A-type proanthocyanidins: Sources, structure, bioactivity, processing, nutrition, and potential applications

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COMPREHENSIVE REVIEW

A-type proanthocyanidins: Sources, structure, bioactivity, processing, nutrition, and potential applications

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Abstract

A-type proanthocyanidins (PAs) are a subgroup of PAs that differ from B-type PAs by the presence of an ether bond between two consecutive constitutive units. This additional C–O–C bond gives them a more stable and hydrophobic character. They are of increasing interest due to their potential multiple nutritional effects with low toxicity in food processing and supplement development. They have been identified in several plants. However, the role of A-type PAs, especially their complex polymeric form (degree of polymerization and linkage), has not been specifically discussed and explored. Therefore, recent advances in the physico-chemical and structural changes of A-type PAs and their functional properties during extraction, processing, and storing are evaluated. In addition, discussions on the sources, structures, bioactivities, potential applications in the food industry, and future research trends of their derivatives are highlighted. Litchis, cranberries, avocados, and persimmons are all favorable plant sources. A-type PAs contribute directly or indirectly to human nutrition via the regulation of different degrees of polymerization and bonding types. Thermal processing could have a negative impact on the amount and structure of A-type PAs in the food matrix. More attention should be focused on nonthermal technologies that could better preserve their architecture and structure. The diversity and complexity

Abbreviations: (m) DP, (mean) degree of polymerization; AML, acute myeloid leukemia; CAT, catalase; CTB-1, cinnamon B-1; ECG, epicatechin-3-O-gallate; EGCG, epigallocatechin-3-O-gallate; ExPEC, extra-intestinal pathogenic *Escherichia coli*; G-6-Pase, glucose-6-phosphatase; GSH, glutathione; HPLC, high-performance liquid chromatography; HPP, high pressure processing; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; PAs, proanthocyanidins; POD, peroxidase; PPO, polyphenol oxidase; RSM, response surface methodology; SOD, superoxide dismutase; UC, ulcerative colitis; UTI, urinary tract infection.

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of these compounds, as well as the difficulty in isolating and purifying natural A-type PAs, remain obstacles to their further applications. A-type PAs have received widespread acceptance and attention in the food industry but have not yet achieved their maximum potential for the future of food. Further research and development are therefore needed.

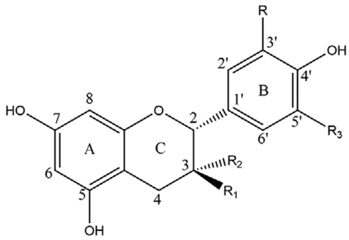
KEYWORDS
derivatives, flavanol, gut microbiota, plants, processing

1 | INTRODUCTION

Proanthocyanidins (PAs), also known as condensed tannins, are secondary metabolites formed by the condensation of flavan-3-ol monomers (Prior et al., 2001). They are also the end product of the flavonoid biosynthesis pathway (Alejo-Armijo et al., 2020; Rauf et al., 2019). PAs are found in a wide range of plant foods and beverages, including berries, stone fruits, cocoa, legumes, whole grains, tea, red wine, and so on, and are considered a source of astringency in beverages, such as wine, juice, and tea (Dixon et al., 2005; Remy-Tanneau et al., 2003; Zeng et al., 2023). PAs are also the second most abundant natural phenolic substances in nature after lignin (Liu, Le Bourvellec et al., 2021; Zhou et al., 2023). Some studies have found that tannins as chelators inhibit the absorption of dietary minerals, such as iron, copper and zinc. This “anti-nutritional” effect is also thought to cause anemia due to iron deficiency in the body. However, the harmful effects of ingesting single, isolated compounds or phytochemicals are frequently quite different from the effects of the same compound in a complex food matrix. Therefore, epidemiological evidence does not demonstrate any association between iron deficiency anemia and flavanol intake. Moreover, ascorbic acid contained in many tannin-rich foods may further promote the absorption of nonheme iron. The health benefits of consuming a wide variety of plant-based, tannin-rich foods and beverages far outweigh the negative effects of tannins on the human body. The overall benefits of tannins intake in humans outweigh the harms (Petroski & Minich, 2020; Petry et al., 2010). Based on the hydroxylation pattern of the A and B rings that make up the flavan-3-ol constituent subunits, PAs could be classified into three subclasses. PAs consisting of (epi)catechins referred to as procyanidins, whereas with (epi)afzelechin or (epi)gallocatechin as a subunit are referred to as propelargonidins and prodelphinidins, respectively (Figure 1) (Alejo-Armijo et al., 2020; Sieniawska et al., 2019). Procyanidins are the most commonly reported in plants (Rasmussen et al., 2005).

The flavanol monomers that make up PAs (e.g., catechins and epicatechin) are flavonoids, that is, they have a typical C6–C3–C6 skeleton: two aromatic rings A and B and a pyran ring (heterocycle C) (Patanè et al., 2023). Due to their unique structural features, there are different ways to classify them. First, depending on the degree of polymerization (DP), PAs are arbitrarily divided into oligomers and polymers. PAs with a DP of 2–4 are called oligomeric PAs (OPAs), whereas those with a DP of 5 or more are collectively referred to as polymeric PAs (PPAs) (Chen et al., 2020; Nie et al., 2023). The physicochemical and biological properties of PAs depend mainly on their structure, especially the DP. Dimeric and trimeric OPAs are the mainstay of PAs research, with clear chemical structures, relatively high bioavailability, and relatively easy absorption by the human body (Cires et al., 2017). Larger PPAs are not directly absorbed into the human body. Some of them are excreted, although others are metabolized by the intestinal microbiota that convert them into small molecules, which could be reabsorbed and active at the same time (Cires et al., 2017; Déprez et al., 2000). PAs could also contribute to the astringency of wine through their ability to interact strongly with proteins (e.g., salivary proteins), with the association ability increasing as the DP of PAs increases (Guyot et al., 1998). Second, PAs are classified into A-type and B-type based on the difference in the inter-flavan linkages between the flavanol monomers (Liu, Le Bourvellec et al., 2021). The flavanol monomers in B-type PAs are connected by only one C–C bond, which is mainly located at C4–C8 or, less commonly, C4–C6 (Gabetta et al., 2000). In contrast, A-type PAs are characterized by additional ether bonds connecting carbon C2 and C7 (C2–O–C7) or C2 and C5 (C2–O–C5) (Gu et al., 2002). Historically, OPAs were named according to the type of bond between these molecules. In the case of procyanidins, for example, procyanidin A is a dimer connected by an A-type bond, which is further divided into procyanidin A1 and procyanidin A2 depending on the constitutive units. For polymers, the naming is specified by the DP. For example, a procyanidin A with a DP of three is called a A-type trimer, a DP of four is called a A-type tetramer, and so on. Procyanidin dimers are listed in Figure 1 as procyanidin A1, A2, A6, and A7 as well as three common A-type

(I) Proanthocyanidin monomers



	R	R1	R2	R3
(+)-catechin	H	OH	H	OH
(-)-epicatechin	H	H	OH	OH
(+)-gollocatechin	OH	OH	H	OH
(-)-epigollocatechin	OH	H	OH	OH
(+)-afzelechin	H	OH	H	H
(-)-epiafzelechin	H	H	OH	H

(II) A-type proanthocyanidin Oligomers

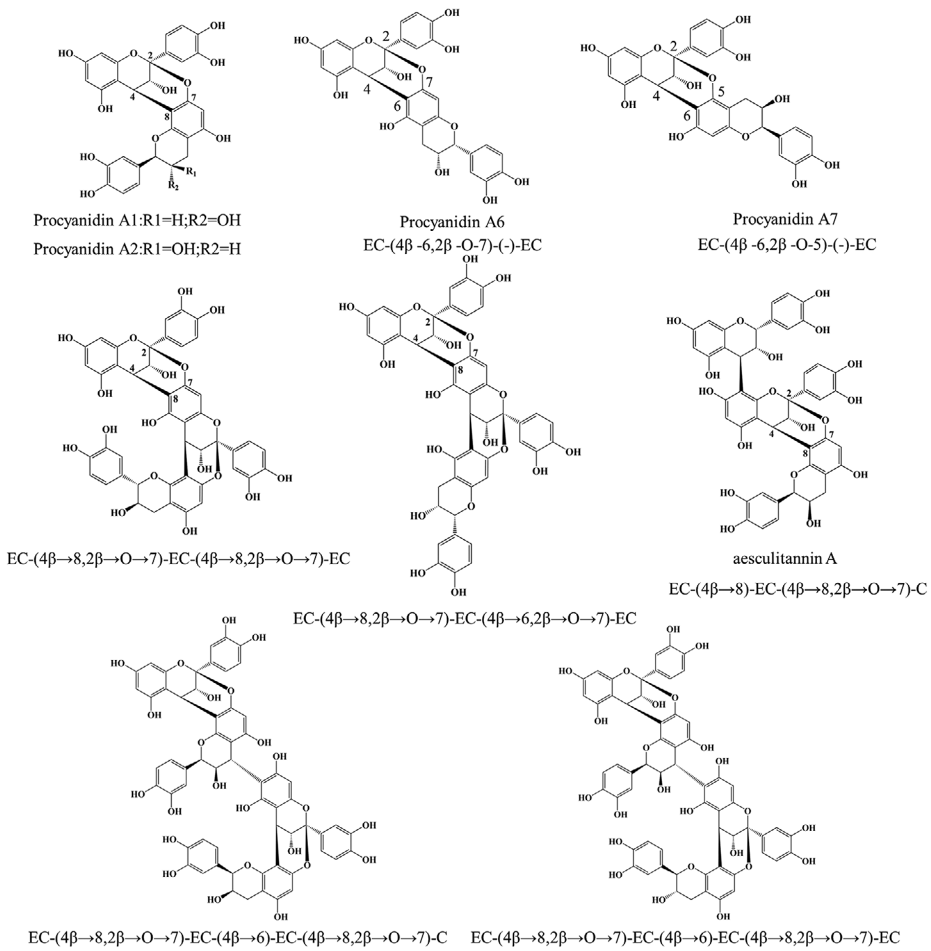


FIGURE 1 Proanthocyanidin (PA) monomers and some A-type PA dimers, trimers, and tetramers (Dudek et al., 2017; Lou et al., 1999).

trimers and two A-type tetramers (Gu et al., 2004; Li et al., 2012; Liu, Le Bourvellec et al., 2021). A- and B-type PAs are general present in plants simultaneously, but their content is dominated by one structural type. Two types could be interconverted under appropriate temperature and pH conditions, catalyzed by oxygen radicals and polyphenol oxidase (PPO) (Chen et al., 2020). Li et al. (2020) demonstrated that blueberry extracts originally enriched in B-type PAs yielded A-type PAs after processing. They promoted the formation of A-type PAs through the addition reaction of anthocyanins and flavanol monomers, and two colorless dimeric adducts, A-type cyanidin–epicatechin and A-type delphinidin–epicatechin, were obtained under optimal conditions (pH 2.0, 90°C, 80 min, aerobic). They were linked by bicyclic bonds (C4–C8 and C2–O–C7), as detected in A-type PAs. This provides a theoretical basis for the interconversion of A/B-type PAs. In addition, A-type PAs have a hard three-dimensional shape that B-type does not, making them more hydrophobic than B-type PAs, and therefore it could have more potentially docking sites (Dudek et al., 2017; McRae et al., 2010).

Some reviews have summarized recent advances in the chemical structure, food sources, and biological activities of PAs (B-type) and discussed recent developments and trends in PA-derived products (Alejo-Armijo et al., 2020; Maffei et al., 2022; Nie et al., 2023; Qi et al., 2022; Rauf et al., 2019; Redondo-Castillejo et al., 2023; Tao et al., 2019; Unusan, 2020; Yang, Tuo et al., 2021). Redondo-Castillejo et al. (2023) comprehensively validated the different effects of PAs on intestinal dysfunction in metabolic syndrome induced by high-fat diet, distinguishing between prophylactic and therapeutic roles, with a special emphasis on the effects of PAs on the intestinal microbiota. Nie et al. (2023) summarized the molecular structure and natural origin of OPAs, their general synthetic pathways in plants, their antioxidant capacity, and their potential applications, especially their anti-inflammatory, antiaging, cardiovascular disease preventive, and antitumor functions. Alejo-Armijo et al. (2020) reviewed the synthesis of A-type PAs and their analogs, and this synthetic knowledge opens the way to generate a library of bio-assessed congeners. Unusan (2020) discussed the history, chemical structure, occurrence, metabolism, and bioavailability, and industrial applications of grape seed PAs, as well as their mechanistic and protective effects against various diseases in recent years. Yang, Tuo et al. (2021) summarized the relationship between the DP of PAs from dietary sources and their antioxidant, anticancer, antidiabetic, anti-obesity, and cardioprotective effects, as well as their potential mechanisms. Maffei et al. (2022) reviewed the antiviral activity and mechanism of action of A-type PAs and their potential as broad-spectrum antiviral agents against current and future viral infections. Tao et al. (2019) explored the chemical, absorption, and metabolic pathways of PAs from monomers to polymers, as well as the interactions between PAs and the gut microbiota. However, there is no systematic summary or comparison in the literature of the food sources, processing, evolutionary patterns in food systems, biological activities, and industrial applications of A-type PAs. Although a great deal of work has been performed on A-type PAs in food, no review has synthetized the results of studies related to A-type PAs in food systems. Therefore, in addition to presenting the unique traits of A-type PAs, we provide an updated resource for the relevant literature. Moreover, we aim to compile and discuss the effects of dietary sources, processing, and storage on the variation and/or transformation of A-type PAs in food system and their nutrition effects. The current research gaps in A-type PAs, possible suggestions for future research, and speculation on potential food sources of A-type PAs are discussed. These results provide comprehensive knowledge of the content, diversity, and bioactive potential of A-type PAs in plant products. Meanwhile, it could contribute to the search for new and abundant natural sources of A-type PAs, as well as in the application and formulation of functional foods for personal daily consumption, industrial commercialization, and nutritional well-being.

