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REVIEW

Phenolic Fraction from Peanut (*Arachis hypogaea* L.) By-product: Innovative Extraction Techniques and New Encapsulation Trends for Its Valorization

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Abstract
Peanut skin is a by-product rich in bioactive compounds with high nutritional and pharmaceutical values. The phenolic fraction, rich in proanthocyanidins/procyanidins, is a relevant class of bioactive compounds, which has been increasingly applied as functional ingredients for food and pharmaceutical applications and is mostly recovered from peanut skins through low-pressure extraction methods. Therefore, the use of green high-pressure extractions is an interesting alternative to value this peanut by-product. This review addresses the benefits of the phenolic fraction recovered from peanut skin, with a focus on proanthocyanin/procyanidin compounds, and discusses the improvement of their activity, bioavailability, and protection, by methods such as encapsulation. Different applications for the proanthocyanidins, in the food and pharmaceutical industries, are also explored. Additionally, high-pressure green extraction methods, combined with micro/nanoencapsulation, using wall material derived from peanut industrial processing, may represent a promising biorefinery strategy to improve the bioavailability of proanthocyanidins recovered from underutilized peanut skins.

Keywords Procyanidins · Peanut skins · Green extractions · Bioavailability · Encapsulation

Introduction

Food industries are redesigning their production chains to address the emerging consumer demand for high-nutritional foods, products with enhanced functional and physical properties, and enriched with health-promoting constituents (Galanakis, 2021). With population growth, emphasis is directed towards the reprocessing of agro-industrial by-products, as a contribution to circular economy, valuing the biorefinery concept by means of green processes applications (Benvenutti et al., 2021).

Peanut (*Arachis hypogaea* L.) is an important oilseed cultivated and appreciated worldwide. The processing of peanut oilseeds provides various popular peanut goods, generating large amounts of by-products (Sorita et al., 2022). Among them, peanut meal (derived from oil production), skins, and shells are the main by-products of peanut processing, which are mostly used for animal feed (Sorita et al., 2020). Particularly, peanut skins are valuable by-products from peanut processing operations, with more than one million tons produced worldwide every year and presenting considerably high contents of proanthocyanidins and their isomers (Xu et al., 2022).

The phenolic-rich fraction recovered from peanut skins is becoming increasingly popular due to the growing demand for functional foods, beyond the interest from pharmaceutical industries. The use of the peanut-phenolic fraction (rich in procyanidins) in food and pharmaceutical formulations can promote several health benefits, such as antioxidant (Constanza et al., 2012), anti-cancer (Liu et al., 2020), cardioprotective (Rauf et al., 2019), anti-diabetic and anti-obesity (Unusan, 2020), antimicrobial (Camargo et al., 2017b), neuroprotective (Singh et al., 2017), antiviral (Makau et al., 2018), and anti-asthmatic (Kandhare et al., 2013).

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In connection to that, this review evaluates possible uses for the phenolic-rich fraction from peanut skin, mainly composed by proanthocyanidins/procyanidins components, in food and pharmaceutical formulations, adding value to this underestimated by-product. For this purpose, a fast search at SCOPUS Database (up to June, 2022) shows that 2538 studies are relate to peanut and its by-products ("peanut") AND ("by-products" OR "waste" OR "residue"). Refining the search, 86 works were founded related to peanut skin and phenolic compounds ("phenolic" AND "peanut skin"), showing the growing interest from the scientific community about phenolic compounds from food by-products, particularly peanut skin. Specifically, in the last 10 years (2012–2021), 61 works were published (71% of total studies), and 5 studies were published up to June 2022. The criteria used for article selection were within the title, abstract, and keywords. The USA, with 27 works, was the first in publication ranking, followed by Brazil (22 studies) and Argentina (9 studies). Additionally, among the 86 studies, 62 are related to agricultural and biological sciences; 32 to chemistry; 19 to biochemistry, genetic, and molecular biology; and 15 are related to chemical engineering, showing the multidisciplinary enrolled in this subject, rising the application possibilities.

To identify alternative sources of phenolic compounds and the efficient methods for their recovery is of utmost scientific and industrial interest. Then, within the viable sources of this relevant fraction, peanut skin emerges with high potential due to the relevant content of these components that can promote several health benefits. Because the recovery of phenolics from peanut skin can be achieved by several methods, this review provides an update about the extraction techniques, focusing on green methods with non-toxic solvents, such as supercritical fluid extractions (SFE), pressurized liquid extraction (PLE), subcritical water extraction (SFE), ultrasound-assisted extraction, and microwave-assisted extractions (MAE) and its combination, in a biorefinery concept.

Although some phenolic characteristics, such as fast delivery and degradation, combined with low solubility and bioavailability, may restrict its direct use in pharmaceutical and food formulations (Xu et al., 2022), nevertheless, encapsulation processes are exciting alternatives to overcome the restrictions for its applications, and these options are also compiled in this review.

Association of sustainable extraction methods (for selective extractions), health benefit characteristics, and encapsulation strategies can be an interesting way to value food by-products, allowing further applications of the recovered fractions in food and pharmaceutical products.

Therefore, the present review provides the connection of two strategies for the valorization of peanut by-product, the innovative and sustainable extraction methods and green encapsulation procedures. This approach can stimulate the circular economy, integrating the industry 4.0 design by means of developing green process and products.

Peanut: Increase in By-product Generation

The world population growth connected to the increasing use of oilseed commodities as input for biofuel production had led to higher demand for oil production, affecting consequently the oil prices (Shokoohi & Saghaian, 2022). For that reason, the oilseed production and market are growing fast, and the 5 main world producers of peanut in 2021 are shown in Fig. 1 (USDA, 2022).

China, India, Nigeria, the USA, and Sudan, the main peanut producers in 2021, were responsible for 69% of the world production, where China contributed most, with 36% of word production (18.2 K MT). India and Nigeria were the second and third highest peanut producers, being responsible for 14% (6.8 K MT) and 8% (4.22 K MT), respectively, followed by the USA and Sudan (6 and 5% of world production), providing 2.9 and 2.3 K MT, respectively.

The projection for 2022, related to peanut meal, destined for industrial uses, and oil consumption, indicates near historic levels, reaching the peanut production in the USA, while the Brazilian production is estimated to increase by 60% of the production compared to 2018/2019. Still for 2022, it is projected a peanut production rise in 17% related to whole seed, oils, and food uses (USDA, 2022).

Considering that most peanut-based products do not contain the red skin layer, the amount of this by-product is increasing. Besides, taking into account the circular economy context, the transformation of agro-industrial residues (like peanut skin), as sources of valuable products, contributes to sustainable industrial processes, and can be of relevance to contribute to peanut industrial processing. Then, because peanut skin represents about 3% of the peanut weight (Lorenzo et al., 2018; Sorita et al., 2020), and the world peanut production in 2021 was 50.22 K MT (USDA, 2022), it is estimated that approximately 1.50 K MT of peanut skin were generated in 2021. Also, considering the representative amount of phenolic compounds from peanut skin, this by-product can be considered an emerging and promising feedstock for the recovery of bioactive ingredients.

Therefore, with the increase in peanut skin generation, worldwide studies (mainly from the USA, Brazil, and Argentina, as reported in the "Introduction" section) have been focusing on the extraction of the phenolic-rich fraction from this valuable by-product, rising food and pharmaceutical applications, as substitute of synthetic additives, as discussed in the next sections.

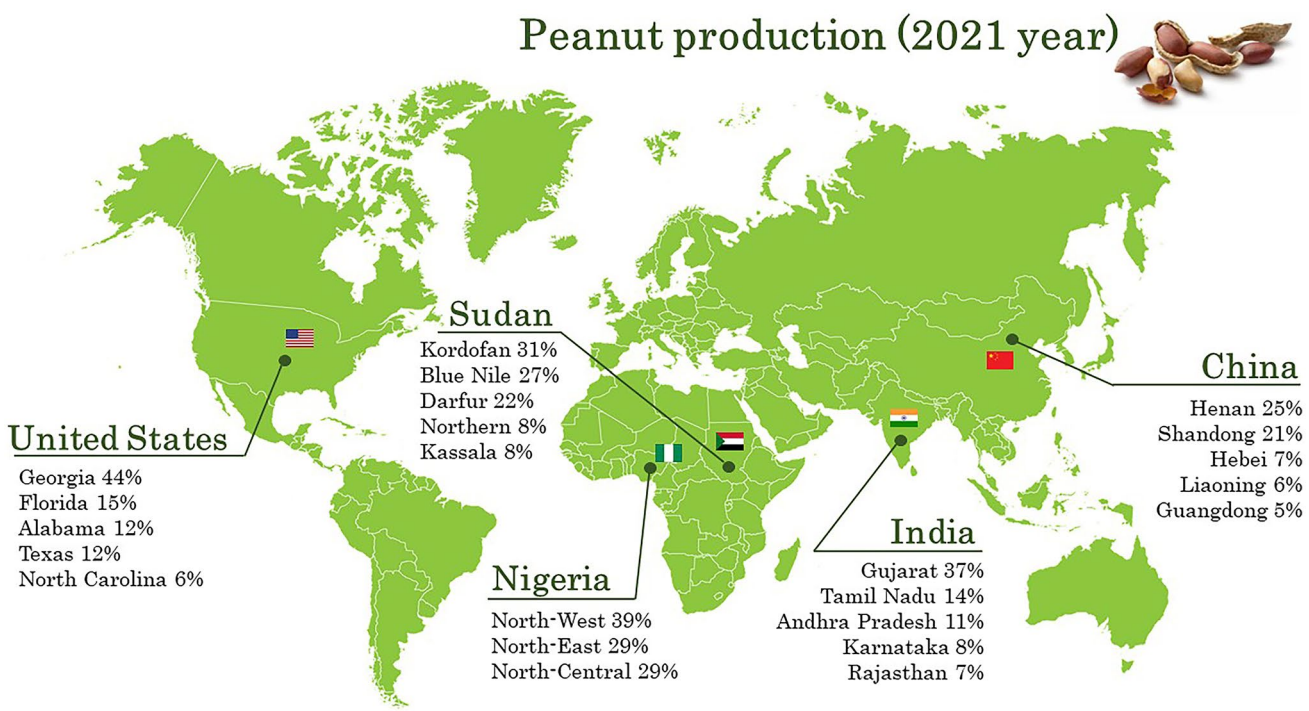


Fig. 1 The five most peanut producers worldwide in the 2021 year. Source: USDA (2022)

Phenolic Compounds in Peanut By-products

Peanut skin contains several compounds (mainly phenolic components) with diverse potential biological activities. In nature, the phenolic compounds from plants (generally concentrated at the skins or peels) are responsible for color, taste, and flavor attributes, indicating the plant maturity. These compounds have two main functions: (i) protect against insects, pathogens, and herbivorous animals, and (ii) attract insects for flower pollination.

