

Fruit Peel Lipids: From Lipidomic Characterization to Phytopharmaceutical Applications

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Abstract

Fruit peels are a major untapped resource of agro-industrial biomass and a rich source of structurally diverse bioactive lipids with immense pharmaceutical potential. These lipids are involved in essential processes such as membrane stability, stress tolerance, and quality preservation and among them lie cuticular waxes, phospholipids, sterols, triterpenoids, and very long-chain fatty acids. The study of the lipid composition and its dynamic remodeling in fruit peels have been comprehensively characterized in recent years using the techniques of lipidomics, especially liquid chromatography mass spectrometry and nuclear magnetic resonance. New green extraction methods have also made it easier to efficiently extract these valuable lipid fractions. The antioxidant, anti-inflammatory, antimicrobial, and anticancer properties of the fruit peel lipids have been increasingly gaining attention, indicating their potential application in nutraceutical, cosmeceutical, and pharmaceutical formulations. However, there are still several problems associated with feedstock variability, extraction efficiency, and standardization of analysis. The potential for lipidomics, Green Extraction Technologies, and formulation science in future integration could expedite the translation of fruit peel lipids to high value pharmaceutical products from plants and new therapeutic systems. Relevant literature was retrieved from PubMed, Scopus, and Web of Science databases and critically analyzed.

Key words: Bioactive lipids, circular bioeconomy, cuticular waxes, fruit peel lipids, green extraction, phytopharmaceuticals

INTRODUCTION

The global generation of agri-food waste has highlighted the paradigm shift for sustainable biorefineries toward the upcycling and valorization of secondary streams as high-quality industrial resources. Fruit processing wastes make up a significant portion of the raw product, typically 20–50% of the weight being the outermost dermal layer, the peel.^[1] Fruit peels were traditionally regarded as low-value agricultural waste but recent work with analytical techniques has identified fruit skins as complex biochemical matrices with local concentrations of phytochemicals 10 times greater than found in the corresponding edible pulp.^[1] The general role of the plant cuticle as the main physiochemical barrier of the aerial

epidermis in protecting it from environmental variations, mechanical damage, ultraviolet radiation, and disease-causing pathogenesis the most basic function.^[2] Structurally diverse hydrophobic complexes are embedded within this cross-linked macromolecular polyester network, which includes intracuticular and epicuticular waxes, long-chain aliphatic

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compounds, and highly specialized secondary triterpenoids.^[2] These hydrophobic barriers represent an untapped high-density source of lipid-based bioactives perfectly suited to high value drug delivery systems and therapeutics.

With the introduction of high resolution lipidomics, the landscape of the complex fruit peel lipidomes has been revolutionized both qualitatively and quantitatively. Advanced liquid chromatography coupled with high-resolution mass spectrometry can offer the unparalleled mass accuracy, resolution, and fragmentation pattern of the structures of compounds.^[3] This technology enables the unambiguous distinction of complex isomeric and isobaric lipids and speeds up mapping of structural profiles in plants.^[3] Analytical lipidomic analysis of the cuticular waxes of fruits reveals that they are extremely rich in polycyclic triterpenoids, biosynthetically derived from the linear hydrocarbon squalene.^[4]

These specialized lipophilic fractions isolated from resilient plant cuticles require efficient extraction methods to achieve the best yield with minimal molecule damage. Conventional methods for extracting lipids involve the use of volatile organic solvents such as chloroform, hexane, and methanol.^[5] To overcome these limitations, some new green technologies have been developed, which optimize the lipid extraction yield and reduce the consumption of energy; ultrasound-assisted extraction (UAE) uses acoustic cavitation (20–100 kHz) to break the resilient cuticular matrices and microwave-assisted extraction (MAE) is based on the principle of dielectric heating to break cells in a short time.^[6] Supercritical fluid extraction (SFE) supercritical carbon dioxide (scCO₂) is therefore an excellent solvent-free technology for highly non-polar targets with its gas-like diffusivity and liquid-like solvating capacity above the critical points ($T_c \geq 31^\circ\text{C}$, $P_c \geq 7.38\text{ MPa}$) that can be modified by ethanol to capture semi-polar fractions.^[6] Likewise, pressurized liquid extraction (PLE) is performed at high temperatures (50–200°C) and pressures (10–15 MPa) that can decrease the use of sustainable solvents by more than 70% than the traditional Soxhlet extraction; in addition, biodegradable natural deep eutectic solvents (NADES) can be customized to extract amphiphilic and polar lipid metabolites from citrus and pomegranate residues.^[6,7]

The present review seeks to fill this significant gap by offering an up-to-date and comprehensive review on the fruit peel lipids as emerging phytopharmaceutical resources. This review outlines the pharmacology and formulation issues of fruit peel lipids and offers a strategy for the next generation of lipid-based treatments for their use as underutilized bioresources by researchers and the pharmaceutical industry.