2 | FOOD SOURCES OF A-TYPE PAS

The human health benefits of fresh fruits have been widely explored, and they are known to be a powerful source of dietary antioxidants, especially condensed tannins, also known as PAs (Guyot et al., 2001; Xi et al., 2023). B-type PAs are widely distributed in various parts of plants, such as fruits, vegetables, nuts, bark, and leaves, and are particularly abundant in grape seeds. In contrast, natural A-type PAs have a narrower distribution and are present in only a few plant species and tissues (Table 1), the exploitation of which could be a sustainable source of A-type PAs and is described below. The proportions of A-type PAs and mean degree of polymerization (mDP) in several representative foods are presented in Figure 2.

2.1 | Litchi

Litchi (*Litchi chinensis* Sonn.) belongs to the Sapotaceae family and its fruit consists mainly of the pericarp, the pulp (aril), and the seed. This flavorful fruit is native to southern China and is found in tropical and subtropical regions (Zhao, Wang et al., 2020).

Litchi pericarp is a rich source of A-type PAs. It can be extracted with organic solvents (ethanol, methanol, and acetone). The extracts are rich in oligomeric procyanidins composed of (epi)catechins as monomers, accounting for about 15% of the total weight of fresh litchi, with a dominance of A-type procyanidins. Some studies have shown that A-type procyanidins accounted for 41.7% of the total procyanidins in litchi pericarp, whereas B-type only 24.1%, with an mDP of 6.4 calculated from high-performance liquid chromatography (HPLC) analysis of thiolysis reactions (Le Roux et al., 1998; Li et al., 2012, 2016; Miranda-Hernández et al., 2019). A study characterized OPAs from litchi pericarp by HPLC–ESI–MS/MS (HPLC–electrospray tandem mass spectrometry) and found that they consisted mainly of procyanidin A1, procyanidin A2, catechin, and (−)-epicatechin. A-type procyanidins accounted for 38.76% of the total extract, whereas B-type procyanidins accounted for only 8.66% (Sui et al., 2016). Litchi pulp and seeds are also good sources of A-type PAs, mainly consisting of A-type procyanidin dimers and A-type procyanidin trimers

TABLE 1 Food sources, extraction methods, and major findings of A-type proanthocyanidins (PAs).

Type of PAs	Sources	Extraction method	Main findings	References
A-type procyanidins	LP and MP	70% EtOH aqueous solution, in the dark, at room temperature	Two procyanidin monomers, five dimers, three trimers, and one tetramer were identified in LF and MP extracts	Xie et al. (2023)
A-type procyanidins	Litchi seeds	95% EtOH aqueous solution, 80°C	The oligomeric procyanidins in litchi seeds were composed primarily of A-type procyanidins dimers, trimers, and tetramers	Man et al. (2017)
A-type prodelphinidins and procyanidins	Persimmon (*Diospyros kaki* L.) peel	70% acetone aqueous solution, in the dark, at room temperature	PPPAs contained 25.21% of procyanidins and 74.79% of prodelphindins and had a high degree of 3-O-galloylation (>74.79%). The mDP was calculated to be 10.18 and have A-type linkage and galloylation	Ye et al. (2022)
A-type procyanidins	Açaí seed (*Euterpe oleracea* Mart.)	100% MeOH, 60% EtOH aqueous solution, distilled water, 40°C	The extracts were mainly composed of B-type and A-type oligomeric procyanidins with an mDP of 11.4 (>3000 Da), which were formed by C and EC as the initiating and elongating subunits, respectively	Martins et al. (2020)
A-type PAs	Bird cherry *(Prunus padus)*	Solvent (acetone: ethanol: water = 2:2:1), at room temperature	Bird cherry PAs were oligomerized by (epi)catechins and (epi)gallocatechins, with a mDP of 5.6. These PAs had A-type and B-type linkages for connection of (epi)catechins and (epi)gallocatechins	Zhang, Li et al. (2022)
A-type PA trimers	Laurel tree (*Laurus nobilis* L.)	EtOAc extraction	Three flavan-3-ols, 4 dimeric B-type PAs, and 2 trimeric A-type procyanidins were isolated	Alejo-Armijo et al. (2019)
A-type PAs	The leaves of persimmon and loquat	70% acetone aqueous solution, at room temperature	Persimmon leaves PAs mainly consist of catechin with B-type link along with a small portion of GC, CG, and A-type link. Loquat leaves PAs consist of C, GC, GCG, and afzelechin with B-type link along with a small portion of A-type link	Tao et al. (2022)
A-type procyanidins	Peanut skins	70% EtOH aqueous solution, 80°C	Five compounds were separated and identified from peanut skin, including EC-(2$\beta \rightarrow$ O $\rightarrow$ 7, 4$\beta \rightarrow$ 8)-ent-EC, EC-(2$\beta \rightarrow$ O $\rightarrow$ 7, 4$\beta \rightarrow$ 8)-EC, EC-(2$\beta \rightarrow$ O $\rightarrow$ 7, 4$\beta \rightarrow$ 8)-EC-(4$\beta \rightarrow$ 6)-C, EC-(2$\beta \rightarrow$ O $\rightarrow$ 7, 4$\beta \rightarrow$ 8)-EC-(4$\beta \rightarrow$ 8)-C, and EC-(4$\beta \rightarrow$ 6)-EC-(4$\beta \rightarrow$ 8, 2$\beta \rightarrow$ O $\rightarrow$ 7)-C	Zhao et al. (2022)
A-type PAs	*Canthium venosum* fruits	100% MeOH, at room temperature	A new double-stranded A-type PA trimer was isolated:EC-(2β→O→7, 4β→8)-C-(5→O→2β, 6→4β)-C [venosum tannin A-1]	Dongmo et al. (2020)

(Continues)

TABLE 1 (Continued)

Type of PAs	Sources	Extraction method	Main findings	References
Procyanidin dimer (A1 or A2)	*Chamaecyparis obtusa* VAR. FORMOSANA	Boiling deionized water extraction	The PAs with higher mDP, higher proportions of procyanidin dimer (A1 or A2) and (epi)afzelechin of extension units and a lower proportion of EC of terminal units displayed high α-glucosidase-inhibitory activities	Hsu et al. (2018)
A-type procyanidins	Avocado seed and seed coat	50% EtOH aqueous solution, 200°C, 11 MPa	Five A-type dimers and tetramers were found in both seed and seed coat, five A-type trimers were found in avocado seed, and seven A-type trimers were found in seed coat	Figueroa et al. (2018)
A-type trimers	Pear (*Pyrus pyrifolia* Nakai) fruit peel	100% MeOH, at room temperature	Identified three A-type PA trimers from pear peel for the first time, namely, (−)-EC-(4β → 8, 2β → O-7)-(−)-EC-(4β → 8)-(−)-C (cinnamtannins B1), (−)-EC-(4β → 8)-(−)-EC-(4β → 8, 2β → O-7)-(−)-EC (aesculitannin A), (−)-EC-(4β → 6)-(−)-EC-(4β → 8, 2β → O→7)-(−)-EC	Jeong et al. (2017)
A-type PAs	*Prunus spinosa*	MeOH extraction	ent-EC-(4α → 8; 2α → O → 7)-C and ent-EC-(4α → 8;2α → O → 7)-EC were identified	Kolodziej et al. (1991)
A-type PAs	Stem-bark of *Pavetta owariensis*	MeOH extraction	A new A-type PA, ent-EC (4α→8, 2α→O→7)-ent-C, was isolated and named pavettannin A1	Baldé et al. (1991)

Abbreviations: C, catechin; CG, catechin gallate; EC, epicatechin; EtOAc, ethyl acetate; EtOH, ethanol; GC, gallocatechin; GCG, gallocatechin gallate; LF, litchi fruitlet; LSE, litchi seed extracts; mDP, mean degree of polymerization; MP, mature pericarp; PAs, proanthocyanidins; PPPAs, persimmon peel proanthocyanidins.

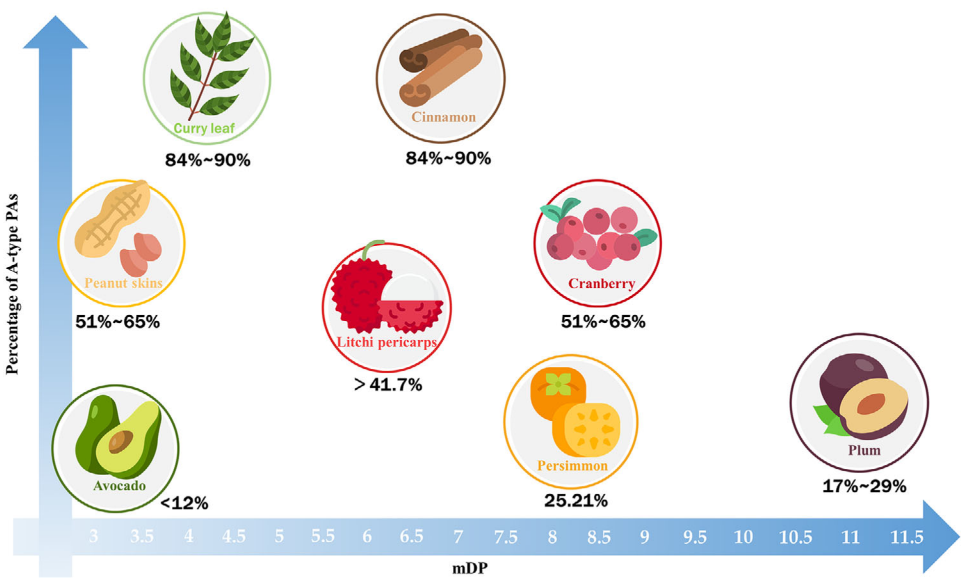


FIGURE 2 Proportion of A-type proanthocyanidins (PAs) to total PAs (black bold numbers) and mean degree of polymerization (mDP) in several plant foods (Gu et al., 2003; Li et al., 2012; Ye et al., 2022).

(Lv et al., 2015; Xu et al., 2010). Generally, the content of PAs in immature fruits is higher than that in mature fruits (Renard et al., 2007). A-type procyanidins are abundant in litchi fruitlets and can exist at high levels stably. The content of A-type procyanidins in the fruitlets of different varieties of litchi accounted for more than 60% of the total procyanidins, which is about 1.5–3.6 times of that of the pericarp content of mature fruits (Xie et al., 2023). Zhou et al. (2011) showed that the PPAs in both litchi pericarp and stone were dominated by epicatechin as the main monomeric unit, and A-type procyanidins were predominant. In addition, the DP of procyanidins in the litchi stone was higher than that of procyanidins in the pericarp, and the antioxidant activity was also higher (Zhou et al., 2011).

2.2 | Peanut skin

Peanut (*Arachis hypogaea* L.) is a Leguminosae of great interest for its lipid- and protein-rich seeds. Peanut skins, which are pink in color and astringent in taste, constitute less than 3% of the peanut weight. They are usually removed from the seeds during rinsing and after dry roasting. Their fate is either to be discarded as waste or to be used as an animal feed ingredient (Constanza et al., 2012; Lorenzo et al., 2018). However, the fact that peanut skin is a rich source of phenolic compounds is overlooked. It contains about 17% procyanidins, most of which are oligomers with a polymerization degree of 2–4 (Yu et al., 2006). The polymeric flavan-3-ols in peanut skin are mainly in the form of A-type PAs (mostly dimers and trimers) with a DP up to 12, in contrast to the predominance of monomers and B-type PAs in hazelnuts and almonds (Monagas et al., 2009). Chang et al. (2020) showed that PAs in peanut skin are mainly A-type procyanidins with (+)-catechin and (−)-epicatechin as monomers. The dimers isolated from peanut skin were identified as epicatechin-(2-O-7, 4−8) -catechin (A1), epicatechin-(2-O-7, 4–8)-epicatechin (A2), epicatechin-(2-O-7, 4–6)-catechin by Appeldoorn, Sanders et al. (2009), and epicatechin-(2-O-7, 4–8)-catechin isolated from peanut skin for the first time. Oldoni et al. (2016) also successfully isolated procyanidin A1 and A2 from peanut skin, which has the function of antioxidation. Muñoz-Arrieta et al. (2021) studied the PAs spectra of peanut skins from three varieties (Spanish, Valencia, and Virginia type). The matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) indicated that the main mass was typical with catechin monomers of “A-type” inter-flavan linkages. Deconvolution of overlapping isotopic patterns observed using MALDI-TOF-MS showed that, in all peanut skins, 95% of PA oligomers contained one or more A-type bonds. Hence, peanut variety had little effect on the percentage of A-type PAs in peanut skin.

2.3 | Cranberry

Cranberries (*Vaccinium macrocarpon*), native to the North America (mainly found in the Massachusetts, Wisconsin, New Jersey, Oregon and Washington of the United States, Quebec and British Columbia of Canada), are mostly processed into juices, jams, dried fruits, and supplements. These berries, as well as their derivatives, have a high phenolic content (Sun et al., 2002; Vinson et al., 2008). For example, lowbush cranberries accumulate up to 6.2 mg/g fresh weight (FW) of total phenolics and 2.8 mg/g FW of PAs, which are much higher than blueberries (Grace et al., 2014). Although PAs are present in almost all berry fruits, PAs isolated from cranberry have an unusual A-type linkage structure. A study showed that more than 91% of the oligomers have at least one A-type linkage (Feliciano et al., 2012). Three PA trimers possessing A-type inter-flavan linkages, epicatechin-(4β→6)-epicatechin-(4β→8, 2β→O→7)-epicatechin, epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin, and epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-epicatechin, were isolated from the ripe fruits of cranberry (*Vaccinium macrocarpon*) (Foo et al., 2000). Bresciani et al. (2021) identified a total of 12 flavan-3-ols from cranberry extracts, with A-type procyanidins being the most abundant.