Phenolic compounds can be classified in four subgroups (categories): phenolic acids, flavonoids (including flavonols, flavones, flavanols, anthocyanidins, and isoflavones), tannins, and stilbenes (An et al., 2021; Neuenfeldt et al., 2022; Singh et al., 2017). Figure 2 illustrates the phenolic compounds identified in peanut by-products.

Phenolic acids are a minor phenolic group from peanut skins, mainly composed by coumaric, caffeic, and ferulic acids, and this class of components are represented by the phenolic compounds with one carboxylic acid group. Protocatechuic, ferulic, caffeic, and p-coumaric are the main compounds identified and quantified in peanut skin. Chlorogenic acids (and their monomers, quinic acid) can also be founded in peanut skin, although rarely, but their presence can be associated to peanut cultivars and industrial processing (Dean, 2020; Lan et al., 2020; Ma et al., 2013; Sarnoski et al., 2012a).

Stilbenes, also identified from peanut skin, are extensively recovered from numerous food by-products due to their valuable biological activities. Resveratrol is the main stilbene from peanut skin, among other derivatives such as isopentadienylresveratrol, piceatannol, piceid, and some prenylated resveratrol analogs. The resveratrol content varies with peanut cultivar and processing; for instance, Spanish skins (15.04 μg g^{-1}) have higher content than Runner and Virginia types (4.30 and 3.66 μg g^{-1}, respectively) (Francisco & Resurreccion, 2009).

Flavonoid components (monomeric and condensed) are the main fraction of phenolic compounds from peanut skin, such as catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate, epigallocatechin gallate, quercetin, and proanthocyanidins and a complex series of procyanidins oligomers, which have been already identified and quantified from this by-product. Then, because procyanidin (A-type procyanidin dimer, trimers, and tetramers) can achieve a remarkable value of 85.7% of the total phenolic components from peanut skin (Xu et al., 2022), the present study focuses on the flavonoid group (specifically, in proanthocyanidins/procyanidins oligomers), which is presented in terms structures and the biological activities associated.

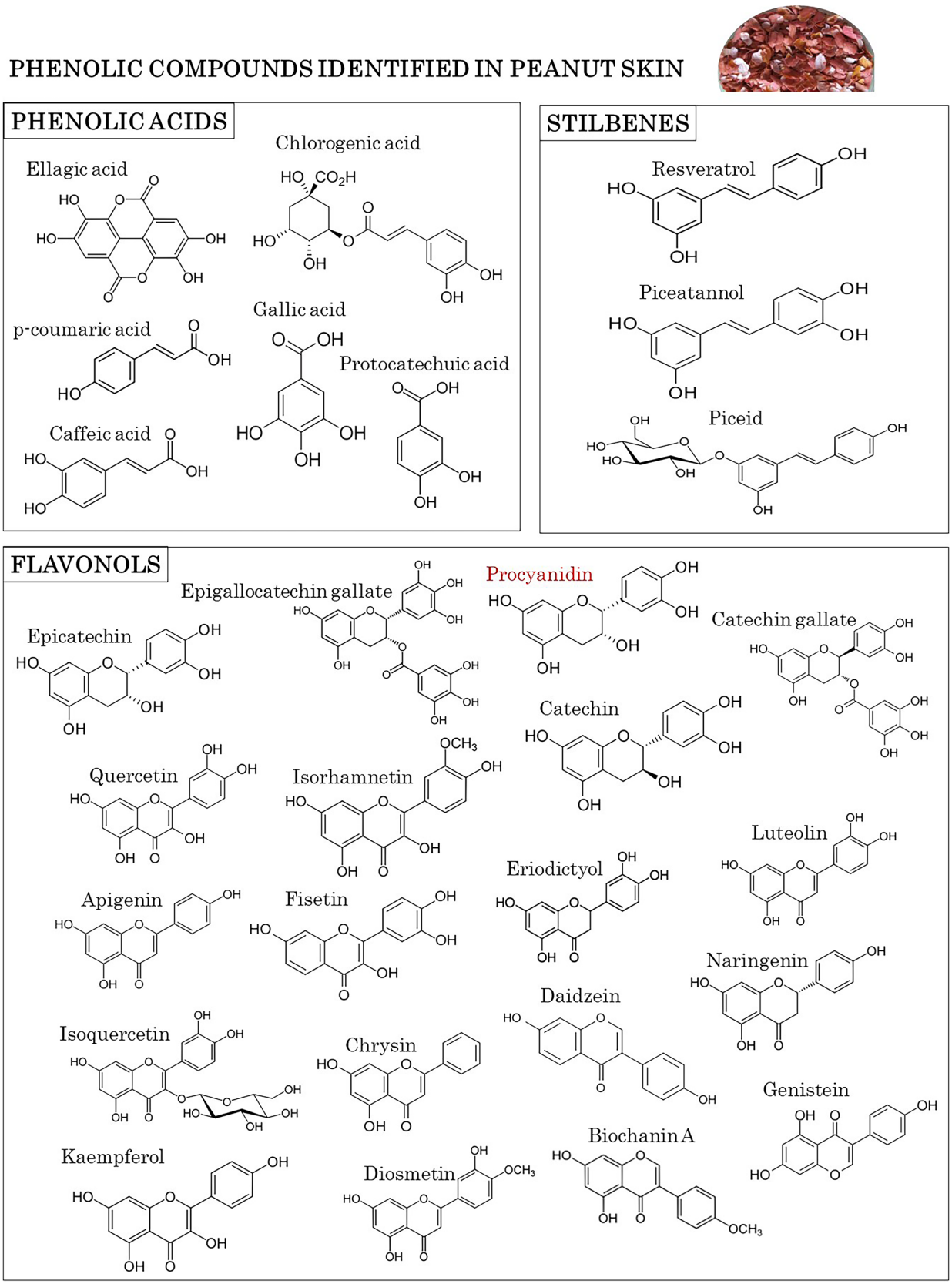


Fig. 2 Phenolic groups identified in peanut skin

Proanthocyanidins and Its Structures

Proanthocyanidins are high molecular weight polyphenolic compounds, which, for peanut skin, are originated from the polymerization of flan-3-ol by saturated linkage between two carbon molecules (C–C), and occasionally by C–O–C bonds, as shown in Fig. 3.

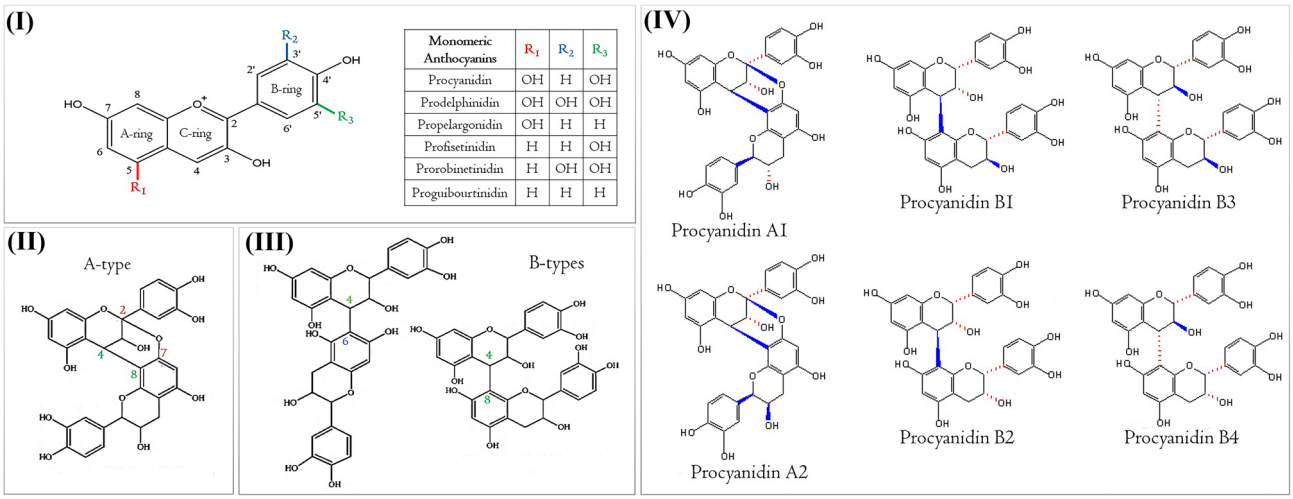
In Fig. 3(I), a general molecular structure of common monomeric anthocyanins (subclasses), such as procyanidins, prodelphinidins, propelargonidins, profisetinidins, prorobinetinidins, and proguibourtinidins, is shown (Xie & Dixon, 2005). These subgroups are obtained from depolymerization and/or decomposition at high temperature in acid medium. The most common subgroups from proanthocyanidins are the procyanidins, oligomers of (epi)catechin units, and their galloyl derivatives (Bansode et al., 2014), widely present in peanut skin.