METHODOLOGY

Literature was collected from PubMed, Scopus, Web of Science, and Google Scholar using keywords such as “fruit

peel lipids,” “phytopharmaceuticals,” “bioactive lipids,” “green extraction,” and “nutraceutical applications.” Articles published in English between 2000 and 2025 were considered. Duplicate studies, conference abstracts, and non-English publications were excluded.

STRUCTURAL ORGANIZATION AND LIPIDOMICS OF FRUIT PEELS

Peels of fruit tissues are dominated by lipids which are the building blocks of the peel, in contrast to storage tissues, are chemically specialized and present in the extracellular cuticular layers and the inner membranes and, thus, constitute a dynamic system, which can respond to dehydration, temperature fluctuations, and oxidative stress.^[8]

Structural organization of peel lipids

The fruit cuticle is an extracellular lipid polyester, which is mainly composed of ester-linked C₁₆–C₁₈ hydroxy fatty acids, interspersed with crystalline domains of wax. Changes in the distribution of wax chains length, degree of saturation, and mechanical resistance to the peel surface directly depend on the distribution of the wax chain length.^[9] The phospholipids and sterols contained in peel epidermal membranes regulate membrane cohesion and thermal stability of postharvest storage. The increase of unsaturation of membrane lipids is strongly associated with high chilling tolerance preventing the phase transitions, leading to the facilitation of electrolyte leakage.^[10] Sterol-enriched membranes exhibit greater resistance to oxidative destabilization and the membrane lipid composition as a predictive indicator of postharvest resilience and a passive structural property should be considered.^[11,12]

The presence of intracellular membrane lipids, especially the level of unsaturation of phospholipids, is critical in defining the ability of the fruit to endure chilling injury. A higher level of unsaturation promotes the fluidity of the membranes, and this is important to retain cellular integrity when stored at low temperatures. The multilayer organization of these lipid components within fruit peel tissues is schematically represented in Figure 1.

Major lipid classes in fruit peels

Cuticular waxes

Cuticular waxes are the outermost protective barrier of fruit surface that are predominantly aliphatic very long chain compounds and alicyclic triterpenoids to control water permeation, mechanical strength, and resistance against biotic and abiotic stresses.^[13,14] In fruits like apple, grape, and nectarine, waxes have high content of ursolic acid and oleanolic acid which has significant anti-inflammatory and antimicrobial bioactivities useful for developing

phytopharmaceuticals, besides contributing to the structural integrity of the cuticle.^[4,15]

Very long-chain fatty acids (VLCFAs)

The fruit peel cuticular waxes are composed of VLCFAs and their derivatives such as alkanes, alcohols, and aldehydes of chain length (C20–C35).^[16,17] Wax coating of the fruit surface by VLCFA has been observed to get thicker during ripening in wampee (*Clausena lansium*), which was accompanied by decreased water loss and enhanced barrier properties.^[13]

Phospholipids

Amphipathic lipids, phospholipids, are important structural lipids that keep tissues in fruit skin compartmentalized and enable signal transduction within the cells. In postharvest bananas, stored at chilling temperatures (6°C), lipidomics analysis, performed on a broad range of lipids, revealed a relevant remodeling of phospholipid species, particularly phosphatidylcholines and phosphatidylethanolamines, a cluster of lipids especially correlated with development of chilling injury and alteration of membrane integrity, was strongly correlated with chilling injury and loss of membrane integrity.^[18]

Sterols

Sterols, especially phytosterols, such as β -sitosterol, stigmasterol, and campesterol, are found in fruit peel membranes and play a role in regulating the fluidity and permeability similar to that of cholesterol in animal cells.^[4] Sterols are co-occurring with triterpenoids in mango peel and are responsible for the antioxidant activity of lipophilic extracts.^[19] Steroidal components with possible bioactivity have been detected in *Citrus sinensis* peel, such as a steroidal fatty acid ester of stigmasterane origin.^[20]

Triterpenoids

Triterpenoids are one of the most important groups of lipids found in fruit peels that have been extensively discussed as fruits of medical importance, particularly the pentacyclic ones such as ursolic acid, oleanolic acid, and their derivatives, which are copiously reported in apple peel, mango peel, blueberry peel, and rose hip peel.^[4,16,19] Ursenoic acids contained in the peel extracts of apple fruits show strong lipase inhibitory activity and may have anti-obesity properties,^[21] whereas the triterpenoids obtained from lingonberry (*Vaccinium vitis-idaea*) cuticular waxes are cytotoxic to cancer cell lines.^[22]

Tocopherols

Antioxidants (tocopherols, especially α - and γ -tocopherol (Vitamin E isoforms)) present in some fruit peel lipid extracts have lipid solubility and can protect the polyunsaturated fatty acids (PUFAs) from oxidative degradation. Tocopherols are more known for their presence in seeds and oils but have been found in the peel fractions of some fruits as part of a larger phytochemical profile.^[23]