2.4 | Persimmon peel

Persimmon (*Diospyros kaki* L.) is a widely cultivated tree species in some countries of Asia, such as China, Japan, and Korea (Giordani et al., 2011). Persimmon PAs have a special main extension unit, which is formed by the polymerization of epigallocatechin-3-O-gallate (EGCG) and epicatechin-3-O-gallate as flavan-3-ol monomers. They have a high 3-O-galloylation degree (72%) (grape seed tannins is about 13%) and also contain both A- and B-type inter-flavan linkages (Peng et al., 2018). Persimmon peel PAs are shown by MALDI-TOF-MS to contain 25.2% procyanidins and 74.8% prodelphinidins and have a high degree of 3-O-galloylation (>75%) and a mDP calculated as 10 (Ye et al., 2022). Highly galloylated A-type prodelphinidins and procyanidins in persimmon peel are unique for their structural features and may have better bioactivities (Ye et al., 2022).

2.5 | Others

In addition to the above sources, A-type PAs are also present in various plant tissues, such as cocoa (De Taeye et al., 2017), apple puree (Keenan et al., 2011), cinnamon

(Killday et al., 2011), pear (Jeong et al., 2017), avocado seeds (Figueroa et al., 2018), and seed coats (Figueroa et al., 2018). Procyanidin A2 was detected in raw cocoa beans, fermented cocoa beans, and roasted cocoa beans (De Taeye et al., 2017). Procyanidin A2 was also found in apple puree made from apples (*cv*. Bramley's Seedling), with levels as high as 1.3 μmol/g dry weight (DW) (Keenan et al., 2011). Two A-type trimers (i.e., cinnamon tannin B-1 and cinnamon tannin D-1) and two A-type tetramer PAs (i.e., parameritannin A-1 and cassiatannin A) are isolated from cinnamon by preparative HPLC and countercurrent chromatographic fractionation, respectively. The latter of which has not been previously described (Killday et al., 2011). Jeong et al. (2017) identified three A-type PA trimers from pear (*Pyrus pyrifolia* Nakai *cv*. Chuhwangbae) peel for the first time, namely, (−)-epicatechin-(4β → 8, 2β → O-7)-(−)-epicatechin-(4β → 8)-(−)-epicatechin (cinnamtannins B1), (−)-epicatechin-(4β → 8)-(−)-epicatechin-(4β → 8, 2β → O-7)-(−)-epicatechin (aesculitannin A), and (−)-epicatechin-(4β → 6)-(−)-epicatechin-(4β → 8, 2β → O→7)-(−)-epicatechin. The presence of A-type procyanidin dimers in the seeds and seed coats of avocados was also reported by Figueroa et al. (2018). Kolodziej et al. (1991) identified ent-epicatechin-(4α → 8; 2α → O → 7)-catechin and ent-epicatechin-(4α → 8; 2α → O → 7)-epicatechin from *Prunus spinosa*. This finding extends the spectrum of natural A-type dimer PAs. Baldé et al. (1991) isolated a new A-type PA, ent-epicatechin (4α → 8,2α → O → 7)-ent-catechin, from the stem-bark of *Pavetta owariensis*, named pavettanin A1. With advances in detection methods, the presence of A-type PAs is increasingly being identified in different plants.

3 | REACTION PATTERNS OF A-TYPE PAS IN FOOD SYSTEMS

During the extraction of A-type PAs and the processing of foods, many factors could lead to changes in their structure, content, and bioavailability. In general, some thermal (e.g., heat pump drying, heating, and roasting) and nonthermal (e.g., freeze-drying, vacuum drying, spray drying, high pressure treatment, ultrasound, and irradiation) physical interventions should be considered to assess their effects on their content, stability, degradation, polymerization, and differentiation. Their changes during thermal and nonthermal processing of fruits and vegetables are discussed in the following section and summarized in Table 2.

3.1 | Thermal processing

Thermal processing is the most traditional method of food processing, which relies on heat to reduce the growth of microorganisms, retard the growth of foodborne pathogens, and make the food fit for consumption. Common thermal food processing methods mainly include steaming, boiling, and drying, but these treatments have also been shown to severely damage nutrients in the food source (Jiang et al., 2023; Sadler et al., 2021).

3.1.1 | Heat treatment

Most fruit and vegetables, in addition to being eaten directly, are cooked (e.g., steamed, boiled, and microwaved) for consumption, which may result in various changes in their physicochemical properties (Liu, Le Bourvellec et al., 2022). Boiling resulted in the most detrimental changes in A-type PAs in treated sweet chestnut samples, with the 15 min boiling process resulting in a loss of 4.8%, 9.3%, and 11.1% of procyanidin A2 in seeds, inner shells, and outer shells, respectively. Moreover, significant changes in antioxidant capacity are also observed compared to untreated raw sweet chestnuts (Mustafa et al., 2021). In addition, the highest levels of procyanidin A2 (0.3 mg/g DW) and procyanidin B2 (0.02 mg/g DW) are found in the roasted inner shells, whereas the lowest levels (0.01 mg/g DW) were found in the boiled outer shells. The concentration of procyanidin A2 is higher than that of procyanidin B2 in all treated shell samples compared to the seeds (Mustafa et al., 2021). Some studies have analyzed that during boiling, the heat causes rupture of both the cell walls and the cellular components, and nutrients can diffuse into the boiling water as a result, resulting in the loss of the more water-soluble PAs (Bohn, 2014). A-type procyanidin trimer was the most unstable polyphenol, with its concentration decreasing to 53.0%, 42.8%, and 36.1% of that of fresh blueberries after 15 min of baking, 10 min of boiling, and 45 s of microwaving, respectively, whereas catechins were the most stable, with no significant change in concentration. In general, microwave heating caused the greatest loss of polyphenols when cooking blueberries (Zhao et al., 2017).

Heat treatment is also widely used in the food industry for its efficacy in enzyme inactivation and prevention of microbial spoilage. It has also been shown to be effective in retaining PAs, probably due to PAs that could be oxidized by a couple oxidoreduction reaction with other polyphenols. However, high temperature accelerates the release of bound PAs from the pericarp matrix (Alves Filho et al., 2018; You et al., 2018). Su et al. (2019) investigated the effect of different heat treatments on the procyanidin A2 content of different varieties of litchi. Procyanidin A2 content of the juice of three varieties of litchi (*Guiwei, Huaizhi*, and *Nuomici*) is significantly increased compared to the untreated group after heat treatments at 70 and 121°C. The 121°C treatment is better than the 70°C treatment. The

TABLE 2 Impact of physical processing on the content and epimerization of A-type proanthocyanidinsPAs.

Samples	Product type	Processing conditions	Name of A-type PAs	Impact on A-type PAs	References
Thermal processing					
Litchi	Pericarp	Steam blanching combined with hot air oven drying at 60 and 80°C, open air drying, and hot air oven drying at 40, 60, 70, 80°C	Procyanidin A2	↓ Procyanidin A2 for steam blanching combined with hot air oven drying at 80°C, open air drying, and hot air oven drying; ↑ for steam blanching combined with hot air oven drying at 60°C	Kessy et al. (2016)
Litchi	Pulp	Heat pump drying at 65°C for 3, 6, 8, 15, 21, 27, 33 h	Procyanidin A2	↑ Procyanidin A2	Shu et al. (2022)
Grape	Skin	Conventional oven drying	Procyanidin A2	↓ Procyanidin A2 for conventional oven drying	Silva et al. (2020)
Litchi	Juice	After heating at 70 or 121°C for 30 min, storing at 4°C (up to 168 h), and or 45°C (up to 72 h)	Procyanidin A2	↑ Procyanidin A2 after heating at 70 or 121°C	Shu et al. (2022)
Sweet chestnuts (*Castanea sativa* Mill.)	Seed, inner and outer shell	Boiling in water at a ratio of 1:2, w/v, at 100°C for 15 min	Procyanidin A2	↓ Procyanidin A2	Mustafa et al. (2021)
Sweet chestnuts (*Castanea sativa* Mill.)	Seed, inner and outer shell	Baking in an electric oven at 180°C for 25 min or in a microwave oven for 4 min	Procyanidin A2	↑ Procyanidin A2 in inner shells and outer shells; ↓ Procyanidin A2 in seeds	Mustafa et al. (2021)
Sweet chestnuts (*Castanea sativa* Mill)	Seed, inner and outer shell	Deep frying in a kitchen frying pan for 10 min	Procyanidin A2	↑ Procyanidin A2 in inner shells and outer shells; ↓ Procyanidin A2 in seeds	Mustafa et al. (2021)
Litchi	Canned pulp	After heating at 70 or 121°C for 30 min, storing at room temperature up to 13 days (70°C samples) or 25 days (121°C samples)	Procyanidin A2	↑ Procyanidin A2 after heating at 70 or 121°C	Wang, Wu et al. (2020)
Nonthermal processing					
Nonthermal drying					
Cranberry	Juice	Freeze drying, vacuum drying at 40, 60, 80, and 100°C and spray drying	A-type procyanidin-dimers	↓ A-type procyanidin-dimers for vacuum drying; ↑ for spray drying	Michalska et al. (2018)
Saskatoon berry	Whole fruit	Freeze drying at −60°C, convective drying at 70°C, microwave-vacuum drying (480–120 W) and combined drying	A-type procyanidin dimer, trimer	↓ A-type procyanidin dimer, trimer	Lachowicz et al. (2019)
Grape	Skin	Freeze-drying	Procyanidin A2	↓ Procyanidin A2 or freeze drying	Silva et al. (2020)

(Continues)

TABLE 2 (Continued)

Samples	Product type	Processing conditions	Name of A-type PAs	Impact on A-type PAs	References
High pressure					
Hawthorn berry	Juice	300 MPa, 600 MPa for 2, 6 min	Procyanidin A2	↓ Procyanidin A2	Lou et al. (2022))
Apple	Puree	500 MPa for 90 s followed by storing at 4°C for up to 30 days	Procyanidin A2	↑ Procyanidin A2	Keenan et al. (2011)
Irradiation					
Cranberry	Syrup	Gamma-irradiation (5 kGy), store for 6 months at 25 or 40°C	Procyanidin A2	↑ Procyanidin A2	Rodríguez-Pérez et al. (2015)
Peanut	Skin	Gamma-irradiation (2.5 or 5 kGy)	Procyanidin dimer A, prodelphinidin A	↑ Procyanidin dimer A; ↓ Prodelphinidin A	de Camargo et al. (2015)

Note: ↑, ↓, Decrease compared to control; Increase compared to control.
Abbreviation: kGy, kilo Gray.

most obvious increase is the 121°C treatment group of the *Huaizhi* variety, with procyanidin A2 content increasing nearly by five times, probably due to the oxidation of B- to A-type during processing (Su et al., 2019). Similar studies have demonstrated that the total phenolic content, procyanidin A2 content, and antioxidant activity of canned lychee can be improved by high-temperature treatment (Wang, Wu et al., 2020). It is also reported that open-air drying reduced the procyanidin A2 content of litchi peel by 30.5%, that hot-air oven drying above 40°C degraded procyanidin A2 by nearly 51%, and that a combination of steam blanching and hot-air oven drying at 60°C significantly increased the concentration of procyanidin A2 ($p < .05$) (Kessy et al., 2016). This could be due to inactivation of enzymes such as PPO and peroxidase (POD) and enhanced release of bound procyanidins from the pericarp matrix, or it is possible that procyanidin A2 acts as a substrate for PPO enzyme-catalyzed oxidation, leading to their degradation during drying and dehydration (Renard et al., 2001; Sun et al., 2010).

3.1.2 | Heat pump drying

Fresh fruits and vegetables have a high moisture content and are classified as highly perishable commodities, in which phenolics are easily lost. Drying is an alternative method to extend their shelf life and to preserve their nutritional value (Rodríguez-Pérez et al., 2015). Mild heat pump drying (c.a. 65°C) resulted in a significant increase in procyanidin A2 content in litchi pulp, after 33 h of drying, the procyanidin A2 per kilogram of DW litchi pulp was nearly 1.4 times higher than that of the undried one. Phenolics are usually present in plants in free, esterified, and insoluble bound forms (Remy-Tanneau et al., 2003). Free phenolics generally refer to phenolics that can be extracted using different solvents. The esterified and insoluble bound forms of phenolics typically bind to cell wall polysaccharides or proteins to form insoluble stable complexes (Acosta-Estrada et al., 2014; Wang et al., 2019). It is noted that during heat pump drying of litchi pulp, free phenolics can be converted to bound phenolics, producing new substances that result in an increase in antioxidant activity (Shu et al., 2022). Some other studies reported that drying may also cause a decrease of A-type PAs in fruits. Compared to fresh grape skins, the procyanidin A2 content of conventionally oven- and freeze-dried grape skins decreased by 23% and 72%, respectively (Silva et al., 2020). Similar effects have been observed in other fruits, such as saskatoon berry (Lachowicz et al., 2019). However, the rate of decline varied, which may be related to the drying method and the variety of fruit. Early studies have reported that polyphenol losses during processing can be minimized by adding different prebiotics (inulin and oligofructose), which can be taken into account (Keenan et al., 2011). Overall, heat pump drying promotes an increase in certain types of A-type PAs, but whether it is the processing that drives the conversion of other monomeric phenols is not clear.

3.2 | Nonthermal processing

Some heat-sensitive foods undergo changes at the physical, chemical, and microbiological levels, including changes in taste, color, and texture, after heat treatment. This inevitably triggers the need for extensive research and in-depth development of existing food processing technologies (Singla & Sit, 2021). Some of the creative and effective alternatives to thermal processing currently used in food processing, including supercritical fluid extraction, high-pressure processing, pulsed electric fields, cold plasma, ultrasound, and ultraviolet irradiation, are collectively referred to as nonthermal processing (Barbhuiya et al., 2021).