The proanthocyanidin molecular structures, considering linkage types, are presented at Fig. 3(II, III), which show A-type (C_4–C_8 and C_2–O_7) and B-type (C_4–C_8 and C_4–C_6) proanthocyanidins, respectively. The linkage of monomeric units (Fig. 3(I)) occurs mostly between C_4 from the "upper" monomeric unit and C_8 or C_6 from the "lower" monomeric unit (B-type, Fig. 3(III)), called B-type because the linkage is based on the lower unit, the B-ring. The most common B-type proanthocyanidin dimers are found in nature, frequently from plant tissues, the B_1, B_2, B_3, and B_4, which are related to C_4–C_8 bonding (Fig. 3(IV)). Types B_5, B_6, B_7, and B_8 are less frequent and related to C_4–C_6 bonds. Sometimes, an extra ether group is found between C_2 and O_5 or O_7, and the structure is called A-type due to linkage based on A-ring; more specifically, the C-ring of the "upper" monomeric unit is linked with the A-ring of the "lower" monomeric unit (Fig. 3(II)) (Neto et al., 2020; Rauf et al., 2019), with A_1 and A_2 as the most common A-type proanthocyanidins (Fig. 3(IV)). The synthesis of proanthocyanidins from the chemical, biochemical, and molecular genetic perspectives is presented in detail by Xie and Dixon (2005).

The structure, the monomeric composition, the degree of polymerization, and the specific linkages of the proanthocyanidins affect their bioactivities (Dong et al., 2013). For instance, according to Andersen-Civil et al. (2021), the bioavailability, stability, and activity of polyphenolic compounds, such as proanthocyanidins, may be correlated with the amount of hydroxyl groups, mean polymerization, and/or bond type and position between the monomers. Besides, Vazquez-Flores et al. (2018) suggested that proanthocyanidins with low degree of polymerization are more apt to inhibit digestive enzymes, such as intestinal lipase, amylase, and proteases, due to their capacity to bind with specific cavities from the enzymes, better than polymer or oligomer molecules.

Proanthocyanidins/Procyanidins from Peanut By-products

Proanthocyanidins/procyanidins derived from plant and food by-products emerged as functional ingredients, attracting attention from the food industry and health organizations due to their well-being beneficial properties, such as the protective effect against diabetic retinopathy (Sun et al., 2016), complementary and alternative strategy to prevent



Monomeric Anthocyanins	R_1	R_2	R_3
Procyanidin	OH	H	OH
Prodelphinidin	OH	OH	OH
Propelargonidin	OH	H	H
Profisetinidin	H	H	OH
Prorobinetinidin	H	OH	OH
Proguibourtinidin	H	H	H

Fig. 3 (I) General molecular structure of common monomeric anthocyanins, (II) molecular linkage structure for A-type proanthocyanidins (C_4–C_8 and C_2–O_7), (III) molecular linkage structure for B-type proanthocyanidins (C_4–C_8 and C_4–C_6), and (IV) procyanidins A1, A2, B1, B2, B3, and B4 types. Source: Adapted from Neto et al. (2020), Xie and Dixon (2005) and He et al. (2008)

skin cancer by attenuating the adverse UV radiation effects (Katiyar et al., 2017), and also atherosclerosis prevention, cardiovascular protection, and reduction of total cholesterol from blood plasm (Blade et al., 2010). Besides that, proanthocyanidins are related to maintaining vascular elasticity and normal blood pressure (Odai et al., 2019), among other health-promoting characteristics.

The linkage types from A- and B-proanthocyanidins affect their activities; for instance, A-type (peanut skin) has higher trypsin inhibitor activity and higher affinity for α-casein (useful for wall material attributes, facilitating encapsulation) and strongly inhibits α-amylase, compared to B-type (Le Bourvellec & Renard, 2018). Besides, A-type proanthocyanidins help prevent recurrent urinary tract infections, a property not observed from B-type proanthocyanidins (Liu et al., 2012). A comprehensive approach of the benefits of A- and B-type proanthocyanidins is discussed below.

Recently, several researchers have shown that peanut skins are excellent sources of phenolic compounds, particularly proanthocyanidins/procyanidins, present in high concentration (~86%) (Xu et al., 2022) with innumerous biological activities (Appeldoorn et al., 2009; Bodoira et al., 2019; Munekata et al., 2016; Oldoni et al., 2016). Then, Table 1 summarizes the scientific works related to the recovery of proanthocyanidins from peanut skin, associating with extraction methods, processing conditions applied, and the main results detected.

It is important to point that the content of proanthocyanidins from peanut skin by-products varies with the source, as well as the recovery and quantification procedures (Table 1 data). Besides, the proanthocyanidin content can be affected by several factors, such as (i) peanut cultivation, for instance, specie or variety, climate, and soil conditions; (ii) peanut processing, like mechanical peeling and roasting; and (iii) extraction conditions.

Chukwumah et al. (2012) compared the total proanthocyanidin content (in cyanidin chloride equivalent (CCE)) of twenty-seven cultivars from different regions, with results ranging from 0.101 to 1.030 mg CCE g^{-1} of peanut skins, where the lower value was from Valencia variety while the higher content was from Runner variety. Yu et al. (2006) showed that peanut processing (oilseed roasting) affected the procyanidin content from the skin, compared with non-roasted peanut skin. For instance, the content of trimer and tetramer proanthocyanidins reduced with temperature increase, from 0.221 and 0.296 mg g^{-1} (non-roasted skin) to 0.157 and 0.204 mg g^{-1} (roasted skin), respectively. Otherwise, the dimers' content increases, from 0.111 (non-roasted skin) to 0.143 mg g^{-1} (roasted skin), due to degradation of larger proanthocyanidins into lower ones (dimers).

Most studies for the recovery of proanthocyanidins from peanut skins apply conventional extraction methods (maceration and Soxhlet extraction), which are generally highly time- and solvent-consuming. Mostly, these methods have low selectivity, resulting in less pure extracts, with residual solvent, that compromises its use for food industries (Belwal et al., 2020). In addition, the long extraction time that is normally required can cause proanthocyanidin degradation, reducing their antioxidant and antimicrobial properties (Bodoira et al., 2017).

Usually, conventional extraction of proanthocyanidins from peanut skin requires two steps: lipid extraction by nonpolar solvents that act as a barrier for proanthocyanidins extraction, followed by polar solvent extraction, from defatted peanut skin, to obtain the polyphenol fraction (e.g., proanthocyanidins) (Tamkutė et al., 2020).

Larrauri et al. (2016) recovered proanthocyanidins from peanut skin by conventional three-step extraction: (1) lipid extraction by Soxhlet with *n*-hexane for 6 h, followed by (2) polyphenol extraction by maceration with ethanol/water (70:30 v/v) at room temperature for 24 h, and (3) purification with ethyl acetate in a column (Sephadex LH-20) eluted with ethanol. Fractions (2) and (3) were analyzed by HPLC–ESI–MS/MS, detecting phenolic acids (quinic, gallic, and cumaric acids), flavonoids (catechin, epicatechin, quercetin, isoquercetin, genistein, isorhamnetin, apigenin, chrysin, procyanidins, and proanthocyanidins), and stilbenes (resveratrol). The main proanthocyanidins from fraction (3) were as follows: procyanidin dimer A-type (31.49%), proanthocyanidin dimer (24.33%), and procyanidin dimer B-type (14.15%). Using four-step extraction, Munekata et al. (2016) recovered proanthocyanidins from peanut skin by (1) stirring maceration (ethanol/water 80:20 v/v) at 60 °C for 50 min, (2) 15-min sonication, (3) centrifugation (6000 rpm for 15 min), and (4) filtration.

The number of extraction steps, process conditions, recovery efficiency, and quality of the recovered fractions can be modified by the extraction method and solvent used. Alternative high-pressure methods and environmentally friendly solvents may contribute to green processes, stimulating the sustainable development (Benvenutti et al., 2021).

Innovative Extraction of Proanthocyanidins/Procyanidins

Recently, with the increasing demand of natural products, additives, or bioactive extracts for foods, cosmetics, and pharmaceutical applications, the extraction specialists have focused on improving the processes efficiency, reducing extraction time, number of operations, energy consumption, and amount of solvent, which reduce environmental impact, economical costs, and generated waste, but simultaneously keeping attention on the extract's quality (Chemat et al., 2019).