Essential fatty acids

Certain fruit peels are rich in neutral lipids and polar lipids, especially in their major components of linoleic acid (C18:2 ω -6) and α -linolenic acid (C18:3 ω -3). The green peels of *Opuntia ficus-indica* (cactus pear) are rich in linoleic acid (29.18%) and linolenic acid (29.27%) as well as palmitic acid, highlighting their status as a valuable source of PUFAs with anti-inflammatory and cardioprotective properties.^[24]

Species-specific lipid signatures and phytopharmaceutical significance of major fruit peels

Comparative lipidomic studies across different fruit species have revealed both conserved functional characteristics and species-specific lipid signatures with potential phytopharmaceutical applications. The major lipid constituents and their reported pharmaceutical significance in selected fruit peels are summarized in Table 1.

Analytical platforms enabling peel lipidomics

Lipidomics analytical tools that can facilitate analysis of the fruit peels are instrumental in the demystification of the lipid profiles of these agro-industrial by-products, which subsequently facilitates their use in other industries. Using recent analytical methods makes this possible and enables both the comprehensive identification, quantification, and structural characterization of thousands of unique lipid species found in fruit peels.^[47] The major analytical platforms used for the characterization of fruit peel lipidomes are summarized in Figure 2.

Liquid chromatography-Tandem mass spectrometry

Liquid chromatography-mass spectrometry is commonly used due to its ability to separate intricate lipid mixtures before interaction, making it possible to identify and determine the huge range of lipid species, such as isomers. This is especially useful in fruit peels, where lipid components may be very heterogeneous and may represent many classes, including fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, and sterol lipids.^[47]

Gas chromatography-mass spectrometry (GC-MS)

GC-MS method is frequently employed to differentiate fatty acid profiles, typically after converting fatty acids to methyl esters. This method provides crucial information on the composition of fatty acids, which influences the physical and chemical properties of derived oleochemicals.^[48]

Nuclear magnetic resonance (NMR)

NMR Spectroscopy offers non-destructive analysis and compliments MS. Although the lipidomics of fruit peel is not explicitly described in the given situation, solid-state

