatment of colon, prostate, and breast cancers [117, 118].

Fruits are nutritious plant-based foods that contain vitamins, minerals, fiber, antioxidants, and bioactive compounds. Therefore, their daily consumption may help prevent cancer. Eating more fruits and vegetables is associated with a lower risk of cancer in various body parts. Combined phytochemical constituents in fruits and vegetables are more effective in preventing cancer than individual components. Edible phytochemicals offer a suitable and accessible basis for cancer control and management.

A study by Mondal *et al.* demonstrated that the aqueous methanolic extract of Nendran banana peel had significant cytotoxic activity against MCF-7 breast cell lines [119]. Additionally, banana peel crude extract could be used to synthesize gold nanoparticles that were cytotoxic to human lung cancer cells and inhibited the biofilm formation of Gram-positive bacteria *Enterococcus faecalis*. The researchers postulated that the flavonoids present in the banana peel contributed to its anticancer properties. They could inhibit ROS-scavenging enzyme activities, inducing apoptosis, arresting the cell cycle and suppressing tumor growth [114].

Zaini *et al.* and Phacharapiyangkul *et al.* discovered that ferulic acid, which is highly identified in Sucrier banana peel, potentially acts as anti-melanogenesis agent by regulating the growth factor of vascular endothelial expression [114, 120]. This acid initiates nitric oxide synthase and acts as a suppressor gene of the tumor. Previous studies have shown that the banana peel extract prepared from hexane solvent exhibited the highest toxicity towards HCT-116 (colorectal carcinoma cell line from humans), with 64.02% inhibition of cell proliferation [114]. Similarly, citrus peels and related extracts have shown remarkable efficacy against many malignancies, mainly due to high flavonoid contents in them. Various biological features crucial to health and illness have been identified [121].

4. Source of dietary fiber

Dietary fiber is an essential constituent of a balanced diet, and the scientific community has established its good association with human health [122]. Oligosaccharides, lignin, resistant starch, tannins, and other plant components are all found in dietary fibers. Dietary fibers are classified into two categories based on their water solubility: soluble (pectin, gums, mucilage, and some hemicelluloses) and insoluble (cellulose, other forms of hemicelluloses, and lignin). Several authors have stated the benefits of appropriate fiber intake, including intestinal transit management and the prevention or treatment of diabetes, cardiovascular disease, and colon cancer [123]. Further, dietary fibers lower the risk of hyperlipidemia, hypercholesterolemia, and hyperglycemia by modulating food consumption and influencing nutrient digestion, absorption, and metabolism [124].

The leading cause of death in patients with diabetes is cardiovascular disease, which increases mortality two to four times. Doctors advise most diabetic patients to avoid or limit their intake of highly nutritious fruits, such as bananas, as they can lead to hyperglycemia and weight gain. However, recent studies have shown that banana fruit has potential antidiabetic properties, leading to further exploration of its antihyperglycemic effect. Starch hydrolysis in the pulp (about 20%) during maturation results in sucrose, glucose, and fructose accumulation, making it sweeter and more palatable. On the other hand, the unripe peels contain only about 3% of starch, leading to a less sweet taste even after ripening.

Studies have indicated that dietary fiber intake is associated with lower levels of total and low-density lipoprotein cholesterol [125]. Interestingly, soluble dietary fiber from *Musa paradisiaca* in tested dosages (50–250 mg of dietary fiber) is more effective in reducing cholesterol absorption than insoluble dietary fiber [126]. Oxidized low-density lipoprotein increases the expression of pro-inflammatory genes that cause monocyte recruitment into the vascular endothelial cells of a dysfunctional blood vessel wall. Oxidized low-density lipoprotein is destroyed by generating free radicals, making it crucial to inhibit its oxidation in managing cardiovascular disease and atherosclerosis. The methanol and ethyl acetate extracts of *M. paradisiaca* effectively prevented low-density lipoprotein oxidation, with IC_{50} values of 169.52 and 217.45 μg/mL, respectively. Angiotensin-I-converting enzyme is an enzyme that transforms angiotensin I into angiotensin II, a potent vasoconstrictor that plays a crucial role in blood pressure regulation. Angiotensin II has been associated with insulin resistance and the progression of vascular complications in diabetes. Therefore, inhibiting the angiotensin-I-converting enzyme is a clinical approach to treating diabetes. Several studies have demonstrated that *M. paradisiaca* extracts have an inhibitory effect on this enzyme comparable to the positive control, captopril (100–200 μg/mL) [114].