Table 1 Studies related to the extraction of proanthocyanidins and oligomers from peanut skins

Study objective	Conventional extraction method	Extraction conditions	Quantification/identification	Highlight results	Reference
Develop a simple method for preparing sufficient amount of A-type dimers from peanut skins and persimmon pulp	Soxhlet extraction	3 followed extractions with 20% (v/v) of methanol followed by filtration and lyophilization	HPLC–MS	A-type proanthocyanidin content: 378.3 mg kg^{-1} dry peanut skins (88.72% of purity)	Dong et al. (2013)
Inhibitory activity of proanthocyanidins from peanut skin on inflammatory cytokine production and melanin synthesis in cultured cell lines	Maceration followed by ultrasound, filtration, and evaporation	Maceration: acetone/water (70:30 v/v) for 24 h Ultrasound: 30 min	UPLC-DAD-EIS-MS	11 proanthocyanidins were identified Peanut skin extracts decreased melanogenesis in cultured human melanoma	Tatsuno et al. (2012)
Determine the effects of processing on phenolic composition of peanut skin and identify/quantify peanut skin procyanidins	Maceration with stirring followed by centrifugation	Ethanol/water (8:92 v/v)	LC–MS	Procyanidin dimer, trimers, and tetramers content were 0.111, 0.221, and 0.296 mg g^{-1} of non-roasted peanut skin and 0.143, 0.157, and 0.204 mg g^{-1} of roasted peanut skin	Yu et al. (2006)
Isolation of A-type (from peanut skins) and B-type (from grape seeds) dimers by combining normal phase (NF), reversed phase (RF), and HPLC chromatography	Soxhlet extraction followed sonication	Soxhlet: methanol/water (20:80 v/v) Ultrasound: water/ethyl acetate (50:50 v/v) for 10–15 min at room temperature followed by lyophilization	NF-RF-HPLC-NMR	Yields increased 20–400 times for A-type dimers and 10 times for B-type dimers compared to other methods	Appeldoorn et al. (2009)
Provide scientifically valuable information of proanthocyanidins for better utilization of peanut skin	Maceration followed by ultrasound, filtration, and evaporation	Maceration: acetone/water (70:30 v/v) for 24 h Ultrasound: 30 min	UPLC-DAD-EIS-MS	A type proanthocyanidin trimer was identified, isolated, and purified This compound presented strong antioxidant activity and inhibition on sucrase	Zhang et al. (2013)
Evaluate the antioxidant activity of crude extract and fractions of peanut skin, and isolate proanthocyanidins by bioassay-guided fractionation technique	Extraction with water acidifier followed by filtration, evaporation and lyophilization	23 g of peanut skins Solvents: acetone/water (60:40), acidified to pH 1.5 with 0.1 mol/L HCl, in a thermostatic bath at 70 °C for 30 min	Quantification: HPLC Identification: NMR	The authors isolated proanthocyanidins A_1 and A_2 type Proanthocyanidins A_1 proved to be more active than A_2 related to antioxidant activity	Oldoni et al. (2016)

Table 1 (continued)

Study objective	Conventional extraction method	Extraction conditions	Quantification/identification	Highlight results	Reference
Peanut skins and dry-blanched peanuts as sources of phenolic compounds and evaluate their antimicrobial effect	Maceration with stirring followed by centrifugation	Mass of skin: 2.5 g Time of extraction: 20 min Acetone/water (70:30 v/v) Temperature: 30 °C Liquid/solid ratio of 1:5 (w/v)	HPLC–DAD-ESI–MS	Phenolic acids content: 175.3 μg g^{-1}, proanthocyanidins: 4959 μg g^{-1} and monomeric flavonoids 791.3 μg g^{-1} of dry biomass Extracts inhibited the growth of gram-positive and gram-negative bacteria	Camargo et al. (2017a)
Compare proanthocyanidin composition of single solvent and multistep extraction procedures of peanut skins by HPLC–UV-vis absorbance	Ultrasound	Mass of skins: 1 g Solvents: acetone, ethanol, methanol, or boiling water (99.7 °C) for 15 min followed by filtration Solid/liquid ratio of 1:10	HPLC–MS-UV–vis absorbance	A-type proanthocyanidins was identified Multistep extraction procedure is an effective means of concentrating procyanidins	Sarnoski et al. (2012a)
Compare flavan-3-ol composition and antioxidant capacity of roasted skin obtained by peanut, hazelnut, and almonds	Sharking water bath followed by evaporation	Solvent: acetone/water (80:20 v/v) Solid/liquid ratio of 1:10 (w/v) Temperature: 50 °C Time of extraction: 30 min	HPLC–DAD-fluorescence and HPLC–DAD/ESI–MS	Peanut presented both A- and B-type proanthocyanidins (A forms were predominant) with higher antioxidant capacity compared to almond	Monagas et al. (2009)
Chemical composition and antioxidant activities of extracts and purified fractions obtained from the peanut skins separated by blanching and roasting processes	Maceration followed by evaporation	Solvent: ethanol/water (70:30 v/v) Room temperature at 24 h	HPLC–ESI–MS/MS	The major component of factionary extracts was procyanidin dimer type A (31.49%), proanthocyanidin dimer (24.33%), and procyanidin dimer type B (14.15%)	Larrauri et al. (2016)
Isolate proanthocyanidins from peanut skin extracts and evaluate their activity against hyaluronidase	Boiling water	Solvent: distillated water Time of extraction 2 h	HPLC and ^{13}C NMR	Proanthocyanidin A_1 and proanthocyanidin A_2 were identified with substantial activity against hyaluronidase	Lou et al. (2001)
Compare profiles of proanthocyanidins extracted from peanut skins and cranberry	Ultrasound followed by centrifugation, evaporation and freeze dried	Solvent: acetone/water/acetic acid (70:28:2, v/v/v) 5 min of extraction	HPLC and MALD-TOF MS	Peanut skins and cranberries have similar proanthocyanidins composition; they contain both A-type and B-type proanthocyanidins, with the A-type being predominant	Ye and Neilson (2016)

Table 1 (continued)

Study objective	Conventional extraction method	Extraction conditions	Quantification/identification	Highlight results	Reference
Produce a dried extract from the peanut skin using the spray-drying technology and evaluate the processing conditions	Ultrasound followed by centrifugation, filtration, and evaporation	Solvent: ethanol/water (80:20 v/v) Temperature of 60 °C for 15 min Centrifugation at 6000 rpm for 15 min	HPLC–DAD-UV	Encapsulated procyanidins presented remarkable antioxidant activity, bacteriostatic activity against Gram-positive bacteria (*S. aureus* and *L. monocytogenes*), and bactericidal activity against *S. aureus*	Calomeni et al. (2017)
Evaluate the phenolic profile and antioxidant activity in vitro of peanut skin extract and their effect on characteristics of sheep patties during storage	Maceration followed by sonication, centrifugation, and filtration	Mass of skin: 30 g Solvent: ethanol/water (80:20 v/v) Temperature of 60 °C; and 50 min of extraction; then the mixture was sonicated for 15 min at room temperature	HPLC–ESI–MS	The major group of phenolic compounds in peanut skin was the proanthocyanidins Lipid and protein oxidation in sheep patties was effectively inhibited by the extracts	Munekata et al. (2016)
Determine the antioxidant activity and anti-inflammatory properties of peanut skin extracts	Maceration with stirring followed by filtration and freeze-dryer	Solvent: acetone/water (50:50 v/v) or ethanol/water (90:10 v/v)	HPLC–MS	Procyanidins were present in acetone extracts in the range 0.4 to 31.9 mg g^{-1} of skin and 0.2 to 13.2 mg g^{-1} of skin in ethanol extracts The extracts presented antioxidant and anti-inflammatory effects	Lewis et al. (2013)
Produce spray-dried powders from peanut skin extracts with high antioxidant activity and procyanidin content that could be used as value-added food ingredients	Stirring followed by filtration and evaporation	Solvent: ethanol/water (70:30 v/v) Solid–liquid ratio: 1:5 w/v Time of stirring: 20 min	HPLC–ESI–MS	Spray-drying increased the proportion of flavan-3-ols and degree of polymerization 2 procyanidins in the extracts The power presented higher antioxidant capacity and total phenolics and increased solubility compared to milled skins	Constanza et al. (2012)
Define the structure elucidation of four new naturally occurring A-type procyanidins from peanut skins, also develop an analytical protocol for accurately defining the chemical structure of the A-type procyanidins	Percolation	1st extraction: 30% MeOH 2nd extraction: 70% acetone 1st and 2nd extracts were combined and portioned three times	Reversed-phase HPLC combined with ^{13}C NMR	Four new A-type procyanidins of tri- and tetrameric structures were identified, also tetramers presented anti-inflammatory cytokines	Dudek et al. (2017)

Table 1 (continued)

Study objective	Conventional extraction method	Extraction conditions	Quantification/identification	Highlight results	Reference
Determine proanthocyanidins profiles of peanut skins from three varieties of peanuts (Virginia, Spanish, and Valencia)	Ultrasound	Ethanol (100%) for 15 min	MALDI-TOF MS	Monomers of "A-type" interflavan bonds were predominant in the extracts, indicating that 95% of the proanthocyanidins oligomers presented in the extracts contain one or more A-type bonds	Muñoz-Arrieta et al. (2021)

Green extractions, besides reducing energy consumption, also allow the use of generally recognized as safe (GRAS) solvents and are applied for renewable natural products or underused by-products from industrial processes (Chemat et al., 2019; Moro et al., 2021; Wang et al., 2022). High-pressure methods such as supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE) are within the promising techniques for the recovery of proanthocyanidins from peanut skin because they are fast processes with low solvent consumption, generally green solvents, such carbon dioxide, ethanol, water, or their mixtures (Mazzutti et al., 2017; Rifna et al., 2021).

High-pressure methods and other alternative techniques (like MAE and ultrasound) are established procedures, with well-known properties and advantages. Ameer et al. (2017) presented a comprehensive review about these green methods for polyphenol extraction, comparing efficiencies, applications, and characteristics. Also, several works proposed sequential high-pressure extractions to value different biomasses, such as peanut (Sorita et al., 2020), cacao (Mazzutti et al., 2018), and tamarind (Martins et al., 2020) by-products.