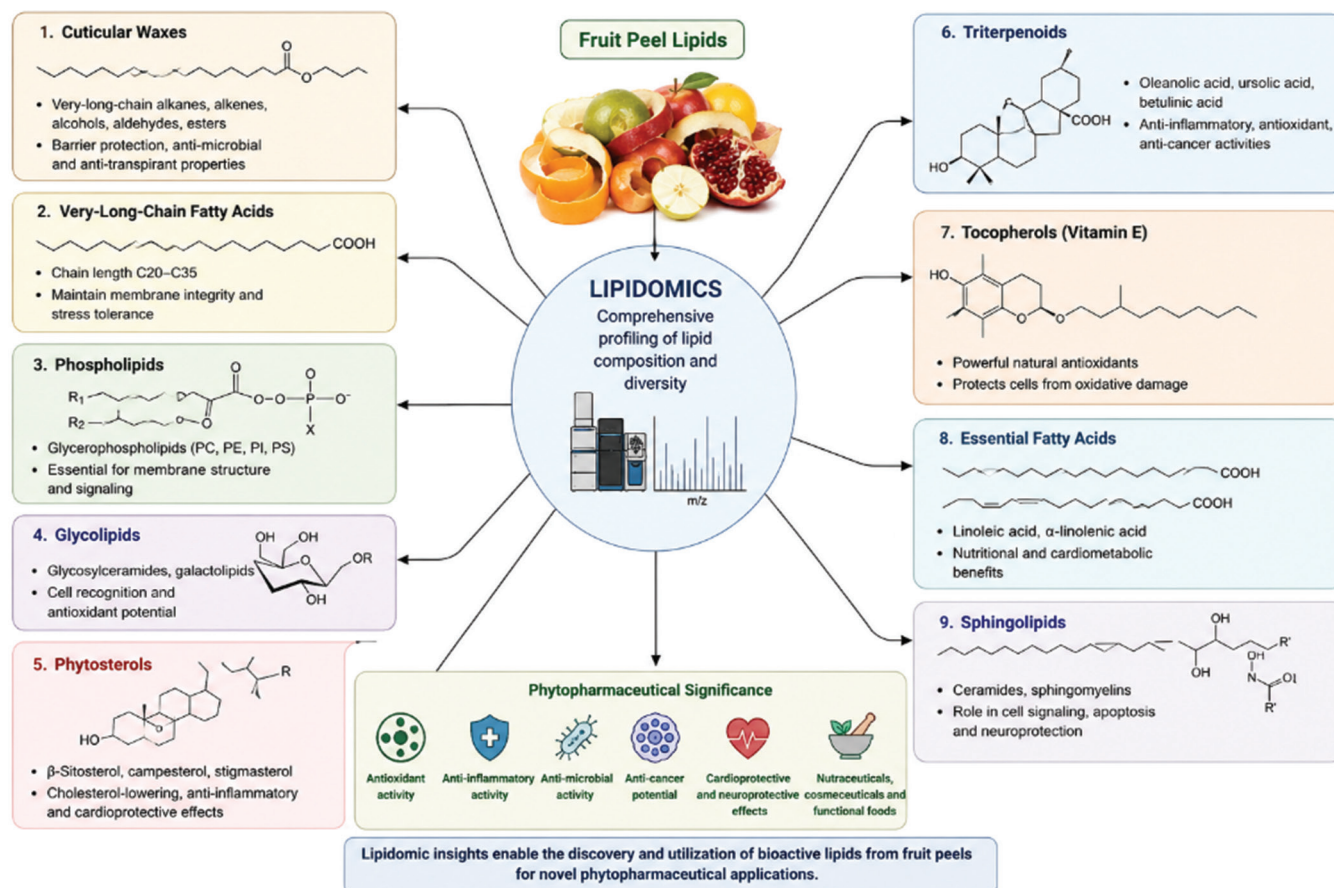


Figure 1: Schematic representation of the multilayer lipid architecture of fruit peel tissues

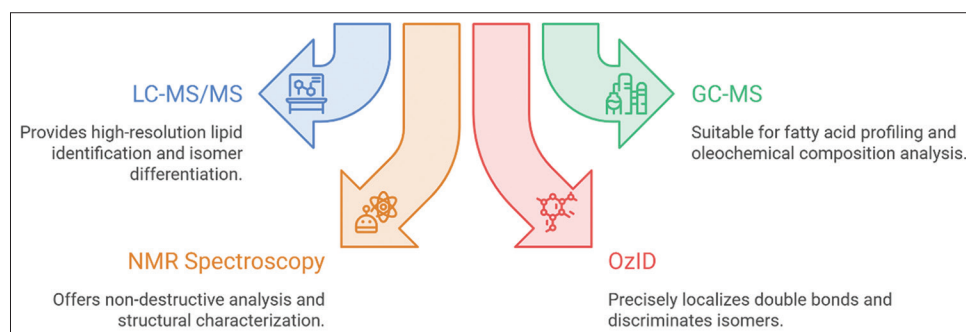


Figure 2: Analytical platforms enabling the lipidomics of fruit peels

carbon-13 NMR has been applied to outline the architectural structure of biopolymers in native and genetically modified tomato fruit cuticles, with the ability to describe the structural information on the molecular level.^[49]

Ozone-induced dissociation (OzID)

Emerging platforms, such as OzID, have improved the abilities of MS by providing detailed structure information about lipids. OzID precisely locates carbon-carbon double bonds in lipid molecules, thus differentiating structural isomers and mapping complicated lipids including triacylglycerols and phospholipids. This is vital for understanding how *cis/trans* configurations and double bond positions affect lipid properties and industrial applications.^[47]

GREEN EXTRACTION TECHNOLOGIES OF FRUIT PEEL LIPIDS

The green extraction technologies for lipids from fruit peels are a significant research field that contributes to the sustainable use of agricultural waste to achieve net-zero and further circular bioeconomic objectives.^[50,51] The major green extraction approaches and their potential pharmaceutical applications are summarized in Figure 3.

SFE

SFE, specifically with scCO_2 commonly developed advanced green extraction methods, as it is non-toxic,