3.2.1 | Nonthermal drying

Some mild drying methods such as freeze-drying and vacuum drying can also affect the content of A-type PAs. Vacuum drying caused the greatest degradation of A-type procyanidin dimers in cranberry juice, whereas spray drying and freeze drying retained the A-type procyanidins content well (Michalska et al., 2018). In other words, spray drying and freeze drying could retain the content of A-type PAs well, whereas PAs are easily affected by high thermal degradation or the combination of thermal oxidation and enzymatic oxidation in traditional heat pump drying resulting in a decrease in content. But mild heat pump drying combined with short time blanching could effectively blunt the enzymatic activity and also have the effect of preserving A-type PAs.

3.2.2 | Ultrasonication

The strong vibrations generated by ultrasound (i.e., cavitation effect) can disrupt the cell walls of plants (Wang, Guo et al., 2018). Using this principle to apply ultrasound to A-type PA extraction can accelerate the entrance of the solvent into the cells and improve the extraction efficiency. Ultrasonic extraction can be used in combination with other extraction techniques to achieve optimal extraction rates. For instance, it has been shown that the extraction of oligomeric procyanidins from litchi pericarp can be enhanced by using a combination of enzymatic and ultrasonic treatments (Li, Yang et al., 2018). The optimized ultrasonic treatment parameters (cell wall cleavage enzyme concentration 0.12 mg/mL, ultrasonic power 300 W, ultrasonic time 80 min, liquid–solid ratio 10 mL/g) were obtained by RSM (response surface methodology) experimental design. Based on the optimal extraction conditions, the extraction rate reaches 13.5%, which is six times higher than that of the conventional ethanol extraction (Li, Yang et al., 2018). Although the relative procyanidin content of the extract of the combined extraction process was 89.6%, which was slightly lower than that of the enzyme-assisted extraction, it showed a more abundant content in various oligomers. The presence of epicatechin and procyanidins A2 and A3 in the extracts of the ultrasound-assisted extraction process was confirmed by comparison with the retention time and UV spectra of the standards. An isomer of A2 was also detected and inferred to be procyanidin A1, epicatechin-(4β→8, 2β→O→7)-catechin. This could be due to the conversion of procyanidin A2 to A1 by the energy effect of ultrasound. The above phenomenon suggests that ultrasound can catalyze the conversion of flavanol compounds during the extraction process. In other words, extraction techniques involving ultrasound treatment have the potential to be scaled up and used universally for the production of procyanidins from plant resources. A coupled extraction technique similar to the combination of enzymatic and ultrasonic treatment can be considered a novel green, simple, rapid, and efficient method for the extraction of bioactive components.

3.2.3 | High pressure processing

High pressure processing (HPP) is one of the most successful commercially available nonthermal treatment technologies. It can efficiently extend the shelf life of food products while maintaining organoleptic properties and nutritional value. Some studies have reported that HPP also improves the bio-accessibility of bioactive compounds through molecular compression and volume reduction, thereby promoting structural changes and molecular interactions between macromolecules and small molecules. In recent years, HPP has been widely used in the processing of fruit juices and beverages (Putnik et al., 2019).

Keenan et al. (2011) reported that HPP was superior to pasteurization in maintaining the stability of procyanidin A2 in apple puree during storage. The content of PA A2 in hawthorn juice was significantly reduced by 23.4%–57.1% after being subjected to 300 and 600 MPa ultrahigh pressure treatment for 2 or 3 min. The loss of PA A2 content was more than 73.5% after heating and sterilization at 65°C for 30 min. This may be due to the accelerated depolymerization of PA A2 in the HPP treatment and may also induce the increase of flavanols. In contrast, after in vitro gastrointestinal digestion, the content of PA A2 in hawthorn juice without HPP and hawthorn juice treated with 600 MPa for 6 min reached sevenfold (1.2 μg/ mL) and eightfold (0.9 μg/ mL), respectively, compared to that before digestion. The increase in PA A2 may be due to the chemical reaction of procyanidin B2 resulting from the periodic oxidation of o-diphenol B to the corresponding highly reactive o-quinone. It is also possible that HPP induced a higher DP of PA A2, thereby increasing the chemical composition of PA A2 (Lou et al., 2022).

3.2.4 | Irradiation

Food irradiation is a nonthermal, energy-efficient, nonchemical food preservation technology that exposes food to a variety of ionizing and non-ionizing radiation to eliminate pathogenic microorganisms and thereby extend shelf life, with less impact on the original flavor, color, nutritional value, and other characteristics of the food (Bisht et al., 2021). The effects of radiation have been scientifically proven for a long time (at least 40 years), but it has had problems with consumer and regulatory acceptance, and many consumers have misconceptions about the technology, believing that irradiation makes food radioactive (Wilcock et al., 2004).

The effect of irradiation on A-type PAs is mainly reflected in changes of content and the oxidation, hydrolysis, and isomerization. de Camargo et al. (2015) reported that γ-irradiation at 5.0 kGy reduced the microbial population of peanuts, whereas total phenol and total PA content, ABTS radical cations, DPPH radicals, HO and hydroxyl radical scavenging capacity, and reducing power of the samples increased in both free and insoluble bound phenolic fractions after γ-irradiation. Of note was the increase in procyanidin dimer A in all phenolic fractions, with the highest increase of 130% in the insoluble-bound phenolic fraction in both peanut species tested. In contrast, procyanidin dimer B was relatively reduced, which may be due to the ability of γ-irradiation to convert procyanidin dimer B to A-type, whereas depolymerization may occur in the free and esterified fractions and cross-linking may occur in the insoluble bound fractions. γ-irradiation may increase the bioavailability of procyanidins through depolymerization, which may enhance the biological activity of these compounds. Rodríguez-Pérez et al. (2015) stored commercial cranberry syrup after γ-irradiation (5 kGy) at 25°C and 60% relative humidity for 6 months under accelerated storage conditions and found that most compounds such as quercetin and some of its derivatives could be highly stable at 25°C for 1 month. A significant increase ($p < .05$) in procyanidin A2 (from 83 to 93 μg/ml) was observed after irradiation compared to nonirradiated syrups, which may be related to the degradation of A-type procyanidin trimers or pentamers.

4 | BIOACTIVE PROPERTIES OF A-TYPE PAS

There has been a great interest in the biological activity of natural compounds and their beneficial effects on human health. Numerous studies have confirmed that A-type PAs have varied and pronounced biological activities. Studies on the health benefits and medicinal properties of A-type PAs in the last 5 years are summarized in Table 3. The bioactive properties of A-type PAs for humans are summarized in Figure 3.

4.1 | Antioxidant effect

Oxidation is a necessary process for all organisms to generate energy for biological processes (Hu et al., 2011). However, the emergence of many diseases is directly related to the uncontrolled production of oxygen radicals, such as cancer, rheumatoid arthritis, and atherosclerosis, as well as degenerative processes associated with human aging (Mau et al., 2002). A-type PAs have a wide range of applications as antioxidants, and the antioxidant mechanisms include scavenging of free radicals as well as inhibition of PPO, as has been demonstrated in several studies (Ishihara et al., 2018; Liu et al., 2007; Xu et al., 2010). H_2O_2-induced oxidative stress in prostate DU145 cells would disrupt the normal cell cycle and initiate apoptosis, while decreased levels of antioxidants, such as total superoxide dismutase (SOD), catalase, and glutathione (GSH) (Yan et al., 2021). Procyanidin A1 and procyanidin A2, extracted from peanut skin, were found to ameliorate these abnormalities, in addition to reducing the expression of proapoptotic proteins (Bax, cleaved caspase-9, and cleaved caspase-3) and increasing the expression of antiapoptotic proteins (Bcl-2). A-type procyanidin dimers were found to block phosphorylation of the MAPKs signaling pathway, which is closely related to the antioxidant activity of A-type PAs (Yan et al., 2021). Cranberry concentrate enriched with A-type PAs enhanced GSH peroxidase activity and improved cardiac SOD activity in a d-galactose-induced aging mouse model (Jiao et al., 2017).

4.2 | Contribution to control of blood sugar

Long-term consumption of a diet rich in procyanidins could prevent and reduce the risk of type 2 diabetes (Zhang

TABLE 3 The main biological activities of A-type proanthocyanidins (PAs).

Type of PAs	Sources	Assay model	Nutritional prevention mechanism	References
Antioxidant activity				
Highly polymeric A-type PAs	Seed Shells of Japanese Horse Chestnut (*Aesculus turbinata* BLUME)	Bright light-induced retinal damage in rats	Inhibiting oxidative stress and apoptotic mechanisms.	Ishihara et al. (2018)
A-type PAs	Cranberry	D-galactose-induced aging mouse	Enhanced glutathione peroxidase activity and improved cardiac superoxide dismutase activity	Jiao et al. (2017)
Anti-diabetic activity				
A-type oligomeric procyanidins	Litchi pericarps	HFD and STZ induced diabetic mice	Regulation of hepatic and muscle glucose metabolism, improving glucose homeostasis by modulating mTOR signaling, and oxidative stress	Li et al., 2016 (2018)
Procyanidin A2	Tender shoots of *Wendlandia glabrata* DC	STZ-induced diabetic mice	Decrease of protein content (G-6-pase) and suppressed mRNA levels and increase glucose uptake in CC1 hepatocytes and C2C12 myoblasts	Sheikh et al. (2019)
A-type procyanidins	Peanut skins	STZ-induced diabetic mice	Decrease of symptoms of T2DM by reducing inflammation, modulating gut microbiota and improving gut integrity	Liu, Huang et al. (2022)
A-type PAs	*Cinnamomum osmophloeum* twigs	HFD and STZ induced diabetic mice	Inhibits intestinal disaccharidase, amylase, and lipase activities, increases HDL-cholesterol levels, reduces leptin levels and protects bilirubin from oxidative stress	Lin et al. (2018)
A-type procyanidin oligomer	Litchi seeds	HFD and STZ-induced diabetic Sprague-Dawley rats	Decrease of the insulin resistance index and the levels of glucose in urine through elevating the mRNA level of insulin. Regulation of the glucose and fatty acid metabolisms via increasing the expression of Glu2, Glu4, IR, and IRS2	Man et al. (2017)
Hepatoprotective effect				
Procyanidin A2	Litchi pericarps	Carbon tetrachloride-induced hepatotoxicity in mice	Decrease of serum glutamate oxaloacetate transaminase and glutamate pyruvate transaminase levels, retention of the hexagonal structure of hepatocytes, and reduction of necrotic cells	Chen et al. (2017)
Anti-inflammatory activity				
A-type procyanidins	Peanut skins	UC mice induced with DSS	Alteration of the colon tissue metabolome (taste transduction, mTOR, PI3K-Akt, and FoxO signaling pathway)	Huang, Wang et al. (2022)

(Continues)

TABLE 3 (Continued)

Type of PAs	Sources	Assay model	Nutritional prevention mechanism	References
Anti-atherosclerosis activity				
Procyanidin A2	Litchi pericarps	HFD-induced atherosclerosis in mice	Reduces histological abnormalities, lipid accumulation, oxidative stress, and inflammation in the aorta	Yang, Zhang et al. (2021)
A-type procyanidins	Peanut skins	HFD-induced atherosclerosis in $ApoE^{-/-}$ mice	Reduction of inflammatory responses and enhancement of antioxidant defenses, alleviation of atherosclerosis by modulating gut microbiota	Xu et al. (2022)
Procyanidin A2	Standards	ox-LDL-treated macrophage cells	Inhibition of conversion of macrophage into foam cells via regulating cellular lipid metabolism and suppressing cellular oxidative stress and inflammation	Zhang et al. (2018)
Neuroprotection				
A-type PA oligomer	Cinnamon	MPTP-induced neurotoxicity in mice	Inhibition of the MPTP-induced activation of P38MAPK and P53, along with the downstream expression of BAX in the substantia nigra	Xu et al. (2020)
Procyanidin A2	Litchi seed	Amyloid β-induced BV-2 cells	Upregulation of Bcl-2 and downregulation of Bax protein expression to inhibit Aβ-induced apoptosis of BV-2 cells	Tang et al. (2018)
A-type EGCG dimer	Persimmon fruits	Amyloid β-peptides$_{40}$ (Aβ_{40})	Inhibition of the formation of Aβ_{40} amyloid fibrils	Yan, Zhong et al. (2020)
Anticancer activity				
A-type PAs	Cranberry	Nonobese diabetic/severe combined immunodeficient mice	Decrease AML of tumor burden	Bystrom et al. (2019)
Antiviral activity				
A-type PAs	Cranberry	HSV-1 and HSV-2	Impaired HSV-1 and HSV-2 replication in vitro, prevention of HSV-1 and HSV-2 attachment to target cells, and changes in HSV-1 and HSV-2 envelope glycoproteins	Terlizzi et al. (2016)
Procyanidin A2	Cranberry	IAV and IBV	Prevention of IAV and IBV attachment and entry in target cells; antiviral activity	Luganini et al. (2018)
Anti-hyperuricemia activity				
A-type procyanidin dimer, trimer	Litchi pericarps	Male Sprague-Dawley rats	High inhibitory activity and strong antioxidant activity against xanthine oxidase	Sui et al. (2021)

Abbreviations: AML, Acute myeloid leukemia; BAX, BCL-2 associated X protein; CCl4, carbon tetrachloride; DSS, sodium dextran sulfate; EGCG, epigallocatechin gallate; G-6-Pase, glucose-6-phosphatase; Glu 2/Glu 4, glucose transporter 2/4; HDL, high density lipoprotein; HFD, high fat diet; HSV-1/ HSV-2, herpes simplex virus type 1/ type 2; IAV/IBV, influenza A viruses/influenza B viruses; IR, insulin receptor; IRS2, IR substrate-2; MPP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; ox-LDL, oxidized low-density lipoprotein; P38 MAPK, P38 mitogen activated protein kinase; STZ, streptozotocin; UC, ulcerative colitis.