Porto and Natolino (2017) applied SFE with CO_2, combined with ethanol or water as co-solvents, to recover proanthocyanidins from grape seeds. The process optimization consisted of following a Box-Behnken design to study the effects of pressure, co-solvent amount, and CO_2 flow rate on polyphenol and proanthocyanidins extraction. The best condition (80 bar, CO_2 flow rate of 6 kg h^{-1} and 20% (v/v) of ethanol as co-solvent) provided more than 10 mg g^{-1} of dry biomass of monomeric proanthocyanidins and above 8 mg g^{-1} of dry biomass of oligomeric proanthocyanidins.

PLE, a promising green method, was recently used by Rossi et al. (2020) to obtain proanthocyanidins from peanut skin at 7 MPa, 220 °C, and 7 g min^{-1} of ethanol/water (60:40 v/v) as solvent. The recovered extract had 24 compounds identified by HPLC–ESI–MS/MS, represented by procyanidin dimers (about 75%), monomeric flavonoids (4.31%), and proanthocyanidin dimmers (about 5%). The extract quality suggests the high-pressure PLE method as an alternative to value industrial peanut skin.

Other non-conventional promising techniques, such as MAE (Chen et al., 2016), sub-critical water extraction (SWE) (Bodoira et al., 2017), and ionic liquid extraction (Liu et al., 2012), have also been applied for the recovery of proanthocyanidins from different feedstocks. Table 2 shows different raw materials used as source of proanthocyanidins, recovered by green extraction techniques. Table 2 data also list the solvents used, extraction parameters, content of recovered proanthocyanidins, and suggested applications.

Chen et al. (2020a) used MAE and conventional maceration with ethanol/water (94:6 v/v) to recover proanthocyanidins from grape seeds. Higher content of proanthocyanidins,

Table 2 Recovery of proanthocyanidins and oligomers from different feedstocks

Feedstock	"Green" recovery	Solvent	Parameters of extractions	Proanthocyanidins content	Application	Reference
Peanut skin	Pressurized liquid extraction	Ethanol/water (60:40 v/v)	7 MPa; 220 °C; flow rate of 7 g min^{-1}	Procyanidin dimer ~75% (w/w) Proanthocyanidin dimers ~0.05% (w/w)	Functional ingredients for foods	Rossi et al. (2020)
Peanut skin	Supercritical fluid extraction	CO_2 with ethanol as co-solvent (0.15 mL min^{-1})	10 MPa, 343 K, and 0.15 mL min^{-1} for 30 min	Proanthocyanidin content: 0.352 mg g^{-1} Procyanidin content: 2.464 mg g^{-1}	Unspecified	Putra et al. (2021)
Grape seeds	Supercritical fluid extraction	CO_2 + 20% (w/w) of ethanol	80 bar; 6 kg of CO_2 h^{-1} and 200 min of extraction	Monomeric > 10 mg g^{-1} of dry biomass Oligomeric > 8 mg g^{-1} of dry biomass	Production of dietary supplements, functional food, and antioxidant additives for food and cosmetic products	Porto and Natolino (2017)
Cinnamomi cortex	Microwave-assisted simultaneous distillation	Water	Liquid–solid ratio of 18.0 mL g^{-1}, microwave irradiation power of 374 W for 38 min	1.60 ± 0.07% (w/w)	Food additive	Chen et al. (2016)
Peanut skins	Sub-critical water extraction	Ethanol/water (60.5:39.5 v/v)	7 MPa; 220 °C; flow rate of 7 g min^{-1}; 105 min of extraction	Unquantified	Food applications	Bodoira et al. (2017)
Cinnamomi cortex	Ionic liquid-based microwave-assisted simultaneous extraction	1-butyl-3-methylimidazolium bromide ionic liquid (0.5 M)	20.0 g mass of sample 230 W microwave irradiation power; 15 min of extraction; and 10 mL g^{-1} of liquid:solid ratio	1.24 ± 0.04% (w/w)	Spice; perfumery, flavoring, and pharmaceutical industries	Liu et al. (2012)
Cinnamomum japonicum Sieb. leaves	Solvent-free microwave-assisted distillation followed by homogenate extraction	Distillation: water Microwave: 71% ethanol volume fraction	Microwave extraction: 540 W of microwave power and a 40-min irradiation time Homogenate extraction: 16 mL g^{-1} liquid–solid ratio and 4-min homogenate time	71.97 ± 2.71 mg g^{-1} dry leaves	Foods, perfumery, and Chinese traditional medicine industries	Zhao et al. (2020)
Pinus pinaster (*Maritime pine*)	Microwave-assisted extraction	Ethanol/water (80:20 v/v)	Solid–liquid rate: 1:10; 100 W; 3 min of extraction	37.1 mg g^{-1} dry biomass	Unspecified	Chupin et al. (2015)
Maritime pine (*Pinus pinaster* Ait.)	Supercritical fluid extraction	CO_2/ethanol (70:30 v/v)	25.1 kPa; 303 K; flow rate $7.6.10^5$ kg s^{-1} and 210 min of extraction	19.8% (w/w)	Food and pharmaceutical applications	Seabra et al. (2012)

Table 2 (continued)

Feedstock	"Green" recovery	Solvent	Parameters of extractions	Proanthocyanidins content	Application	Reference
Cranberry pomace	Pressurized liquid extraction	Ethanol	10.3 MPa; 83 °C; dynamic extraction (3 cycles 15 min $cycle^{-1}$)	198.5 ± 2.3 mg g^{-1} of extract	Food application	Tamkutė et al. (2020)
		Water	10.3 MPa; 130 °C; dynamic extraction (3 cycles 10 min $cycle^{-1}$)	532.2 ± 18.0 mg g^{-1} of extract		
Lingonberry (*Vaccinium vitis-idaea L.*) pomace	Pressurized liquid extraction	Ethanol	10.3 MPa; 50–90 °C; dynamic extraction (3 cycles 5–15 min $cycle^{-1}$)	289.59 ± 12.91 mg/1 g of biomass	Functional foods	Kitrytė et al. (2020)
		Water	10.3 MPa; 130 °C; dynamic extraction (3 cycles 10 min $cycle^{-1}$)	806.44 ± 64.17 mg g^{-1} of biomass		

in terms of catechin equivalent (CE), was provided by MAE at 170 °C for 55 min (56.37 mg CE g^{-1} dry peanut skin) compared to maceration (9.70 mg CE g^{-1} dry peanut skin). This behavior is justified by microwaves that increase solvent penetration into the solid material, improving the extraction yield.

The use of high-pressure green methods to obtain proanthocyanidins from different sources is still very limited, particularly from peanut skin. Some proanthocyanidins sources, listed at Table 2, are lingonberry pomace, peanut skin, and cranberry pomace, which provided the highest proanthocyanidins content by PLE recovery. For instance, Kitrytė et al. (2020) and Tamkutė et al. (2020) used SWE at 10.3 MPa and 130 °C to recover proanthocyanidins from cranberry (806.44 mg g^{-1} of biomass) and from lingonberry pomace (289.59 mg g^{-1} of biomass), respectively. Rossi et al. (2020) used ethanol/ water (60:40 v/v) at 7 MPa and 220 °C to recover proanthocyanidins from peanut skin, reaching yield of 75% and 0.05% (w/w) for procyanidin and proanthocyanidin dimers, respectively. These results show that high-pressure methods are sustainable for proanthocyanidin recovery.

Food and Pharmaceutical Uses of Proanthocyanidin/Procyanidin-Rich Extracts from Peanut Skin

Considering the numerous health benefits from proanthocyanidins (the "Proanthocyanidins/Procyanidins from Peanut By-products" section), useful for food and pharmaceutical formulations, it is relevant to develop green strategies that can be industrially used for their successful recovery and quality application. Therefore, it is relevant to know the properties of these components in order to provide successful applications. Table 3 summarizes studies related to food and pharmaceutical uses of proanthocyanidins from peanut by-products, listing applications, bioactivities associated, and most relevant results.

Pharmaceutical Applications Proanthocyanidins show potential benefits for different pharmaceutical applications (Table 3). Tatsuno et al. (2012) show that proanthocyanidin extracts from peanut skin, obtained by water maceration, have beneficial effects on human skins. The use of 200 μg mL^{-1} of extract decreased melanogenesis in cultured human melanoma (HMV-II co-stimulated with phorbol-12-myristate-13-acetate), reducing production of inflammatory cytokines (at 100 μg mL^{-1}), tumor necrosis factor-α, and interleukin-6, in cultured human monocytic THP-1 cell. Proanthocyanidin dimers and trimers had stronger inhibitory activity, related to melanogenesis and inflammatory cytokine production, than the monomer or the tetramers. These promising results inspire the use of SWE or PLE with

Table 3 Food and pharmaceutical applications of proanthocyanidin extracts recovered from peanut skin