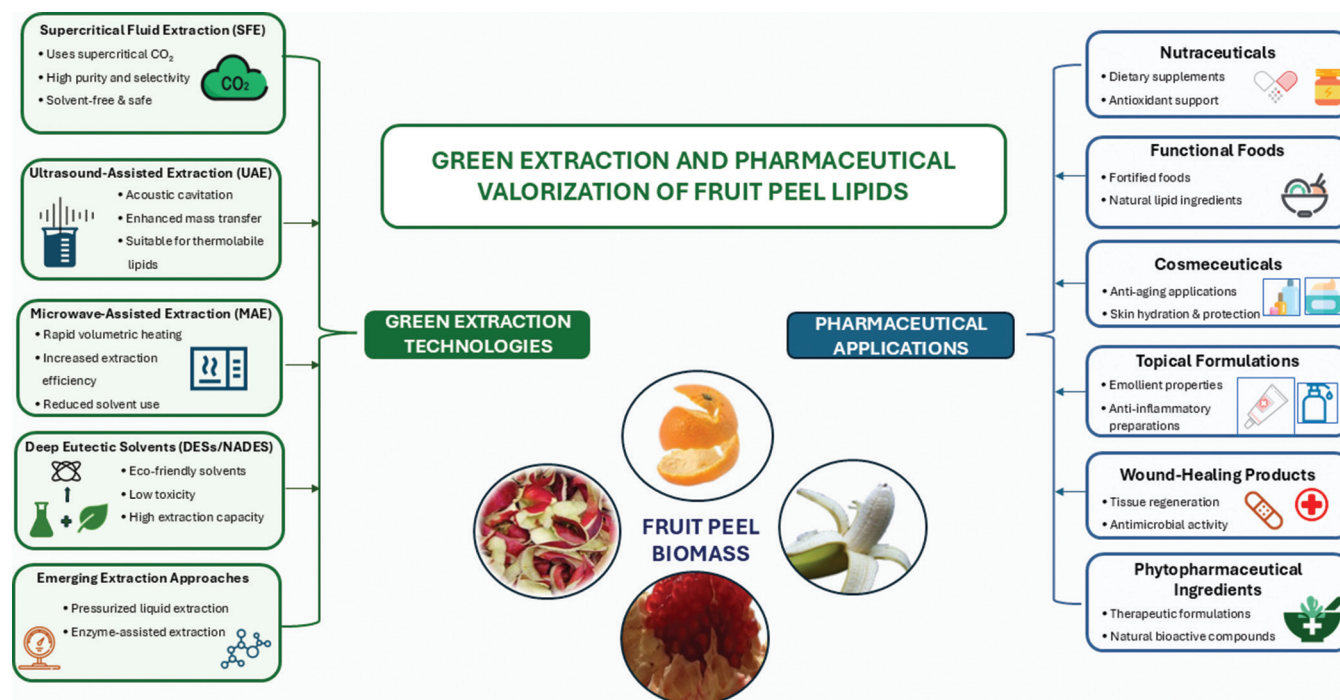


Figure 3: Green extraction and pharmaceutical valorization of fruit peel lipids

Table 1: Species-specific lipid composition and its phytopharmaceutical significance

Fruit Peel	Major lipid constituents	Potential pharmaceutical applications	References
Citrus spp.	PMFs, terpenoids, and fatty acids	Antidiabetic, antihyperlipidemic, and cardiometabolic nutraceuticals	[25-27]
Apple	Ursolic acid, oleanolic acid, and sterols	Antioxidant, anti-obesity nutraceuticals, functional foods, and chemopreventive agents	[28-30]
Banana	Oleic acid, palmitic acid, and fatty acid amides	Natural antioxidant formulations and antidiabetic formulations	[31,32]
Avocado	Phospholipids, sterols, and sphingolipids	Antioxidant, anti-inflammatory, nutraceuticals and cosmeceuticals	[33,34]
Mango	Triterpenoids, phytosterols, and tocopherols	Antioxidant, anti-inflammatory, anti-carcinogenic, chemopreventive nutraceuticals, and cosmeceuticals	[19,35,36]
Pomegranate	PUFAs, omega-3, and omega-6 fatty acids	Cardioprotective formulations, antihyperglycemic, hypolipidemic, and hepatoprotective	[37-39]
Grape	Oleanolic acid, fatty acids, and tocopherols	cardioprotective, antioxidant and antiinflammatory ingredients for functional food, nutraceutical and cosmetic products	[14,40,41]
Tomato	Cutin, and hydroxy fatty acids	Antioxidant, tissue-protective and cosmetic applications	[14,42,43]
Blueberry	Triterpenoids, phytosterols, and tocopherols	Anti-aging formulations, cardiovascular and neuroprotection, prevention of obesity, type 2 diabetes and chronic inflammation	[14,44,45]
Papaya	α -Linolenic acid, and Vitamin E	High antioxidant activity (DPPH, FRAP) <i>in vitro</i> , Nutraceutical applications	[46]

PMFs: Polymethoxyflavones, DPPH: 2,2-diphenyl-1-picrylhydrazyl, FRAP: Ferric reducing antioxidant power, PUFAs: Polyunsaturated fatty acids

non-flammable, and inexpensive and can be tuned by varying to desired pressure and temperature.^[52,53] SFE in citrus peels using co-solvent CO₂ and ethanol has been studied to extract valuable compounds and in particular pressure and temperature conditions (e.g., 300 bar and 45°C) of the extracts produced with high antioxidant activity.^[54]

MAE

MAE uses the microwave energy to heat the solvents and the samples that can be subjected to the solvent to rupture the cells and to increase the release of intracellular compounds.^[53,54] It has been utilized to extract phenolic compounds out of

jackfruit peel waste using NADES, to show the best conditions to achieve a high total phenolic content.^[55] The research also emphasizes on the application of MAE in solvent extraction of bioactive compounds in waste of carrot processing using green solvents, indicating that it could be used to extract the components effectively.^[56]