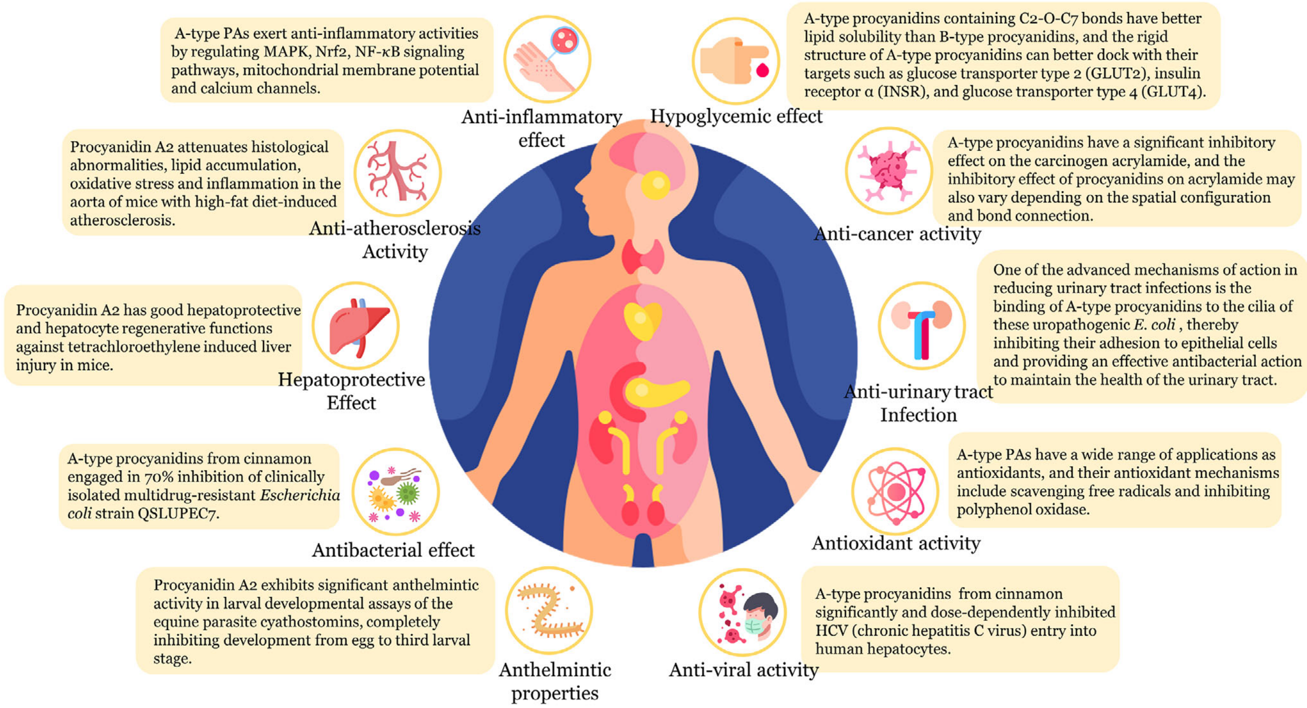


FIGURE 3 Potential benefits of A-type proanthocyanidins for humans.

et al., 2018). Dietary starch is an important source of blood glucose. A important enzyme that catalyzes the conversion of starch to monosaccharides is α-glucosidase (Sheikh et al., 2019; Wei et al., 2017). A-type PAs regulate glucose metabolism and reduce blood glucose levels by inhibiting α-glucosidase activity and slowing down glucose uptake, thereby effectively preventing tissue damage caused by hyperglycemia (Hsu et al., 2018; Zhao, Wen et al., 2020). Zhao,Wen et al. (2020) found that A-type procyanidins may have better α-glucosidase inhibitory activity than B-type procyanidins. Among them, the compound A-type trimer with the best inhibitory effect reversibly inhibits the activity of α-glucosidase in a mixed manner. Another potential target for the prevention of type 2 diabetes is glucose-6-phosphatase (G-6-Pase), which catalyzes the final steps of gluconeogenesis and glycogenolysis to produce glucose. Procyanidin A2 not only significantly inhibits α-glucosidase but also reduces G-6-Pase content and mRNA expression levels in diabetic mice, thereby reducing blood glucose levels (Sheikh et al., 2019). The A-type procyanidins containing the C2–O–C7 bond were more fat-soluble than the B-type procyanidins. The rigid structure enables better binding to targets (Li et al., 2016). Interestingly, A-type procyanidins could also effectively prevent the occurrence of diabetes by inhibiting the aggregation of amyloid polypeptides and promoting the decomposition of existing amyloid polypeptide aggregates (Tanaka et al., 2021). In addition to inhibiting related enzyme activities, A-type procyanidins can also alleviate the symptoms of type 2 diabetes by reducing inflammatory responses, regulating intestinal microbiota, and improving intestinal integrity (Liu, Huang et al., 2022).

4.3 | Anti-inflammatory effect

Inflammation is the host's defense response to tissue damage or infection caused by various stimuli, such as chemicals, physical trauma, and infectious agents (Mbaoji et al., 2020). At present, the anti-inflammatory effects of natural A-type PAs have been widely reported (Galarraga-Vinueza et al., 2020; La et al., 2010; Xie et al., 2023). For the treatment of periodontitis, A-type PAs in cranberry have been shown to inhibit biofilm formation and adhesion of major periodontal pathogens, such as *Porphyromonas gingivalis* (*P. gingivalis*), to reduce the virulence of *P. gingivalis* and to enhance epithelial barrier integrity (La et al., 2010). Cranberry concentrate rich in A-type PAs significantly downregulated the expression of pro-inflammatory cytokines and significantly upregulated the expression of anti-inflammatory factors in macrophages, exhibiting anti-inflammatory effects (Galarraga-Vinueza et al., 2020). Further, studies have shown that litchi fruitlet extract rich in A-type procyanidins has excellent anti-inflammatory activity. A-type procyanidin trimers were significantly correlated with anti-inflammatory activity, indicating that A-type trimers may have higher anti-inflammatory activity (Xie et al., 2023). Procyanidin A2 protects cells from inflammation and oxidative damage by targeting the NF-κB, MAPK, and Nrf2 pathways in RAW264.7 cells. This is a potential strategy for preventing inflammation and oxidative stress (Wang, Gao et al., 2020). Similarly, another A-type dimer, procyanidin A1, also exhibits significant anti-inflammatory effects, suggesting it as a potential method for the prevention of inflammatory (Han et al., 2019).

Ulcerative colitis (UC) is a relapsing chronic inflammatory disease. The main symptom of UC is diarrhea, including bloody stools. Experiments at the animal level have shown that A-type PAs could inhibit inflammation and relieve UC symptoms by restoring the intestinal barrier, regulating oxidative stress levels and inflammatory cytokines, improving intestinal microbiota, and reducing pathogens. However, the underlying regulatory mechanism would be further verified through gene knockout mouse models (Liu, Huang et al., 2022; Nakase et al., 2022; Zhang, Lang et al., 2022).

4.4 | Prevention of anticancer effect

Cancer is the second leading cause of human death worldwide, after cardiovascular diseases (ReFaey et al., 2021). Acute myeloid leukemia (AML) is a heterogeneous cancer characterized by significant toxicity and great variability in response to therapy (Pinto-Merino et al., 2022). Bystrom et al. (2019) demonstrated that A-type PAs could selectively target primary AML cells without damaging healthy $CD34^+$ cord blood cells. Tumor burden was reduced more than two folds compared with controls. Cinnamon B-1 (CTB-1) is a A-type PA trimer isolated from cinnamon. It was found to regulate the expression of proteins with pro- and antiapoptotic functions and downstream molecular targets, with the ability to significantly reduce colon cancer survival and induce apoptosis in colon cancer cells. In addition to its anticancer activity, CTB-1 exhibits minimal cytotoxicity on normal colon epithelial cells, suggesting that CTB-1 has a low potential for adverse effects. CTB-1 could also significantly enhance the efficacy of anticancer drugs and their clinical significance through synergistic drug interactions (Alejo-Armijo et al., 2022; Carriere et al., 2018).

4.5 | Anti-urinary tract infection effect

The prevention and treatment of urinary tract infections (UTIs) is a unique and recognized health effect of A-type PAs. UTI is the most common disease caused by extra-intestinal pathogenic *Escherichia coli* (ExPEC) (Johnson & Russo, 2002; Russo & Johnson, 2003). Numerous scientific studies have confirmed that the A-type PAs bind specifically to bacteria, which prevents them from colonizing and infecting the urinary tract (Table 3). A-type PAs in cranberries could reduce bacterial adhesion by binding and compressing *E. coli* hairs with up to 70% inhibition, and these mechanisms do not kill the bacteria, making the development of resistant strains less likely. Second, A-type PAs affect the agglutination reaction of ExPEC by binding to the bacterial hairs, thereby reducing the ability of these virulence factors to adhere to intestinal epithelial cells (Feliciano et al., 2014; Howell et al., 2005). Prevention of transient intestinal colonization would reduce the likelihood of ExPEC entering and colonizing the urinary tract, thus acting as a prophylactic agent in UTI. A-type PAs also have the potential to affect ExPEC by altering the gene expression of virulence factors in the intestine. In vitro studies have shown that A-type PAs affect ExPEC motility by downregulating the fliC gene, a flagellin-producing subunit, also reducing biofilm formation (Wojnicz et al., 2012). Therefore, they act as an effective antibacterial agent against the adhesion of bacteria such as *E. coli* to the urinary tract wall and help maintaining the health of the urinary tract.

PAs with more A-linked bonds and a higher DP were found to have higher ExPEC agglutination and higher capacity to lower bacterial invasion in cranberry (Feliciano et al., 2014). Meta-analyses of clinical trials have shown that consumption of A-type PAs-rich cranberry juice and cranberry dietary supplements reduced the recurrence of UTI in women and maintained urinary tract health over a 12-month period (Pinzón-Arango et al., 2009). In addition, A-type PAs inhibit the activity of the transcription factor NF-κB to reduce the inflammatory response and thus control the development of infectious diseases of the urinary tract (Feldman et al., 2012). Although positive results on the interaction between A-type PAs and UTIs have been published in the last two decades, the research field still lacks qualitative and quantitative methods to facilitate standardized application of A-type PAs and comparative analysis between different preparations used in clinical trials.

4.6 | Other biological properties

In addition to the abovementioned functions, other biological properties, for example, anti-atherosclerosis, antiviral, antibacterial activity, anthelmintic properties, hepatoprotective effects have also been investigated. Fauvelle et al. (2017) demonstrated that the A-type PA from cinnamon significantly and dose-dependently inhibited HCV (chronic hepatitis C virus) entry into human hepatocytes. Indian scholars Vasudevan et al. (2020) evaluated the antimicrobial and anti-biofilm activities of A-type PAs from *Cinnamomum zeylanicum* against a clinically isolated multidrug-resistant strain of uropathogenic *E. coli*, $QSLUPEC_7$. The A-type PAs did not affect their growth but the formation of biofilms, with an inhibition rate as high as nearly 70%. Alejo-Armijo et al. (2017) came to a similar result of laurel wood extract, that is, the A-type trimeric PAs have antibacterial and anti-biofilm activities. A-type PAs, obtained from *Vaccinium meridionale* Swartz slag, have also been shown to be effective in controlling pathogenic bacteria (Garzón et al., 2020). Procyanidin A2, isolated from the Australian plant *Alectryon oleifolius*, exhibits significant anthelmintic activity in the equine parasite cyathostomins larval developmental assay, completely inhibiting development from egg to third larval stage at concentrations as low as 50 μg/mL, the IC value was 12.6 μg/mL (Payne et al., 2018). Procyanidin A2 extracted from litchi pericarp had excellent liver-protecting and hepatocyte regeneration-promoting functions in mice with carbon tetrachloride-induced liver injury (Chen et al., 2017).

Although A-type PAs have many biological activities that are beneficial to human health, but the depth of research on A-type PAs is still far from enough. Whether added to functional foods or health products, extensive in vivo and in vitro experiments are required to prove their safety and bioavailability before entering the market.

4.7 | Interaction with gut microbiota

The intestinal tract is generally considered a key organ involved in the digestion of food and the provision of nutrients to the body for proper maintenance (Paone & Cani, 2020). In the human intestinal tract, there are hundreds of millions of microorganisms, collectively known as gut microbiota, they are an important part of the body's nutrition, to maintain the normal physiological function of the intestinal tract, and to regulate the host immune systems (Huang, Feng et al., 2022; Tao et al., 2019; Wang, Zhang et al., 2018). PAs could interact with other food components during processing, intake, and digestion (Liu et al., 2020; Liu, Li et al., 2022: Liu, Renard, Bureau, et al.,2021; Liu, Renard, Rolland-Sabaté, et al.,2021) and subsequently interact with the gut microbiota in the human body. On the one hand, PAs are naturally occurring bioactive components of the daily diet, especially in fruits and vegetables, and there are several lines of evidence suggesting that the intake of PAs or PAs-rich diets has a positive impact on the gut microbiota, both in terms of increasing microbial diversity and regulating intestinal homeostasis, as well as in terms of ameliorating intestinal inflammation, immune response, and oxidative stress (Han et al., 2016; Redondo-Castillejo et al., 2023). For example, an increase in *Bifidobacterium* spp. and *Lactobacillus–Enterococcus* was found in human gut microbiota cultures incubated with grapeseed PAs for 36 h in vitro, showing their prebiotic effects, both *Lactobacillus* and *Bifidobacterium* spp. are well-recognized as probiotic bacteria contributing to the integrity of the gastrointestinal barrier, remodeling the gut microbiota, and providing metabolic benefits such as improved insulin sensitivity and anti-inflammatory effects (Ferreira et al., 2023; Zhou et al., 2016). And at the in vivo level, A -type PAs from peanut skin are shown to attenuate weight loss and colon shortening in mice, as well as restoring the intestinal barrier, lowering the level of oxidative stress, and decreasing the secretion of inflammatory cytokines. Meanwhile, the A-type PAs interacted with the gut microbiota, and the relative abundance of beneficial genera, for example, *Bacteroides, Helicobacter, Parabacteroides, Escherichia-Shigella*, and *Erysipelatoclostridium*, was shown to increase at the genus level, and that of detrimental genera, such as *Oscillibacter, Lachnospiraceae, and Roseburia*, was shown to decrease. Meanwhile, they decreased the presence of pathogens in the intestinal tract, suppressed inflammation, and attenuated the symptoms of colitis in mice (Huang, Wang et al., 2022).