Application	Activity evaluated	Relevant results	Reference
Pharmaceutical	Inflammatory and anti-melanogenic activity	Peanut skin extracts showed suppressive activities against melanogenesis (in cultured human melanoma HMV-II co-stimulated with phorbol-12-myristate-13-acetate) and cytokine production (in cultured human monocytic THP-1 cells)	Tatsuno et al. (2012)
	Reduction of dermatological conditions (inflammation and melanogenesis)	Proanthocyanidin extracted from peanut skin by-product inhibited degranulation of RBL-2H3 (basophilic leukemia cells) in rat, mainly by inhibition of signal transduction leading to secretion	Tomochika et al. (2011)
	Reduction of proliferation of liver cancer cells and hepatocellular carcinogenesis	Peanut skin proanthocyanidin B2 appears to bind to the catalytically active kinase domain and regulatory pleckstrin homology domain to lock the protein in a closed conformation, thus suppressing tumor cell proliferation and metabolism	Liu et al. (2020)
	Inhibition of alpha-glucosidase and lipase activity	The crude and fractionated extracts (composed mainly by proanthocyanidin) showed inhibition of alpha-glucosidase and lipase activities, reducing the absorption of glucose and triacylglycerols	Camargo et al. (2017b)
	Cytotoxicity, cytoprotection (antioxidant)	Peanut proanthocyanidin extract did not present cytotoxicity on normal epithelial cells, rat ileum cells, monkey kidney cells, or human peripheral blood mononuclear cells at concentrations with antioxidant effects, also reduced the reactive oxygen species and superoxide dismutase activity in IEC-18 cells against menadione-induced oxidative stress	Rossi et al. (2020)
	Cytotoxicity and genotoxicity of the extracts	Peanut skin extracts rich in proanthocyanidin have low cytotoxicity and genotoxicity, but the treatments with extracts at 2000 mg kg^{-1} revealed (highest concentrations evaluated) some toxicity on blood marrow cells of mice	Candela et al. (2020)
	Antioxidant and membrane effects (availability) of dimer and trimer procyanidins	Absorption of trimers from the gut was extremely limited; otherwise, monomers and dimers can be readily detected in the plasma pool within 2 h after the consumption	Verstraeten et al. (2005)
	Proanthocyanidin bioavailability and reduction of plasm triglyceride	Rats upon extracts' supplementation showed reduced plasm triglyceride, also increasing plasma VLDL-C levels significantly	Bansode et al. (2014)
	Antiviral in vitro activities against H1N1 influenza	Notably, the extract exhibited a potent activity against a clinical isolate of the 2009 H1N1 pandemic, which had reduced sensitivity to oseltamivir. Moreover, a combination of peanut skin extract with the anti-influenza drugs, oseltamivir and amantadine, synergistically increased their antiviral activity	Makau et al. (2018)
Food	Cooking loss, microbial growth, aroma acceptability, and texture	The added extracts did not cause color change (indicated by CIE, L*, a*, and b* values), sensory aroma. Also, the extracts had no effect on the on the cooking loss and not affected the microbial growth	O'Keefe and Wang (2006)
	In vitro antioxidant activity and the effect of peanut skin extract (rich in proanthocyanidin) on characteristics of sheep patties during storage	The addition of peanut skin extracts reduces the microbial growth and caused reduction on the loss of redness and sensory properties over time. In addition, it was effective in the inhibition of lipid and protein oxidation in sheep patties	Munekata et al. (2016)

Table 3 (continued)

Application	Activity evaluated	Relevant results	Reference
	Lipid oxidation and antimicrobial agent in raw ground beef	Peanut skin extracts (rich in proanthocyanidins) inhibited the oxidation of meat pigments, preserving the fresh redness of treated meat, also present complete inhibition of *Bacillus subtilis*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Streptococcus faecalis*, and *Escherichia coli* (at concentration of 0.4% w/w)	Yu et al. (2010)
	Composition, polyphenols, antioxidant properties, and sensory quality	Insoluble fiber was increased by up to 52%; total phenolic content (30%) and antioxidant capacities also increased as evidenced by increases of epicatechin and procyanidin dimers A and B. In addition, sensory evaluation results demonstrated that peanut skin-fortified cookies were well accepted by the consumers	Camargo et al. (2014)
	Effect of gamma radiation on the antioxidant activity in soybean oil	Antioxidant activity of the peanut skins was higher than synthetic antioxidant (BHT). In addition, gamma radiation did not affect the peanut skin extracts' antioxidative properties when added to soybean oil	Camargo et al. (2012)
	Antimicrobial activity	The proanthocyanidins from peanut skin extracts extended the lag phase growth of the 3 yeasts studied (1–10 mg mL^{-1}); yeast growth was totally inhibited for 120 h in apple juice	Sarnoski et al. (2012b)
	Antioxidant activity and quality characteristics of the yoghurt fortified with peanut skin extracts during cold storage	Fortification of yoghurt with peanut skin extracts increased the apparent viscosity, antioxidant activity, total phenolic, acetaldehyde, and diacetyl contents when compared to control. The syneresis effect of fortified yoghurt was reduced, and the final product gained highest acceptability by the consumers at 50 mg L^{-1}	Hamed et al. (2021)
	Lettuce sanitizers	Peanut skin extracts combined with benzethonium chloride (10% w/w) showed good washing effect regardless of pathogenic bacteria type, 3.06 and 2.83 log reductions, for *L. monocytogene* and *E. coli* populations inoculated on romaine lettuce leaves, respectively, compared to washing control (water alone)	Lee et al. (2021)
	Antioxidant	Addition of the peanut skin extract increased the antioxidant capacity of the product, measured by in vitro assays (DPPH)	Dean et al. (2016)
	Inhibition effect on the retrogradation properties of maize starch	Peanut skin proanthocyanidins showed the most substantial inhibition effect on starch retrogradation, which might be attributed to its structural features (determined by DSC, XRD, and SEM analyses), suggesting that peanut proanthocyanidins could be a new type of inhibitor to suppress starch retrogradation	Wang et al. (2020)
	Biodegradable films	Peanut skin extract affected the film surface morphology and increased its surface hydrophobicity; also extracts at 1.0 g 100 mL^{-1} exhibited a strong antioxidant capacity. These results demonstrate that the biodegradable films with peanut skin extracts can be utilized as an eco-friendly packaging material having an antioxidant activity	Ju and Song (2020)

water as solvent due to the high pressure and temperature conditions, which can reduce the solvent's surface tension and viscosity, increasing the proanthocyanidin recovery.

The procyanidins isolated from peanut skins, obtained by deionized boiling water (7.55 mg g^{-1} of peanut skin), also inhibited the degranulation of RBL-2H3 (rat basophilic leukemia cells), suggesting that peanut skin procyanidins are therapeutic effective against allergic diseases (Tomochika et al., 2011).

Liu et al. (2020) shows that procyanidin type B2 (Fig. 3(IV)) suppressed tumor cell proliferation and metabolism at in vitro (docking) and in vivo (xenograft and diethylnitrosamine-induced hepatocellular carcinoma mouse models) assays. They indicate that procyanidin type B2 appears to bind the catalytically active kinase domain of AKT (protein kinase B) and regulatory pleckstrin homology domain (protein domain), associated with liver cancer pathogenesis, and locking the protein in closed conformation, avoiding cancer cell multiplication. Also, A-type proanthocyanidin dimers from peanut skin have a protective effect against oxidative stress damage in prostate cancer (DU145 cells) induced by H_2O_2, maintaining normal cell cycle, inhibiting apoptosis, increasing the levels of antioxidants (catalase, total super oxide dismutase, and restored glutathione), and reducing the content of intracellular reactive oxygen species (Yan et al., 2021).

Camargo et al. (2017a) evaluated the inhibition of alpha-glucosidase and lipase activity by proanthocyanidin-rich extracts from peanut skin (pure and fractionated), obtained by shaker maceration with acetone solution (70%). The fractionated extract reached 76% inhibition of alpha-glucosidase activity, while the pure extract provided up to 94% inhibition of lipase activity. These results highlight the biological activities of peanut skin extracts, helping the control of the absorption of glucose and triglycerides by the inhibition of these enzymes.

Ho et al. (2019) evaluated the alpha-glucosidase inhibition by proanthocyanidins from peanut skin through in silico docking assays. The results show good inhibitory activity performance from A-type proanthocyanidins, with IC_{50} (concentration required to reduce 50% the enzyme activity) of 9.72 μM against alpha-glucosidase, revealing hypoglycemic ability of proanthocyanidins.

Peanut skin extract, obtained by PLE with ethanol/water (60:40 v/v), containing 75% procyanidin dimers and 5% proanthocyanidin dimers, was tested by Rossi et al. (2020) in rat ileal epithelial cells (IEC-18), monkey kidney epithelial cells (Vero), and human peripheral blood mononuclear cells (PBMCs), for toxicity evaluations. Concentrations up to 300 μg mL^{-1} for IEC-18 and Vero, and up to 250 μg mL^{-1} for PBMCs, show no cytotoxic effects. These are very high concentrations compared to IC_{50} between 3 and 12.5 μg mL^{-1}, representing the antioxidant activity by ABTS and DPPH methods. These promising results show that proanthocyanidin-rich extracts from peanut skin have high antioxidant activity, at safe concentrations for normal cells, suggesting its use as excellent and accessible alternative for therapeutic formulations.

Verstraeten et al. (2005) highlighted the ability of types A and B procyanidins (dimers and trimers) from peanut skin to interact with phosphatidyl choline liposomes (specifically the polar headgroup), avoiding membrane cell damages (maintaining bilayer integrity) by oxidants and other molecules. Also, trimer absorption from the stomach was extremely limited, while monomers and dimers were readily detected from blood plasma. As addressed before, high-pressure extractions increase the monomer and dimer fractions from proanthocyanidins, improving food and pharmaceutical applications.

The effect of proanthocyanidin-rich extracts from peanut skin on gastrointestinal absorption of vegetable oil in rats (male Wistar rats) was investigated by Bansode et al. (2015). Rats administered with the extracts showed reduced plasma triglycerides and lower plasma very-low-density-lipoprotein levels compared to rats without peanut skin extract administration, suggesting hypolipidemic properties of the extract.