UAE

UAE makes the use of sound waves of high frequency to form cavitation bubbles in the solvent, which cause disruption of cells and enhanced transfer of target compounds.^[53,57] This method is efficient in the recovery of heat-sensitive chemicals and shortening the time and temperature of extraction.^[58,59] For instance, green extraction of lipids in peach palm fruits using UAE as a co-solvent with the ethanol mixture has been utilized and it is thus possible to compare the lipid extracts of the various colors of fruits.^[60]

Deep eutectic solvents (DESs) and NADES

The DESs and NADESs are a new breakthrough in green chemistry for the extraction and separation processes.^[61] DESs are generally made by combining two or more components through hydrogen bonding, to form a eutectic mixture whose melting point is lower than its components.^[61] DESs generally includes hydrogen bond acceptor mainly choline chloride and a hydrogen bond donor that can be either carboxylic acid, amine, or alcohol.^[61] NADESs are a sub-category of DESs composed of primary natural metabolites such as sugars, amino acids, organic acids, and choline derivatives.^[62]

An example is NADES made of choline chloride and glucose which have been successfully used together with ultrasound extraction to recover polyphenols, including hesperidin, in citrus peels.^[62]

PLE

PLE or accelerated solvent extraction when using water as the solvent as subcritical water extraction applies high temperatures (usually 50–200°C) and pressures (usually 1000–2000 psi).^[63] For example, orange peel waste, which may exceed 32 million tonnes per year, is a considerable source of phenolic antioxidants and limonene that can be recovered using Pressurized Liquid Extraction (PLE).^[50] As an example, PLE with ethyl acetate:γ-valerolactone (20:80 v/v) at 50°C in 6 min resulted into the best extractable phenolic compounds (EPPs), which had strong antioxidant and anti-inflammatory potentials.^[63]

Enzyme-assisted extraction (EAE)

EAE uses specific enzymatic catalysts to break the complex cell wall and membrane structures of plant tissues.^[64] The

often-utilized enzymes include cellulases, pectinases, and hemicellulases as these enzymes attack on the polysaccharide network that traps bioactive compounds as part of the plant matrix.^[63] Among them, the valorization of grapefruit peels in which EAE was used together with UAE to extract both EPPs and non-extractable polyphenols, as well as carotenoids.^[63]

BIOLOGICAL ACTIVITIES AND PHARMACOLOGICAL POTENTIAL OF FRUIT PEEL LIPIDS

Antioxidant activity

The cuticular waxes and associated lipophilic fractions of mango, citrus, and dragon fruit peels contain high levels of triterpenoids (lupeol and α-amyrin), tocopherols, and unsaturated fatty acids that play a major role in the lipophilic antioxidant capacity and prevent lipid peroxidation.^[19] The citrus peel lipids rich in limonene, linoleic, palmitic, and stearic acids exhibit high ferric reducing antioxidant power/cupric ion reducing antioxidant capacity values and are efficient inhibitors of lipid-oxidation compared to some antioxidants of synthetic origin, which makes them suitable for use as natural antioxidants in food and pharmaceutical formulations.^[65-67] Apple, grape, and tomato peels are rich in triterpenoids, which exhibit potent antioxidants and antiproliferative activity, rendering these extracts as a potential source of bioactive ingredients in anti-aging cosmetic products and oxidative stress-modulating phytopharmaceuticals.^[4]

Anti-inflammatory activity

The citrus peel fractions containing limonene fraction and omega 6/other fatty acids fraction have anti-inflammatory properties *in vitro*, which are correlated with the inhibition of inflammatory mediators and anti-hyperalgesic properties, providing potential for topical and systemic anti-inflammatory agents.^[66,67]

Antimicrobial activity

The extracts from citrus peel, rich in lipids containing limonene, linalool, fatty acids, and related terpenoids, exhibited significant antibacterial and antifungal activity, with inhibition zones equal to those of ciprofloxacin against some bacterial and fungal pathogens.^[66,67] The antimicrobial properties of pomegranate peel extracts are significant and correlated with the complex bioactive mixtures that they contain and are used to preserve and treat biomedical materials.^[68,69]

Anticancer potential

Triterpenoid-enriched cuticular waxes, such as ursane- and oleanane-type compounds and other associated lipophiles,

particularly from apple, grape, and tomato peels, have antiproliferative properties, and have been linked to decreased cancer risk in epidemiological and experimental models.^[4] Extracts of citrus and pomegranate peels have anti-cancer and chemopreventive activity attributed to the synergistic antioxidant, anti-inflammatory, and pro-apoptotic effects of the phytochemicals present in these extracts, including lipophilic terpenes and lipophilic fractions.^[39,70,71]