Moreover, the gut microbiota, in turn, can absorb PAs ingested through the diet and convert them into more biologically active compounds (Ou & Gu, 2014; Pierre et al., 2013). Bioavailability is a key determinant of the health impact of polyphenols (Cosme et al., 2020). In contrast, PAs have limited bioavailability in the human body (Yang & Chan, 2017). Although some PA dimers can be absorbed in the small intestine, their bioavailability is only 5%–10% of that of the monomers (Appeldoorn, Vincken et al., 2009). This is due to the fact that as the concentration increases, the solubility of PAs in aqueous solution decreases, as does their bioavailability in the intestine. The most highly absorbed PAs in the intestine have a DP less than or equal to 4 ($DP \leq 4$) (Lin et al., 2014). PAs with a DP greater than 4 are hardly absorbed by the gastrointestinal tract due to their large molecular size and intestinal barrier (Yang, Tuo et al., 2021). It can be said that whether PAs can be effectively absorbed by the human body is highly dependent on their DP (Ou & Gu, 2014; Yu et al., 2022). Most PAs reach the colon intact and are degraded to aromatic acid by the colonic microbiota, and these microbial metabolites may contribute to the health-promoting properties of PAs in vivo (Gonthier et al., 2003; Zhang et al., 2016). Thus, the gut microbiota may play a key role in the biotransformation, absorption, metabolism, and physiological activities of PAs (Chen et al., 2021).

5 | TECHNO-FUNCTIONAL APPLICATIONS OF A-TYPE PAS

A-type PAs are well known for their excellent biological activities, and attempts have been made to rationally apply them in specific practices, such as the food industry, pharmaceuticals, and nutraceuticals. Although the application of A-type PAs in the above fields is still in its infancy, the accumulation of research results over the past few years will be significantly developed in the near future.

5.1 | Inhibition of acrylamide

Acrylamide is a toxic substance that is formed during high-temperature cooking and is common in carbohydrate-rich foods such as cookies and bread, with the highest concentrations found in French fries and coffee. Known for its in vivo neurotoxic and carcinogenic effects, acrylamide is considered a potential human carcinogen (Esposito et al., 2021; Timmermann et al., 2021). Therefore, it is very important to select effective acrylamide inhibitors to reduce the level of acrylamide produced during the thermal processing of food. Some studies have indicated that A-type PAs are also effective in inhibiting such toxic substances. The flavan-3-ol unit and its derivatives have a strong inhibitory effect on acrylamide. As one of the flavan-3-ol polyphenols, A-type procyanidins may be effective and efficient inhibitors of acrylamide. Zhao et al. (2022) isolated and identified five structurally different A-type procyanidins from peanut skins, including epicatechin-($2\beta \rightarrow O \rightarrow 7$, $4\beta \rightarrow 8$)-semi-epigallocatechin, epicatechin-($2\beta \rightarrow O \rightarrow 7$, $4\beta \rightarrow 8$)-epigallocatechin, epicatechin-($2\beta \rightarrow O \rightarrow 7$, $4\beta \rightarrow 8$)-epigallocatechin-($4\beta \rightarrow 6$)-catechin, and epicatechin-($2\beta \rightarrow O \rightarrow 7$, $4\beta \rightarrow 8$)-epigallocatechin-($4\beta \rightarrow 8$)-catechin, epicatechin-($4\beta \rightarrow 6$)-epigallocatechin-($4\beta \rightarrow 8$, $2\beta \rightarrow O \rightarrow 7$)-catechin. All A-type procyanidins inhibited acrylamide formation even at concentrations as low as 5 μg/mL. In particular, epicatechin-($2\beta\rightarrow O\rightarrow 7,4\beta\rightarrow 8$)-ent-epicatechin inhibited acrylamide formation by 73% at a concentration of 50 μg/mL, which was significantly better than the inhibition rate of 40% for the same concentration of catechins and epicatechins. Yan, Zhao et al. (2020) also demonstrated at the cellular model level that procyanidin A1 and its product obtained after gastrointestinal digestion inhibited acrylamide-induced cytotoxicity best, significantly better than catechins, epicatechins, procyanidin B3, and A-type trimers ($p < .05$).

Overall, the present findings contribute to a better understanding of the relationship between the structure of PAs and their inhibitory effect on acrylamide, especially for A-type. It has potential practical implications if one uses A-type PAs as acrylamide inhibitors in thermally processed foods in the future, although sensory consequences would need to be taken into account.

5.2 | Inhibition of starch retrogradation

Starch regeneration often has a negative impact on starch quality. These include reduced organoleptic quality (increased synthesis rate, hardness, etc.), reduced storage stability (shorter shelf-life), and impact on nutritional quality. This results in shorter shelf life, reduced consumer acceptance, significant waste and losses, and limits the range of starch-based food applications (Thakur et al., 2019; Wang et al., 2015). Most of the literature suggests that polyphenols have the potential to retard starch regrowth, which is mainly attributed to the interaction between polyphenols and starch. As a member of the polyphenol family, PAs contain a large number of OH groups in its molecular structure. This may help to enhance the interaction between PA and starch, thereby interfering with the original interaction between starch chains (Xiao et al., 2013). Wang et al. (2021) compared the inhibition of starch regrowth of three PAs derived from grape seeds, peanut skin (PSPA), and pine bark and found that PSPA had the most significant inhibition of starch regrowth. This is possibly due to their A-type inter-flavan linkages and the presence of a high DP, which makes PSPA more hydrophobic. The higher polymerization means more hydroxyl groups, also implying stronger hydrophobicity and hydrogen bonding interactions. In addition, PA (especially PSPA) tended to interfere with the reordering of starch chains and inhibit the regeneration of maize starch. This further confirms that the interaction between PA and starch may be the main reason for the inhibition of starch regeneration (Amoako & Awika, 2016; Du et al., 2019). Therefore, due to structural properties, the interaction between PSPA and maize starch during storage may be enhanced, protecting the starch chain ordering from being disrupted, resulting in a more significant inhibition of starch regrowth by PSPA compared to the other two PAs. This also suggests that A-type PAs may be a novel inhibitor of starch regrowth, not only modifying starch but also adding to its nutritional value (e.g., antioxidant, hypolipidemic effects).

5.3 | Enhance antimicrobial performance of food packaging

Food spoilage and deterioration caused by foodborne pathogens and other microorganisms is a serious problem. As a result, the demand for antimicrobial components in food packaging is growing (Huang et al., 2019). As a natural polyphenol with excellent antimicrobial activity, the application of A-type PAs in the food industry can be further extended to antimicrobial food packaging. It interacts with food surfaces to prevent the growth of foodborne microorganisms. Thus, antimicrobial food packaging not only has minimal negative impact on food but also provides antimicrobial properties that can preserve food for a long time (Huang et al., 2019; Zang et al., 2013). A study combining cranberry extract (rich in A-type PAs) with chitosan developed a new food-active packaging film that significantly reduced biofilm of *E. coli* and *S. aureus*, and the observed antioxidant activity became an added value in extending food shelf life at the same time (Severo et al., 2021). There are two major trends for future food processing applications of A-type PAs due to their remarkable ability to inhibit microbial growth and biofilm formation: (i) food preservatives or disinfectants for processing equipment where foodborne pathogens are located and (ii) for obtaining active plastics or films for food packaging.

5.4 | Improving sperm motility

A-type PAs protect mammalian sperm from oxidative stress through their powerful antioxidant capacity, thereby improving sperm motility. A study has demonstrated for the first time that CNB-1, a A-type PA trimer, as a strong antioxidant, can effectively inhibit oxidative sperm damage in horse deer. Its mechanism of action seems to be through improving sperm progression and velocity, reducing the production of reactive oxygen species, and preventing lipid peroxidation after oxidative damage while also effectively maintaining the persistence of sperm viability; therefore, the addition of CNB-1 to semen is promising (Sánchez-Rubio et al., 2018). At present, the research on A-type PAs to protect animal sperm vitality is not deep enough, and if it can be applied on a large scale, it would be of great significance to the development of animal husbandry in the future.

5.5 | Developed as a novel drug and dietary supplement

As mentioned above, cranberries are rich in A-type PAs that inhibit the adhesion of *E. coli* to urinary tract epithelial cells. This affects tissue colonization and subsequent infection and is a key component in the prevention of UTIs. Prolonged clinical use of antibiotics in immunocompromised patients may lead to the development of antiviral viral strains, which may result in treatment failure. Natural products appear to have emerged as novel sources of drugs that can supplement or replace common antibiotics. Oximacro is a cranberry extract developed by Biosfered. It contains high levels of PAs and a high proportion of A-type PA dimers and trimers. Oximacro was shown to be effective in preventing UTIs in a preclinical double-blind controlled study (Occhipinti et al., 2016).

Meanwhile, Oximacro has been shown for the first time to exhibit potent dose-dependent antiviral activity against clinical isolates of herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), by a mechanism involving inhibition of the initial attachment of the virus to the surface of target cells. The mechanism involves inhibition of initial viral attachment to the surface of target cells. Oximacro is also a promising natural candidate for the development of novel topical microbicides for the prevention of HSV-1 and HSV-2 infections (Terlizzi et al., 2016). Oximacro is also an ideal natural candidate for the development of novel topical microbicides for the prevention of HSV-1 and HSV-2 infections.

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

In terms of the food sources of A-type PAs, it is much less widely distributed than B-type PAs. There is a strong consumer demand for natural actives like A-type PAs to be used in the food and nutritional industries because of their obvious advantages over chemically synthesized substances. However, cost-effective extraction and isolation methods are essential to obtain A-type PAs with high purity. At present, the natural sources of A-type PAs are mainly concentrated in a few plants, such as peanut skins, cranberries, and litchi pericarps, and the extraction methods mainly rely on organic solvent extraction. Therefore, future research could focus on exploring more high-quality and inexpensive plant sources as well as more green and economical extraction methods, for example, deep eutectic solvents.

Evidence was obtained that the levels of A-type PAs increased or decreased after nonthermal processing. The decrease could be due to accelerated depolymerization of A-type PAs by nonthermal processing or induced increase in flavanols. The increase in A-type PAs could be due to the chemical reaction of B-type PAs following cyclic oxidation of o-diphenol B to the corresponding highly reactive o-quinone. It is also possible that nonthermal processing induced higher DP of A-type PAs, which increased the chemical composition of A-type PAs. A-type PAs are highly nutritious and have a variety of nutrition benefits (e.g., regulation of gut microbiota). Meanwhile, A-type PAs have outstanding effects in inhibiting acrylamide production and inhibiting starch regrowth. The physicochemical and biological properties of A-type PAs are closely related to their structural characteristics. However, their conformational relationships, exact metabolic processes, and mechanisms have yet to be deeply explored.

Therefore, future studies could include: (a) focusing on investigating the availability of a wider range of A-type PAs, especially more qualitative and affordable plant sources, and exploring greener and more economical extraction methods; (b) understanding the relationship between different food sources and different polymerization levels of A-type PAs and human digestion, absorption, metabolism, and overall bioavailability, in particular their interactions with the gut microbiota; (c) focusing the innovate processing technology that maximize the preservation/non-destruction of the intact structure and content of A-type PAs; (d) studying the nutritional activity of A-type PAs in the daily diet (as food/food ingredients/dietary supplements).

AUTHOR CONTRIBUTIONS

Yu Zeng: Writing—original draft; visualization; data curation; formal analysis. **Lei Zhao and Kai Wang**: Validation; data curation. **Catherine M.G.C. Renard and Carine Le Bourvellec**: Writing—review and editing; validation; formal analysis. **Zhuoyan Hu**: Project administration; supervision; writing—review and editing; validation. **Xuwei Liu**: Conceptualization; visualization; writing—review and editing; project administration; supervision; resources; formal analysis; validation; methodology; funding acquisition; investigation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest with regard to this study.