Neagu et al. (2015) showed that ethanolic extracts from the plants *Alchemilla vulgaris* and *Filipendula ulmaria*, rich in proanthocyanidins (77.66 and 130.00 μg mL^{-1}, respectively), have acetylcholinesterase inhibitory activity (77.03–98.39% at 3 mg mL^{-1}), useful for the treatment of Alzheimer's and degenerative diseases. In addition, Unusan (2020) indicated that proanthocyanidins from grape seed extracts are therapeutic agents for neuroinflammatory diseases such as Alzheimer's. Therefore, considering the high proanthocyanidins content from peanut skins of 4.959 mg g^{-1} founded by Camargo et al. (2017a), it may be of relevance to evaluate the acetylcholinesterase inhibitory activity, an attribute still not associated with peanut skin extracts.

The ethanolic extract from peanut skin exhibited antiviral in vitro activity against influenza types A and B (IC_{50} of 1.3 μg mL^{-1}). The extract exhibited potent activity against the clinically isolate H1N1 virus from 2009 pandemic, with synergistic effect when combined with the approved anti-influenza drugs, oseltamivir and amantadine, implying that peanut skin extracts may have potential application in the development of new therapeutic approaches for influenza management (Makau et al., 2018).

Recent studies of dynamic molecular simulation (in silico, molecular docking) suggested the proanthocyanidins' potential to inhibit the coronavirus disease (COVID-19 global pandemic), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Maroli et al., 2020; Zhu & Xie, 2020). The coronavirus infective cycle and the main virus structure are presented in Fig. 4 (adapted from Maroli et al., 2020; Zhu & Xie, 2020). Briefly, from Fig. 4A

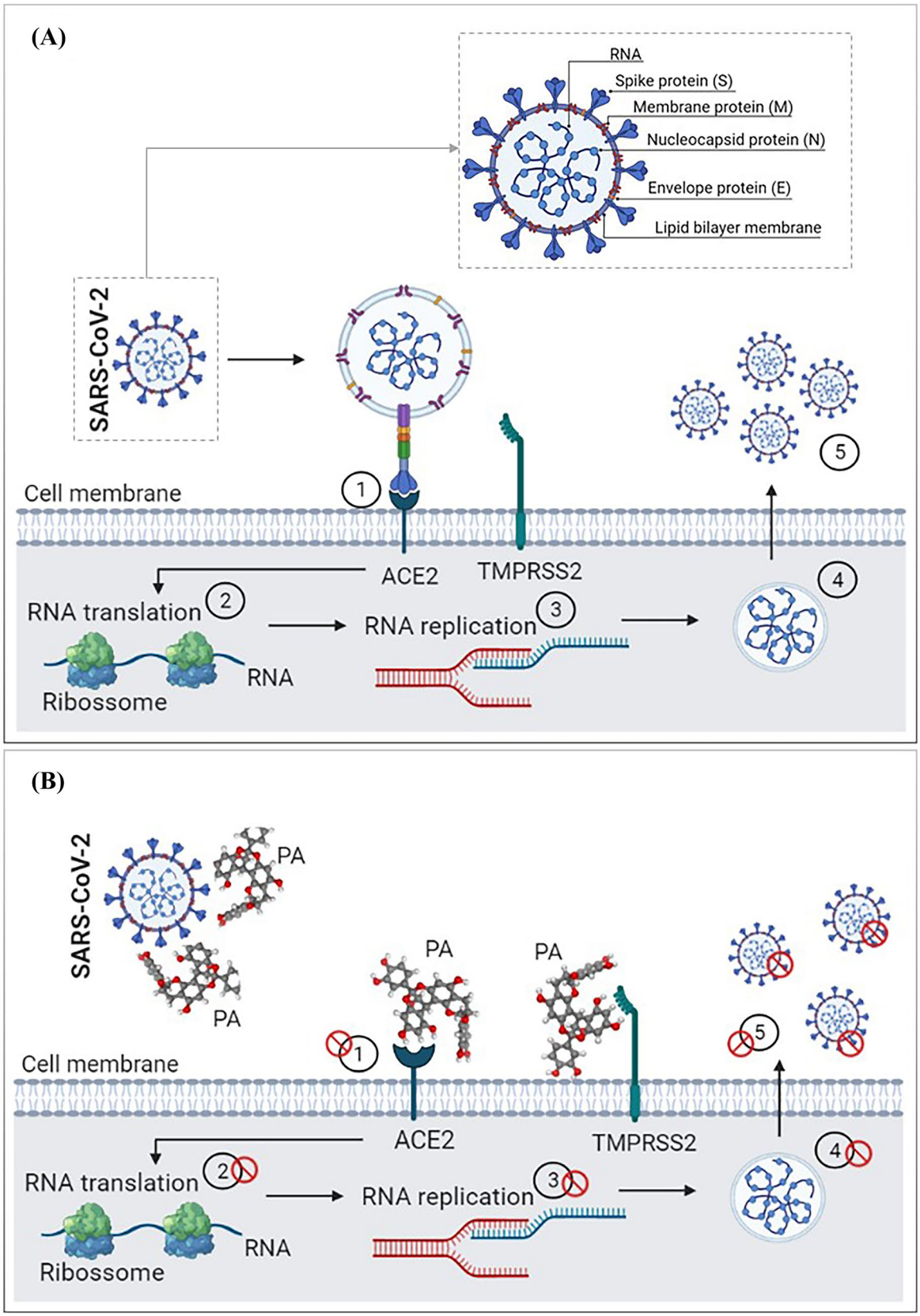


Fig. 4 Life cycle and the main structural features of coronavirus, SARS-CoV2 (**A**) schematic mechanism of action against SARS-CoV2 of proanthocyanidins (**B**). Source: Adapted from Maroli et al. (2020) and Zhu and Xie (2020)

(infective life cycle), the virus spike protein (S) binds to ACE2 enzyme receptor (angiotensin-converting enzyme), the lungs' major binding receptor to SARS-CoV-2, which is activated by proteolytic cleavage with human type 2 transmembrane serine (TMPRSS2), allowing the virus entry into human cells (Fig. 4(A.1)). Then, the uncoated virus delivers RNA into the cytoplasm by translation and replication (Fig. 4(A.2, A.3)). Finally, the replicated RNA virus is coated, and new virus is expelled of the cell (Fig. 4(A.4, A.5)).

The inhibition mechanism of SARS-CoV-2, by therapeutic medicines such as proanthocyanidins/procyanidins, is still poorly elucidated, although molecular docking simulation strategies may justify the therapeutic use of proanthocyanidins/procyanidins (PA) against the COVID-19 virus, with action mechanism suggested at Fig. 4B (Adapted from Maroli et al., 2020; Zhu & Xie, 2020). This mechanism consists in the PA ability to bind with enzymes and proteins involved in the virus replication cycle (Fig. 4B), the SARS-CoV-2 spike protein (S), ACE2 receptor, and the transmembrane serine protein (TMPRSS2), destabilizing the binding between virus and human cell and preventing virus replication (Maroli et al., 2020; Zhu & Xie, 2020). Then, PA activity may alleviate the severity of COVID-19 symptoms and modulate the immune response.

Food Applications Proanthocyanidins have astringency, bitterness, sourness, and sweetness, and contribute to salivary viscosity, aroma, and color formation of food products. Therefore, these components are used as additives in food formulations, enhancing microbial stability, foamability, oxidative, and heat stability (Okino et al., 2021; Rauf et al., 2019). Table 3 also presents the studies related to food applications of proanthocyanidins recovered from peanut skin.

The use of proanthocyanidins from peanut skins successfully inhibited retrogradation properties of maize starch for 21-day storage (Wang et al., 2020). This powerful effect improves quality and extends shelf-life of starch-based food products, suggesting that proanthocyanidin-rich extracts from peanut skin can increase the quality of starch-based foods providing effects such as antioxidant and hypolipidemic.

Peanut skin extracts (methanol maceration), rich in proanthocyanidins, reduced 60% oxidation of ground beef storage for 14 days, reducing cooking loss and microbial growth, without an aroma effect (O'Keefe & Wang, 2006). Munekata et al. (2016) observed redness loss reduction, prevention of lipid and protein oxidation, and decreasing sensory attributes changes (red color intensity, superficial discoloration, and off-odor) in sheep patties added with peanut skin extract (proanthocyanidins rich in pentamers, tetramers, trimers, and oligomers), for 20 days of storage at 2 °C. These results suggest the extract potential as natural antioxidant, replacing synthetic ones such as butylated hydroxytoluene (BHT).

Camargo et al. (2014) shows that peanut skin improved the total phenolic content, fiber, antioxidant capacities, and moisture of cookies (at concentrations from 1.3 to 2.5%), while carbohydrate concentration was decreased. The cookies fortified by peanut skin were well accepted by sensorial analysis. In addition, procyanidin trimers and tetramers were identified by HPLC–DAD-ESI–MS from the phenolic fraction (extracted with acetone water solution 70:30 v/v) of the cookies.

Gamma irradiation of food products has been used to reduce and/or eliminate microorganisms, improving food safety, although it may affect sensory attributes by inducing oxidation. Then, Camargo et al. (2017a) compared antioxidant activity of peanut skin extracts, obtained by acetone:water solution (70:30 v/v), with 4.959 mg of proanthocyanidins g^{-1} dry peanut skin, with that from BHA, a synthetic antioxidant. Then, the extract was added to salmon and submitted to gamma irradiation (3.0 kGy at 3.75 kGy h^{-1}). The results show the extract prevented oxidation up to 63% of non-irradiated salmon samples, and 37% of gamma-irradiated samples. No difference was found comparing the antioxidant activity from BHA and the extract, showing that natural proanthocyanidins can prevent gamma irradiation–induced oxidation. The same extract also inhibited the growth of gram-positive bacteria (*Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, and *Geobacillus stearothermophilus*) and gram-negative bacteria (*Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Salmonella enteritidis*, *Salmonella typhimurium*, and *Escherichia coli*) (Camargo et al., 2017b). Also, Levy et al. (2017) demonstrated the antimicrobial effect of peanut skin extracts, rich in proanthocyanidins, obtained by ultrasound with acetone, water, and acetic acid (70:28:2, v/v/v) from defatted sample, against the pathogens *L. monocytogenes*, *E. coli*, and *S. typhimurium*.