Cardioprotective and neuroprotective effects

The lipid fraction of mango peels is a rich source of phytosterols, tocopherols, and PUFAs, and citrus and pomegranate peels also contain other unsaturated fatty acids and terpenoids, which are known to regulate lipid metabolism and oxidative stress.^[19,71,72] Citrus peel constituents exhibit antihypertensive, antihyperlipidemic and vascular-protective effects, partly attributable to the bioactive components present in citrus peel, which have beneficial effects on endothelial function and on the vascular tissues through their antioxidant and anti-inflammatory properties.^[72-74] Antioxidant and anti-apoptotic effects of pomegranate peel extracts in neural and other tissues suggest the possible neuroprotective effects of pomegranate peel extracts, particularly under oxidative and inflammatory conditions.^[68]

PHARMACEUTICAL APPLICATIONS OF FRUIT PEEL LIPIDS

Nutraceutical applications

The fruit peels of mango, apple, and other fruits are rich in phytosterols and pentacyclic triterpenoids and PUFAs, which are combined to develop cardioprotective and antihyperlipidemic nutraceuticals.^[19,75,76] Lupeol and α -amyrin are encapsulated in the cuticular waxes of mango peels along with α - and β -tocopherols, as lipophilic antioxidants that are of importance for the formulation of dietary products with anti-obesity and antioxidant properties.^[19] The cardiovascular and metabolic protection effects of peel phytosterols and pentacyclic triterpenes are noted as important mediators, and the lipids found in apple peels are associated with the prevention of chronic diseases in functional supplements.^[75,76]

Furthermore, the mango peel has high levels of PUFAs (up to 52% of total fatty acids), supporting its value as a source of essential fatty acids for nutraceutical strategies for the management of dyslipidemia and systemic oxidative stress.^[19]

Functional food applications

The lipids and lipophilic antioxidants extracted from fruit peel are now being investigated as functional food

ingredients, with the potential for improving nutritional and oxidative properties. Mango peels are a good source of PUFAs, triterpenoids, and tocopherols and have been suggested as ingredients for new formulations that can be used in nutraceutical and functional products, to enhance the antioxidant properties of lipid-rich foods and beverages.^[19,77]

Encapsulation technologies, which have been commonly used for fruit and vegetable by-products, can be used to load hydrophobic peel bioactives into functional matrices to safeguard the structure of sensitive lipids and improve their bioavailability in foods and supplements.^[77-89] Peel-derived triterpenoids, sterols, and essential fatty acids can be healthfully incorporated into functional food systems as encapsulated bioactive ingredients, while preventing oxidation and degradation during processing.

Cosmeceutical applications

Cuticular waxes of apple, grape, tomato, and other fruit skins are rich in pentacyclic triterpenoids (such as ursolic- and oleanolic-type) which are under investigation for anti-aging, skin-barrier supporting and photoprotective cosmeceuticals, as well as sterols and tocopherols.^[80,81] The antioxidant and anti-proliferative properties of these peel lipids are strong and are potentially useful in cosmetic emulsions to combat oxidative stress and to regulate dermal cell proliferation and protect against ultraviolet-induced photoaging.^[19,76,80]

Antioxidants like polyphenols extracted from fruit-peels, such as dragon fruit and atemoya peels are already formulated into photoprotective creams, as well as multifunctional cosmeceutical emulsions, where they help in SPF and their antimicrobial effects, while maintaining the integrity of the skin.^[4,80,82] The delivery of the peel-derived bioactives to the epidermal cells is further aided using a more sophisticated delivery system, such as phospholipid vesicles.^[76,80]

Wound healing and tissue protection

The extracts of fruit peelings with lipids as the main solvents are becoming usable as ingredients of preparations for wound healing and as agents that protect tissues from damage with the help of triterpenes like compounds. Lipid-polyphenol systems obtained from the Jabuticaba fruit peel were effective in closing *in vitro* keratinocyte wounds and in preventing oxidative stress, highlighting the potential of these systems in cosmetics.^[76]

CHALLENGES AND FUTURE PERSPECTIVES

Variability in lipid composition among fruit species

The differences in fruit peel lipids among species and cultivars make it difficult to create uniform phytopharmaceutical

ingredients. For instance, mango peels have high levels of pentacyclic triterpenes, tocopherols, and PUFAs, while avocado peels vary considerably in their fatty acid and sterol profile depending on variety.^[19,83] Other environmental conditions, maturity stage, and handling also influence fatty acids and terpenoid-rich fractions.^[84,85] The variability may affect the consistency of the pharmacological effect, dose–response relationships, and regulatory acceptance of peel lipids formulations.