Peel is a prominent by-product of citrus fruit processing and is considered a good source of dietary fiber. It contains approximately 25.71–80.41% of total dietary fiber in a variety of foods [127]. Orange peel contains 57% of total dietary fiber, 47.6% of which is insoluble and 9.41% of which is soluble. Mango contains 51.2% of total dietary fiber [128]. Banana peel is a fruit residue that accounts for 30–40% of the entire fruit weight and contains considerable amounts of carbohydrates, proteins, and fiber [129].

5. Anti-oxidant agent

Free radicals, also known as reactive oxygen species, are by-products of normal metabolic activities. Free radicals are also produced as a result of exposure to air pollution, cigarette smoking, industrial chemicals, ozone, and X-rays. The exposure to free radicals causes damage to various macromolecules such as nucleic acids, lipids, and protein. This damage is responsible for several pathogenic disorders, such as cancer, as well as inflammatory, respiratory, cardiovascular, neurodegenerative, and digestive-tract diseases [130]. According to previous research, dietary antioxidants lower the prevalence of diseases such as cancer, cardiovascular disease, and diabetes associated with oxidative stress [131]. Dietary antioxidants may help prevent and treat certain diseases by scavenging free radicals and lowering oxidative stress. They can also protect food from oxidation, making them a potentially safer alternative to synthetic antioxidants [132].

Because of the low cost and vast quantities of plant biowastes produced, their usage in the food sector can be broadened to include antioxidants for developing novel functional foods. Phenolics are significant secondary metabolites found in banana peels at high levels compared to other fruits. Banana peel contains several phenolic compounds, including catechin, anthocyanin, tannins, epicatechin, and gallic acid [133]. Furthermore, gallocatechin levels in banana peel are five times greater than in banana pulp, making banana peel a rich source of antioxidant chemicals [134]. More than 40 compounds from banana peel have been discovered based on individual phenolics, totaling 47 mg of gallic acid equivalent/g dry matter. These phenolic chemicals can be further classified into four subgroups: flavonols, hydroxycinnamic acids, flavan-3-ols, and catecholamines [114].

Citrus fruit also decreases homocysteine levels and prevents free radical formation. It has anti-carcinogenic, antidiabetic, anti-inflammatory, and anti-arthritic characteristics [135]. Citrus peel contains the highest concentration of natural antioxidants, compared to any other fruit part. They include natural flavonoids, phenolics, ascorbic acid, carotenoids, and reducing sugar. Citrus peel extracts demonstrated the highest antioxidant activity, compared to citrus pulp and seeds [136].

CONCLUSION

The modern fruit processing industry is producing a variety of food products to meet consumers' increasing daily demand, which unavoidably generates a high quantity of fruit peel by-products. Fruit peels that are thrown away possess beneficial bioactive compounds, which makes them a highly efficacious material for the synthesis of edible packaging, biochar, single-cell proteins, carbon dots, nanoparticles, etc. Researchers are getting more interested in mixing nanoparticles with other substances to produce smart biofertilizers for agriculture due to their rapid outcomes. However, very few studies have been conducted in this area. With several articles describing the formation of nano-biofertilizers, there has been no extensive investigation into the mechanism of their action for plant growth. Thus, there is a need to create nano-biofertilizers by correctly combining nanoparticles with biofertilizers.

Our study indicated that fruit peels are a rich source of probiotics that can be employed as biofertilizers to improve the quality and quantity of food crops in agricultural fields. Studies have indicated that fruit peels not only contribute to improved nutritional status and supply of essential antioxidant compounds for disease prevention, but they may also have potential applications in the treatment of cancer and diabetes. Firstly, peels benefit the environment since they are secondary processing materials. Secondly, they provide a new perspective for consumers and producers about value-added food products. Furthermore, employing different methods, such as transcriptomics, proteomics, and metabolomics, can offer a comprehensive understanding of the molecular processes that underpin the health-promoting properties of fruit peels, thereby improving our knowledge of fruit peel phytochemicals as functional ingredients. Yet, there is a need for more advanced research into the applicability of peel waste-based edible packaging material.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding this article.

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