Undesirable non-enzymatic reaction, namely glycation (reaction of free amino groups from proteins with free carbonyl groups of reducing sugar), can occur in foods during processing, producing glycation end products (AGEs). Accumulation of AGEs in human tissues are directly related to diabetic complications, Alzheimer's and cardiovascular disease, and kidney dysfunction. Then, Zhao et al. (2021) showed that peanut skin extracts (with proanthocyanidins content of 85.69%) strongly inhibited the AGE formation, serving as anti-glycation agent for food products. Then, considering the pharmaceutical and food applications of proanthocyanidins, their functions must be preserved for adequate use, for instance by encapsulation strategies (next section) that may avoid structural and functional changes during processing.

Encapsulation Strategies to Improve Proanthocyanidin/Procyanidin Bioavailability

Proanthocyanidin/procyanidin bioavailability affects their bio-accessibility and bioactivity (biological activities). Bio-accessibility makes proanthocyanidins bioavailable for absorption during gastrointestinal digestion (or assimilation through intestinal epithelium), and intestinal and hepatic metabolism. The bioactivity happens after epithelium assimilation and transport to specific tissue, generating the correspondent physiological responses, such as anti-inflammatory, antimicrobial, antioxidant, and others (Galanakis, 2021; Okino et al., 2021).

The in vivo biotransformation of proanthocyanidins, such as pH gastrointestinal degradation, rapid catabolism at upper gastrointestinal tract and liver (or monomer and dimer degradation during transport), fast urinary excretion, and bacterial gastrointestinal metabolism, affects potential bioactivity of proanthocyanidins. Also, they tend to interact with proteins, forming a complex, and with mucus and other intestine components (starches and digestive enzymes), reducing its availability and efficacy with progressing time (Ge et al., 2015).

The direct application of proanthocyanidins in foodstuff and pharmaceutical products can be hindered by their astringent taste and susceptibility to changes induced by temperature, oxygen, extreme pH values, or light exposure (Okino et al., 2021; Xu et al., 2015). Also, the direct application can reduce storage stability, with progressive presence of brown color from oxidation and condensation reactions, affecting appearance and taste (Liu et al., 2017). Furthermore, proanthocyanidins have high water solubility, inhibiting their penetration into food oily systems (Chen et al., 2020b) and also into the cell membrane, since it mainly composed by lipids (specifically phospholipids).

To overcome these limitations and improve the proanthocyanidins' functional properties for food and pharmaceutical applications, encapsulation strategies, by different techniques, have produced micro- or nanoparticles of peanut skin proanthocyanidins (Unusan, 2020). An efficient encapsulation process requires a careful selection of the wall material, followed by the appropriate encapsulation method and a proper characterization of the produced particles. Then, the incorporation of the loaded particles into the food or pharmaceutical matrices and kinetics of biocomponents released from the particles are also relevant to define the adequate strategy.

GRAS Materials Derived From By-products–New Wall Barrier Tendency

Appropriate wall materials should have the ability to isolate and protect the core product, such as proanthocyanidin-rich extracts, from external environmental conditions. It can contribute to incorporate the encapsulated particles (core + wall material) in different food systems, improving solubilization, reducing degradation (oxidation or hydrolysis), and, consequently, protecting its biological activity. The type of wall material also affects the particles' stability and the encapsulation efficiency of loaded compounds, and, ultimately, controls the core release (Geranpour et al., 2020).

For proanthocyanidins, adequate wall materials should suppress the first-pass metabolism alterations, avoiding molecular changes, and allowing circulation to exert their bioactivity (Bora et al., 2018). The most common materials used to encapsulate proanthocyanidins are maltodextrin (Calomeni et al., 2017) vegetable fat (Holkem & Favaro-Trindade, 2020), gum arabic, pectin, cashew gum, carboxymethylcellulose, and κ-carrageenan (Souza et al., 2018).

Besides, GRAS products are the preferential wall materials for food applications, but they also should be inexpensive, tasteless, soluble in typical solvents, biodegradable, and nonreactive with the target compound (Bora et al., 2018; Geranpour et al., 2020).

Recent sustainable policies have encouraged the use of biopolymers, derived from industrial co-products, which stimulate the circular economy, as green alternatives for wall materials (Geranpour et al., 2020). Sorita et al. (2020) suggested the recovery, by green methods, of proteins, carbohydrates, and fibers from peanut meal, a by-product from peanut oil production. Then, these recovered products (proteins, carbohydrates, and fibers) can be applied as wall materials to encapsulate proanthocyanidins from peanut skin, a strategy that contributes to the biorefinery concept, and industrial "zero waste."

Trends and Recent Advancements in Encapsulation Methods

The literature reports three classes of methods that have been used for micro- or nanoparticle formulations. The method used to produce the particles affects the encapsulation efficiency and can be classified as (i) physical methods: spray-drying and freeze-drying (Geranpour et al., 2020; Okino et al., 2021; Sorita et al., 2021; Waterhouse et al., 2017); (ii) physical–chemical methods: coacervation, emulsification, and supercritical fluid micronization (Mendonça et al., 2019; Rudke et al., 2019); and (iii) chemical methods: interfacial polymerization and complexation by molecular inclusion (Vakilinezhad et al., 2019).

Spray-drying is the most common physical method used for the encapsulation of peanut skin extracts rich in proanthocyanidins (or procyanidins), probably due to its feasibility, easy operation, and scale-up, with no organic solvent needed, and good benefit–cost ratio (Geranpour et al., 2020). Calomeni et al. (2017) used a spray-dryer to encapsulate procyanidin-rich extract from peanut skin using maltodextrin as encapsulating agent. The

resulting particles (proanthocyanidin powder) show remarkable 120-day stability, suggesting its use as a natural additive (colorant) in food formulation. A solubility increase, compared to non-encapsulated power, was observed by Constanza et al. (2012) for procyanidin-rich extract, from peanut skin, encapsulated in maltodextrin by spray-dryer.

Complex coacervation was also applied to protect proanthocyanidins and/or procyanidins from peanut skin by Razola-Díaz et al. (2021), with high load capacity and low temperature, avoiding component degradation. Solid-lipid microparticles, composed of proanthocyanidins and probiotics (*Lactobacillus paracasei* and *Bifidobacterium animali* subsp. *Lactis*), were produced by Holkem and Favaro-Trindade (2020) to improve proanthocyanidin solubility in oil systems. These studies show the benefits of encapsulation to improve the use of procyanidin- and/or proanthocyanidin-rich extracts as natural additive for food industries, although complementary data about digestibility, bioavailability, and release from the particles are necessary for specific applications.

Future Perspectives for Proanthocyanidin-Based Products from Peanut Skin

Food by-products are gaining increasing attention as alternative biomasses, within the new biorefinery approach, because they can be converted into high-value chemical components, besides reducing industrial residues. Then, extraction and encapsulation strategies can enable adequate uses of the recovered products in food and pharmaceutical industries. Therefore, green extraction techniques, which have been stimulated by the environmental politics, can provide proanthocyanidin-rich extracts from peanut skin, with high quality and functionalities, as discussed in the "Encapsulation Strategies to Improve Proanthocyanidin/Procyanidin Bioavailability" section. Then, the viability evaluation of extraction and encapsulation methods, based on bioeconomy strategies, is necessary to innovate the peanut industry.

The production of high-value and innovative chemicals from agro-food by-products is an urgent objective, within the Sustainable Development Goals from United Nations (SDG-UN), although the polices are mainly focused on the use of biomasses to obtain bioenergy. Also, the use of by-products in conventional industries presents some resistance, and requires new procedures and equipment, complicating the implementation. To overcome these inconveniences, innovative and long-term wide polices are necessary, such as tax reduction and subsidies for recycling, and increase in research investments to promote the circular economy and by-product industrial use. Additionally, the creation of regional companies or cooperatives for by-product processing would be a promising strategy, reducing initial investments and increasing profitability, adding value to underused by-products (Langen et al., 2021). These strategies for peanut industry may help the circular economy, with the production of proanthocyanidin-rich extracts and other chemical from peanut skin, with several applications.

Conclusions

Phenolic fractions (rich in proanthocyanidins/procyanidins) are health-benefit molecules, valuable for food and pharmaceutical industries, due to effects as antioxidant, anti-inflammation, neuroprotective, anticancer, lipid-lowering, bacteriostatic, and hypotensive. The valorization of peanut skin is relevant for circular economy due to their high proanthocyanidin content, which can be recovered from the biomass, that otherwise would be underused, and reintegrated in the processing chain. Unconventional extractions techniques such as SFE, PLE, MAE, and SWE can overcome the current drawbacks of conventional methods, leading to a greener process. Also, incorporating proanthocyanidins in micro/nanocapsules can improve their bioavailability and solubility in different systems. Then, the use of proanthocyanidins, in micro- or nanoparticles, in foods or medicines, must be validated by large double-blind clinical trials, to attest the nontoxic effect of proanthocyanidins from peanut skin.

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Declarations

Competing Interests The authors declare no competing interests.

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