Standardization and quality control

Even though most studies have concentrated on composing the peels' lipid constituents or maximizing extraction yields, a harmonized extraction methodology has yet to be determined for pharmaceutical-grade peel lipids. Solvent composition, extraction time, and temperature have significant effects on bioactive fraction recovery from fruit peels by ultrasound and pressure extraction, highlighting the importance of controlled and validated extraction methods.^[86,87] The quality and repeatability of lipid preparations from peels are still guaranteed by the standardization of extraction procedures and analytical methods.^[51,52]

Extraction efficiency and scale-up challenges

Alternatives for green extraction of citrus peels and other fruit peels include ultrasound and SC-CO₂, but these methods are often optimized for the extraction of phenolics, and there are few industrial-scale data available.^[85,87] Solvent type, ethanol content, temperature, and solid–liquid ratio are important process parameters that can affect yields and can damage thermolabile lipids if not optimized.^[87,88] Efficiency can be enhanced with the use of ultrasound-assisted and other intensified techniques, but scaling-up studies of peel matrices reveal the presence of viscosity effects, mass transfer, and energy consumption issues.^[87,88] However, it is imperative to retain the quality of PUFA and the tocopherols while keeping the process sustainable and cost-efficient, which is a major challenge for the commercialization of peel lipid extraction in the pharmaceutical industry.^[63]

Safety and toxicological considerations

Most studies on the safety of fruit peel fractions have been on extracts rich in phenolics, with only a few focusing on the isolation of lipids restricting the toxicological evaluation of fruit peel lipids intended for use in the pharmaceutical industry. The cytotoxicity and bioactivity of dragon fruit peel and other by-products has been investigated, revealing variable results depending on the extraction solvent used; therefore, careful fractionation and biocompatibility testing is needed.^[89,90] There are significantly higher residues in peels than in pulps when monitoring apples with pesticides, potentially leading

to the transfer of residues into the lipid fraction of peels, and requiring careful monitoring of residues.^[91] The oxidation of peel oils high in PUFAs is also dependent on the stability and storage conditions, impacting on the safety and shelf life.^[92] Hence, there is a need for specific studies on purified peel lipids such as chronic exposure and dermal/oral safety tests for the use of these lipids in wide-scale pharmaceutical applications.^[93]

Future opportunities in phytopharmaceutical development

Nevertheless, new evidence has emerged on mango, avocado, citrus, and other fruit peels, indicating that the lipid fraction of these fruits, which contain triterpenoids, phytosterols, and PUFAs, could be used as a source of potential nutraceutical and cosmeceutical formulations.^[19,83] The use of green extraction technologies such as scCO₂ and UAE in combination with the advanced lipidomics could be leveraged to enable the development of peel-lipid ingredients with specific composition and activity, which could be incorporated into antioxidant, cardiometabolic, and skin protection products.^[63,87,92] Research on the use of pomegranate and citrus peel in plant protection and food preservation suggests that there is a wider commercial interest in the peel and its actives, which could potentially be used in pharmaceutical contexts, but it is currently limited to clinical trials.^[67,93] Thus, fruit peel lipids are a potential source for future phytopharmaceuticals and targeted pharmacological, pharmacokinetic, and human studies are worthwhile to be pursued to realize the full therapeutic and excipient potential.

CONCLUSION

The lipidomic profile of the fruit peel is highly complex and rich in different compounds such as cuticular waxes, phospholipids, sterols, triterpenoids, tocopherols, essential fatty acids, and sphingolipids, all of which are potential phytopharmaceutical raw materials, previously considered as waste in horticultural production.^[74,94] In recent years, new technologies for lipidomics and green extraction, including SPE and UAE, have contributed to the characterization and recovery of bioactive lipids with the preservation of their functional properties and structural integrity. Studies with citrus, apple, avocado, and grapefruit peels have shown that these constituents exhibit a variety of pharmacological properties, such as antioxidants, anti-inflammatory, antimicrobial, anticancer, cardioprotective, and neuroprotective properties.^[29,95-97] Thus, they could be used as useful bioactive components in nutraceuticals, functional foods, cosmeceuticals, topical formulations, and wound healing formulations, which are the current trends in drug industry for sustainable and natural therapeutics towards global market.

Despite this, major problems still lie ahead, such as the variability in lipid composition between and within species due to cultivar, ripening stage and environmental conditions, as well as the need for standardized extraction methods, quality control, and safety assessment, and harmonization of regulatory frameworks.^[83] Thus, the incorporation of horticultural science into pharmaceutical research is crucial to ensure the utilization of fruit processing by-products as a reliable and high value phytopharmaceutical input. The potential applications of fruit peel lipids in the green pharmacy and circular bioeconomy are intriguing, even in the face of these challenges, which provided that they can be successfully clinically validated and manufactured in an environmentally friendly and sustainable manner. Translational studies connecting the lipidomic characterization, formulation science, and human health outcomes are critically needed to realize the full therapeutic potential of lipids.^[98,99]

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AUTHORS' CONTRIBUTIONS

K. Saran Kumar: Writing; S. T. Bini Sundar: Visualization and supervision; G. Ashok Kumar, K. Divya, K. Gurusamy, and C. Indu Rani: Critical review.

DATA AVAILABILITY STATEMENT

All data supporting this review are obtained from previously published studies cited in the reference section. No new experimental data were generated or analyzed.

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