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REFERENCES

Acosta-Estrada, B. A., Gutiérrez-Uribe, J. A., & Serna-Saldívar, S. O. (2014). Bound phenolics in foods, a review. *Food Chemistry*, *152*, 46–55. https://doi.org/10.1016/j.foodchem.2013.11.093

Alejo-Armijo, A., Glibota, N., Frías, M. P., Altarejos, J., Gálvez, A., Ortega-Morente, E., & Salido, S. (2017). Antimicrobial and antibiofilm activities of procyanidins extracted from laurel wood against a selection of foodborne microorganisms. *International Journal of Food Science & Technology*, *52*, 679–686. https://doi.org/10.1111/ijfs.13321

Alejo-Armijo, A., Ortega-Vidal, J., Salido, S., & Altarejos, J. (2022). Recovery and seasonal variation of cinnamtannin B-1 from laurel (*Laurus nobilis* L.) pruning wood wastes. *Chemistry & Biodiversity*, *19*, e202100807. https://doi.org/10.1002/cbdv.202100807

Alejo-Armijo, A., Salido, S., & Altarejos, J. (2020). Synthesis of A-type proanthocyanidins and their analogues: A comprehensive review. *Journal of Agricultural and Food Chemistry*, *68*, 8104–8118. https://doi.org/10.1021/acs.jafc.0c03380

Alejo-Armijo, A., Tello-Abolafia, A., Salido, S., & Altarejos, J. (2019). Phenolic compounds in laurel wood: A new source of proanthocyanidins. *Journal of Wood Chemistry and Technology*, *39*(6), 436–453. https://doi.org/10.1080/02773813.2019.1636825

Alves Filho, E. G., Silva, L. M. A., de Brito, E. S., Wurlitzer, N. J., Fernandes, F. A. N., Rabelo, M. C., Fonteles, T. V., & Rodrigues, S. (2018). Evaluation of thermal and non-thermal processing effect on non-prebiotic and prebiotic acerola juices using ^{1}H qNMR and GC–MS coupled to chemometrics. *Food Chemistry*, *265*, 23–31. https://doi.org/10.1016/j.foodchem.2018.05.038

Amoako, D. B., & Awika, J. M. (2016). Polymeric tannins significantly alter properties and in vitro digestibility of partially gelatinized intact starch granule. *Food Chemistry*, *208*, 10–17. https://doi.org/10.1016/j.foodchem.2016.03.096

Appeldoorn, M. M., Sanders, M., Vincken, J.-P., Cheynier, V., Le Guernevé, C., Hollman, P. C. H., & Gruppen, H. (2009). Efficient isolation of major procyanidin A-type dimers from peanut skins and B-type dimers from grape seeds. *Food Chemistry*, *117*(4), 713–720. https://doi.org/10.1016/j.foodchem.2009.04.047

Appeldoorn, M. M., Vincken, J.-P., Gruppen, H., & Hollman, P. C. H. (2009). Procyanidin dimers A1, A2, and B2 are absorbed without conjugation or methylation from the small intestine of rats. *The Journal of Nutrition*, *139*(8), 1469–1473. https://doi.org/10.3945/jn.109.106765

Baldé, A. M., Pieters, L. A., Gergely, A., Kolodziej, H., Claeys, M., & Vlietinck, A. J. (1991). A-type proanthocyanidins from stem-bark of *Pavetta owariensis*. *Phytochemistry*, *30*(1), 337–342. https://doi.org/10.1016/0031-9422(91)84150-Q

Barbhuiya, R. I., Singha, P., & Singh, S. K. (2021). A comprehensive review on impact of non-thermal processing on the structural changes of food components. *Food Research International*, *149*, 110647. https://doi.org/10.1016/j.foodres.2021.110647

Bisht, B., Bhatnagar, P., Gururani, P., Kumar, V., Tomar, M. S., Sinhmar, R., Rathi, N., & Kumar, S. (2021). Food irradiation: Effect of ionizing and non-ionizing radiations on preservation of fruits and vegetables–a review. *Trends in Food Science & Technology*, *114*, 372–385. https://doi.org/10.1016/j.tifs.2021.06.002

Bohn, T. (2014). Dietary factors affecting polyphenol bioavailability. *Nutrition Reviews*, *72*, 429–452. https://doi.org/10.1111/nure.12114

Bresciani, L., Di Pede, G., Favari, C., Calani, L., Francinelli, V., Riva, A., Petrangolini, G., Allegrini, P., Mena, P., & Del Rio,

D. (2021). In vitro (poly) phenol catabolism of unformulated- and phytosome-formulated cranberry (*Vaccinium macrocarpon*) extracts. *Food Research International*, *141*, 110137. https://doi.org/10.1016/j.foodres.2021.110137

Bystrom, L. M., Bezerra, D. P., Hsu, H.-T., Zong, H., Lara-Martínez, L. A., De Leon, J. P., Emmanuel, M., Méry, D., Gardenghi, S., & Hassane, D. (2019). Cranberry A-type proanthocyanidins selectively target acute myeloid leukemia cells. *Blood Advances*, *3*, 3261–3265. https://doi.org/10.1182/bloodadvances.201802-6633

Carriere, P. P., Kapur, N., Mir, H., Ward, A. B., & Singh, S. (2018). Cinnamtannin B-1 inhibits cell survival molecules and induces apoptosis in colon cancer. *International Journal of Oncology*, *53*, 1442–1454. https://doi.org/10.3892/ijo.2018.4489

Chang, M., Sun, X., Guo, X., Bai, H., Liu, R., Jin, Q., & Wang, X. (2020). Composition and antioxidant study of procyanidins from peanut skins. *Journal of Food Measurement and Characterization*, *14*, 2781–2789. https://doi.org/10.1007/s11694-020-00523-z

Chen, L., Chang, C., Tsay, J., & Weng, B. B. (2017). Hepatoprotective effects of litchi (*Litchi chinensis*) procyanidin A2 on carbon tetrachloride-induced liver injury in ICR mice. *Experimental and Therapeutic Medicine*, *13*, 2839–2847. https://doi.org/10.3892/etm.2017.4358

Chen, S., Song, J., Du, L., Ma, Y., Ren, S., Ren, J., & Li, S. (2020). Quantitative analysis of solubility parameters and surface properties of larch bark proanthocyanidins. *Polymers*, *12*, 2800. https://doi.org/10.3390/polym12122800

Chen, W., Zhang, L., Zhao, L., Yan, F., Zhu, X., Lu, Q., & Liu, R. (2021). Metabolomic profiles of A-type procyanidin dimer and trimer with gut microbiota in vitro. *Journal of Functional Foods*, *85*, 104637. https://doi.org/10.1016/j.jff.2021.104637

Cires, M. J., Wong, X., Carrasco-Pozo, C., & Gotteland, M. (2017). The gastrointestinal tract as a key target organ for the health-promoting effects of dietary proanthocyanidins. *Frontiers in Nutrition*, *3*, 57. https://doi.org/10.3389/fnut.2016.00057

Constanza, K. E., White, B. L., Davis, J. P., Sanders, T. H., & Dean, L. L. (2012). Value-added processing of peanut skins: Antioxidant capacity, total phenolics, and procyanidin content of spray-dried extracts. *Journal of Agricultural and Food Chemistry*, *60*, 10776–10783. https://doi.org/10.1021/jf3035258

Cosme, P., Rodríguez, A. B., Espino, J., & Garrido, M. (2020). Plant phenolics: Bioavailability as a key determinant of their potential health-promoting applications. *Antioxidants*, *9*(12), 1263. https://doi.org/10.3390/antiox9121263

de Camargo, A. C., Regitano-d'Arce, M. A. B., Gallo, C. R., & Shahidi, F. (2015). Gamma-irradiation induced changes in microbiological status, phenolic profile and antioxidant activity of peanut skin. *Journal of Functional Foods*, *12*, 129–143. https://doi.org/10.1016/j.jff.2014.10.034

Déprez, S., Brezillon, C., Rabot, S., Philippe, C., Mila, I., Lapierre, C., & Scalbert, A. (2000). Polymeric proanthocyanidins are catabolized by human colonic microflora into low-molecular-weight phenolic acids. *The Journal of Nutrition*, *130*, 2733–2738. https://doi.org/10.1093/jn/130.11.2733

De Taeye, C., Caullet, G., Eyamo Evina, V. J., & Collin, S. (2017). Procyanidin A2 and its degradation products in raw, fermented, and roasted cocoa. *Journal of Agricultural and Food Chemistry*, *65*, 1715–1723. https://doi.org/10.1021/acs.jafc.6b05262

Dixon, R. A., Xie, D., & Sharma, S. B. (2005). Proanthocyanidins–a final frontier in flavonoid research? *New Phytologist*, *165*(1), 9–28. https://doi.org/10.1111/j.1469-8137.2004.01217.x

Dongmo, A. K., Nono, R. N., Kaaniche, F., Mawabo, I. K., Frese, M., Chouna, J. R., Nkenfou, C. N., Lenta, B. N., Ngnokam, D., & Nkeng-Efouet-Alango, P. (2020). A-type doubly linked proanthocyanidin trimer and other metabolites from *Canthium venosum* fruits, and their biological activities. *Phytochemistry Letters*, *36*, 134–138. https://doi.org/10.1016/j.phytol.2020.01.020

Du, J., Yao, F., Zhang, M., Khalifa, I., Li, K., & Li, C. (2019). Effect of persimmon tannin on the physicochemical properties of maize starch with different amylose/amylopectin ratios. *International Journal of Biological Macromolecules*, *132*, 1193–1199. https://doi.org/10.1016/j.ijbiomac.2019.04.046

Dudek, M. K., Gliński, V. B., Davey, M. H., Sliva, D., Kazḿierski, S., & Gliński, J. A. (2017). Trimeric and tetrameric A-type procyanidins from peanut skins. *Journal of Natural Products*, *80*, 415–426. https://doi.org/10.1021/acs.jnatprod.6b00946

Esposito, F., Nolasco, A., Caracciolo, F., Velotto, S., Montuori, P., Romano, R., Stasi, T., & Cirillo, T. (2021). Acrylamide in baby foods: A probabilistic exposure assessment. *Foods*, *10*, 2900. https://doi.org/10.3390/foods10122900

Fauvelle, C., Lambotin, M., Heydmann, L., Prakash, E., Bhaskaran, S., Vishwaraman, M., Baumert, T. F., & Moog, C. (2017). A cinnamon-derived procyanidin type A compound inhibits hepatitis C virus cell entry. *Hepatology International*, *11*, 440–445. https://doi.org/10.1007/s12072-017-9809-y

Feldman, M., Tanabe, S., Howell, A., & Grenier, D. (2012). Cranberry proanthocyanidins inhibit the adherence properties of *Candida albicans* and cytokine secretion by oral epithelial cells. *BMC Complementary and Alternative Medicine*, *12*, 6. https://doi.org/10.1186/1472-6882-12-6

Feliciano, R. P., Krueger, C. G., Shanmuganayagam, D., Vestling, M. M., & Reed, J. D. (2012). Deconvolution of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry isotope patterns to determine ratios of A-type to B-type interflavan bonds in cranberry proanthocyanidins. *Food Chemistry*, *135*, 1485–1493. https://doi.org/10.1016/j.foodchem.2012.05.102

Feliciano, R. P., Meudt, J. J., Shanmuganayagam, D., Krueger, C. G., & Reed, J. D. (2014). Ratio of "A-type" to "B-type" proanthocyanidin interflavan bonds affects extra-intestinal pathogenic *Escherichia coli* invasion of gut epithelial cells. *Journal of Agricultural and Food Chemistry*, *62*, 3919–3925. https://doi.org/10.1021/jf403839a

Ferreira, Y. A. M., Jamar, G., Estadella, D., & Pisani, L. P. (2023). Proanthocyanidins in grape seeds and their role in gut microbiota-white adipose tissue axis. *Food Chemistry*, *404*, 134405. https://doi.org/10.1016/j.foodchem.2022.134405

Figueroa, J. G., Borrás-Linares, I., Lozano-Sánchez, J., & Segura-Carretero, A. (2018). Comprehensive characterization of phenolic and other polar compounds in the seed and seed coat of avocado by HPLC-DAD-ESI-QTOF-MS. *Food Research International*, *105*, 752–763. https://doi.org/10.1016/j.foodres.2017.11.082

Foo, L. Y., Lu, Y., Howell, A. B., & Vorsa, N. (2000). The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated *Escherichia coli* in vitro. *Phytochemistry*, *54*, 173–181. https://doi.org/10.1016/S0031-9422(99)00573-7

Gabetta, B., Fuzzati, N., Griffini, A., Lolla, E., Pace, R., Ruffilli, T., & Peterlongo, F. (2000). Characterization of proanthocyanidins from grape seeds. *Fitoterapia*, *71*(2), 162–175. https://doi.org/10.1016/S0367-326X(99)00161-6

Galarraga-Vinueza, M. E., Dohle, E., Ramanauskaite, A., Al-Maawi, S., Obreja, K., Magini, R., Sader, R., Ghanaati, S., & Schwarz, F. (2020). Anti-inflammatory and macrophage polarization effects of cranberry proanthocyanidins (PACs) for periodontal and peri-implant disease therapy. *Journal of Periodontal Research*, *55*, 821–829. https://doi.org/10.1111/jre.12773

Garzón, G. A., Soto, C. Y., López-R, M., Riedl, K. M., Browmiller, C. R., & Howard, L. (2020). Phenolic profile, in vitro antimicrobial activity and antioxidant capacity of *Vaccinium meridionale* Swartz pomace. *Heliyon*, *6*, e03845. https://doi.org/10.1016/j.heliyon.2020.e03845

Giordani, E., Doumett, S., Nin, S., & Del Bubba, M. (2011). Selected primary and secondary metabolites in fresh persimmon (*Diospyros kaki* Thunb.): A review of analytical methods and current knowledge of fruit composition and health benefits. *Food Research International*, *44*, 1752–1767. https://doi.org/10.1016/j.foodres.2011.01.036

Gonthier, M.-P., Donovan, J. L., Texier, O., Felgines, C., Remesy, C., & Scalbert, A. (2003). Metabolism of dietary procyanidins in rats. *Free Radical Biology and Medicine*, *35*(8), 837–844. https://doi.org/10.1016/S0891-5849(03)00394-0

Grace, M. H., Esposito, D., Dunlap, K. L., & Lila, M. A. (2014). Comparative analysis of phenolic content and profile, antioxidant capacity, and anti-inflammatory bioactivity in wild Alaskan and commercial *Vaccinium* berries. *Journal of Agricultural and Food Chemistry*, *62*(18), 4007–4017. https://doi.org/10.1021/jf403810y

Gu, L., Kelm, M., Hammerstone, J. F., Beecher, G., Cunningham, D., Vannozzi, S., & Prior, R. L. (2002). Fractionation of polymeric procyanidins from lowbush blueberry and quantification of procyanidins in selected foods with an optimized normal-phase HPLC– MS fluorescent detection method. *Journal of Agricultural and Food Chemistry*, *50*(17), 4852–4860. https://doi.org/10.1021/jf020214v

Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., Gebhardt, S., & Prior, R. L. (2004). Concentrations of proanthocyanidins in common foods and estimations of normal consumption. *The Journal of Nutrition*, *134*, 613–617. https://doi.org/10.1093/jn/134.3.613

Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., & Prior, R. L. (2003). Screening of foods containing proanthocyanidins and their structural characterization using LC-MS/MS and thiolytic degradation. *Journal of Agricultural and Food Chemistry*, *51*, 7513–7521. https://doi.org/10.1021/jf034815d

Guyot, S., Marnet, N., & Drilleau, J.-F. (2001). Thiolysis–HPLC characterization of apple procyanidins covering a large range of polymerization states. *Journal of Agricultural and Food Chemistry*, *49*(1), 14–20. https://doi.org/10.1021/jf000814z

Guyot, S., Marnet, N., Laraba, D., Sanoner, P., & Drilleau, J.-F. (1998). Reversed-phase HPLC following thiolysis for quantitative estimation and characterization of the four main classes of phenolic compounds in different tissue zones of a French cider apple variety (*Malus domestica* Var. Kermerrien). *Journal of Agricultural and Food Chemistry*, *46*(5), 1698–1705. https://doi.org/10.1021/jf970832p

Han, M., Song, P., Huang, C., Rezaei, A., Farrar, S., Brown, M. A., & Ma, X. (2016). Dietary grape seed proanthocyanidins (GSPs) improve weaned intestinal microbiota and mucosal barrier using a piglet model. *Oncotarget*, *7*(49), 80313–80326. https://doi.org/10.18632/oncotarget.13450

Han, S., Gao, H., Chen, S., Wang, Q., Li, X., Du, L.-J., Li, J., Luo, Y.-Y., Li, J.-X., & Zhao, L.-C. (2019). Procyanidin A1 alleviates inflammatory response induced by LPS through NF-κB, MAPK, and Nrf2/HO-1 pathways in RAW264.7 cells. *Scientific Reports*, *9*(1), 15087. https://doi.org/10.1038/s41598-019-51614-x

Howell, A. B., Reed, J. D., Krueger, C. G., Winterbottom, R., Cunningham, D. G., & Leahy, M. (2005). A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. *Phytochemistry*, *66*, 2281–2291. https://doi.org/10.1016/j.phytochem.2005.05.022

Hsu, C., Lin, G., Lin, H., & Chang, S. (2018). Characteristics of proanthocyanidins in leaves of *Chamaecyparis obtusa* var. formosana as strong α-glucosidase inhibitors. *Journal of the Science of Food and Agriculture*, *98*, 3806–3814. https://doi.org/10.1002/jsfa.8894

Hu, X.-Q., Huang, Y.-Y., Dong, Q.-F., Song, L.-Y., Yuan, F., & Yu, R.-M. (2011). Structure characterization and antioxidant activity of a novel polysaccharide isolated from pulp tissues of *Litchi chinensis*. *Journal of Agricultural and Food Chemistry*, *59*, 11548–11552. https://doi.org/10.1021/jf203179y

Huang, B., Wang, L., Liu, M., Wu, X., Lu, Q., & Liu, R. (2022). The underlying mechanism of A-type procyanidins from peanut skin on DSS-induced ulcerative colitis mice by regulating gut microbiota and metabolism. *Journal of Food Biochemistry*, *46*(7), e14103. https://doi.org/10.1111/jfbc.14103

Huang, C., Feng, S., Huo, F., & Liu, H. (2022). Effects of four antibiotics on the diversity of the intestinal microbiota. *Microbiology Spectrum*, *10*(2), e0190421. https://doi.org/10.1128/spectrum.01904-21

Huang, T., Qian, Y., Wei, J., & Zhou, C. (2019). Polymeric antimicrobial food packaging and its applications. *Polymers*, *11*, 560. https://doi.org/10.3390/polym11030560

Ishihara, T., Kaidzu, S., Kimura, H., Koyama, Y., Matsuoka, Y., & Ohira, A. (2018). Protective effect of highly polymeric A-type proanthocyanidins from seed shells of Japanese horse chestnut (*Aesculus turbinata* Blume) against light-induced oxidative damage in rat retina. *Nutrients*, *10*, 593. https://doi.org/10.3390/nu10050593

Jeong, D. E., Cho, J.-Y., Lee, Y. G., Jeong, H. Y., Lee, H. J., & Moon, J.-H. (2017). Isolation of five proanthocyanidins from pear (*Pyrus pyrifolia* Nakai) fruit peels. *Food Science and Biotechnology*, *26*, 1209–1215. https://doi.org/10.1007/s10068-017-0157-4

Jiang, Z., Han, Z., Zhu, M., Wan, X., & Zhang, L. (2023). Effects of thermal processing on transformation of polyphenols and flavor quality. *Current Opinion in Food Science*, *51*, 101014. https://doi.org/10.1016/j.cofs.2023.101014

Jiao, J., Wei, Y., Chen, J., Chen, X., & Zhang, Y. (2017). Anti-aging and redox state regulation effects of A-type proanthocyanidins-rich cranberry concentrate and its comparison with grape seed extract in mice. *Journal of Functional Foods*, *30*, 63–73. https://doi.org/10.1016/j.jff.2016.12.039

Johnson, J. R., & Russo, T. A. (2002). Extraintestinal pathogenic *Escherichia coli*: "the other bad *E coli*". *Journal of Laboratory and Clinical Medicine*, *139*, 155–162. https://doi.org/10.1067/mlc.2002.121550

Keenan, D. F., Brunton, N., Butler, F., Wouters, R., & Gormley, R. (2011). Evaluation of thermal and high hydrostatic pressure processed apple purees enriched with prebiotic inclusions. *Innovative*

Food Science & Emerging Technologies, *12*(3), 261–268. https://doi.org/10.1016/j.ifset.2011.04.003

Kessy, H. N. E., Hu, Z., Zhao, L., & Zhou, M. (2016). Effect of steam blanching and drying on phenolic compounds of litchi pericarp. *Molecules (Basel, Switzerland)*, *21*, 729. https://doi.org/10.3390/molecules21060729

Killday, K. B., Davey, M. H., Glinski, J. A., Duan, P., Veluri, R., Proni, G., Daugherty, F. J., & Tempesta, M. S. (2011). Bioactive A-type proanthocyanidins from *Cinnamomum cassia*. *Journal of Natural Products*, *74*, 1833–1841. https://doi.org/10.1021/np1007944

Kolodziej, H., Sakar, M. K., Burger, J. F. W., Engelshowe, R., & Ferreira, D. (1991). A-type proanthocyanidins from *Prunus spinosa*. *Phytochemistry*, *30*(6), 2041–2047. https://doi.org/10.1016/0031-9422(91)85064-7

La, V. D., Howell, A. B., & Grenier, D. (2010). Anti-*Porphyromonas gingivalis* and anti-inflammatory activities of A-type cranberry proanthocyanidins. *Antimicrobial Agents and Chemotherapy*, *54*, 1778–1784. https://doi.org/10.1128/AAC.01432-09

Lachowicz, S., Michalska, A., Lech, K., Majerska, J., Oszmiański, J., & Figiel, A. (2019). Comparison of the effect of four drying methods on polyphenols in saskatoon berry. *Lebensmittel-Wissenschaft & Technologie*, *111*, 727–736. https://doi.org/10.1016/j.lwt.2019.05.054

Le Roux, E., Doco, T., Sarni-Manchado, P., Lozano, Y., & Cheynier, V. (1998). A-type proanthocyanidins from pericarp of *Litchi chinensis*. *Phytochemistry*, *48*(7), 1251–1258. https://doi.org/10.1016/S0031-9422(97)01070-4

Li, S., Xiao, J., Chen, L., Hu, C., Chen, P., Xie, B., & Sun, Z. (2012). Identification of A-series oligomeric procyanidins from pericarp of *Litchi chinensis* by FT-ICR-MS and LC-MS. *Food Chemistry*, *135*, 31–38. https://doi.org/10.1016/j.foodchem.2012.04.039

Li, S., Yang, Y., Li, J., Zhu, Z., Lorenzo, J. M., & Barba, F. J. (2018). Increasing yield and antioxidative performance of litchi pericarp procyanidins in baked food by ultrasound-assisted extraction coupled with enzymatic treatment. *Molecules (Basel, Switzerland)*, *23*, 2089. https://doi.org/10.3390/molecules23092089

Li, W., Zhang, J., & Zhang, L. (2020). Assessment of the formation of A-type proanthocyanidin by model reaction to blueberry extract and epicatechin. *Lebensmittel-Wissenschaft & Technologie*, *134*, 110169. https://doi.org/10.1016/j.lwt.2020.110169

Li, X., Sui, Y., Li, S., Xie, B., & Sun, Z. (2016). A-type procyanidins from litchi pericarp ameliorate hyperglycaemia by regulating hepatic and muscle glucose metabolism in streptozotocin (STZ)-induced diabetic mice fed with high fat diet. *Journal of Functional Foods*, *27*, 711–722. https://doi.org/10.1016/j.jff.2016.08.010

Li, X., Wu, Q., Sui, Y., Li, S., Xie, B., & Sun, Z. (2018). Dietary supplementation of A-type procyanidins from litchi pericarp improves glucose homeostasis by modulating mTOR signaling and oxidative stress in diabetic ICR mice. *Journal of Functional Foods*, *44*, 155–165. https://doi.org/10.1016/j.jff.2017.12.024

Lin, G., Hsu, C., & Chang, S. (2018). Antihyperglycemic activities of twig extract of indigenous cinnamon (*Cinnamomum osmophloeum*) on high-fat diet and streptozotocin-induced hyperglycemic rats. *Journal of the Science of Food and Agriculture*, *98*, 5908–5915. https://doi.org/10.1002/jsfa.9286

Lin, L.-Z., Sun, J., Chen, P., Monagas, M. J., & Harnly, J. M. (2014). UHPLC-PDA-ESI/HRMSn profiling method to identify and quantify oligomeric proanthocyanidins in plant products. *Journal of Agricultural and Food Chemistry*, *62*(39), 9387–9400. https://doi.org/10.1021/jf501011y

Liu, L., Xie, B., Cao, S., Yang, E., Xu, X., & Guo, S. (2007). A-type procyanidins from *Litchi chinensis* pericarp with antioxidant activity. *Food Chemistry*, *105*(4), 1446–1451. https://doi.org/10.1016/j.foodchem.2007.05.022

Liu, M., Huang, B., Wang, L., Lu, Q., & Liu, R. (2022). Peanut skin procyanidins ameliorate insulin resistance via modulation of gut microbiota and gut barrier in type 2 diabetic mice. *Journal of the Science of Food and Agriculture*, *102*, 5935–5947. https://doi.org/10.1002/jsfa.11945

Liu, X., Le Bourvellec, C., Guyot, S., & Renard, C. M. G. C. (2021). Reactivity of flavanols: Their fate in physical food processing and recent advances in their analysis by depolymerization. *Comprehensive Reviews in Food Science and Food Safety*, *20*, 4841–4880. https://doi.org/10.1111/1541-4337.12797

Liu, X., Le Bourvellec, C., & Renard, C. M. G. C. (2020). Interactions between cell wall polysaccharides and polyphenols: Effect of molecular internal structure. *Comprehensive Reviews in Food Science and Food Safety*, *19*(6), 3574–3617. https://doi.org/10.1111/1541-4337.12632

Liu, X., Le Bourvellec, C., Yu, J., Zhao, L., Wang, K., Tao, Y., Renard, C. M. G. C., & Hu, Z. (2022). Trends and challenges on fruit and vegetable processing: Insights into sustainable, traceable, precise, healthy, intelligent, personalized and local innovative food products. *Trends in Food Science & Technology*, *125*, 12–25. https://doi.org/10.1016/j.tifs.2022.04.016

Liu, X., Li, J., Rolland-Sabaté, A., Perez, S., Le Bourvellec, C., & Renard, C. M. G. C. (2022). Experimental and theoretical investigation on interactions between xylose-containing hemicelluloses and procyanidins. *Carbohydrate Polymers*, *281*, 119086. https://doi.org/10.1016/j.carbpol.2021.119086

Liu, X., Renard, C. M. G. C., Bureau, S., & Le Bourvellec, C. (2021). Interactions between heterogeneous cell walls and two procyanidins: Insights from the effects of chemical composition and physical structure. *Food Hydrocolloids*, *121*, 107018. https://doi.org/10.1016/j.foodhyd.2021.107018

Liu, X., Renard, C. M. G. C., Rolland-Sabaté, A., & Le Bourvellec, C. (2021). Exploring interactions between pectins and procyanidins: Structure-function relationships. *Food Hydrocolloids*, *113*, 106498. https://doi.org/10.1016/j.foodhyd.2020.106498

Lorenzo, J. M., Munekata, P. E. S., Sant'Ana, A. S., Carvalho, R. B., Barba, F. J., Toldrá, F., Mora, L., & Trindade, M. A. (2018). Main characteristics of peanut skin and its role for the preservation of meat products. *Trends in Food Science & Technology*, *77*, 1–10. https://doi.org/10.1016/j.tifs.2018.04.007

Lou, H., Yamazaki, Y., Sasaki, T., Uchida, M., Tanaka, H., & Oka, S. (1999). A-type proanthocyanidins from peanut skins. *Phytochemistry*, *51*(2), 297–308. https://doi.org/10.1016/S0031-9422(98)00736-5

Lou, X., Xiong, J., Tian, H., Yu, H., Chen, C., Huang, J., Yuan, H., Hanna, M., Yuan, L., & Xu, H. (2022). Effect of high-pressure processing on the bioaccessibility of phenolic compounds from cloudy hawthorn berry (*Crataegus pinnatifida*) juice. *Journal of Food Composition and Analysis*, *110*, 104540. https://doi.org/10.1016/j.jfca.2022.104540

Luganini, A., Terlizzi, M. E., Catucci, G., Gilardi, G., Maffei, M. E., & Gribaudo, G. (2018). The cranberry extract Oximacro® exerts in vitro virucidal activity against influenza virus by interfering with hemagglutinin. *Frontiers in Microbiology*, *9*, 1826. https://doi.org/10.3389/fmicb.2018.01826

Lv, Q., Luo, F., Zhao, X., Liu, Y., Hu, G., Sun, C., Li, X., & Chen, K. (2015). Identification of proanthocyanidins from litchi (*Litchi chinensis* Sonn.) pulp by LC-ESI-Q-TOF-MS and their antioxidant activity. *PLoS ONE*, *10*(3), e0120480. https://doi.org/10.1371/journal.pone.0120480

Maffei, M. E., Salata, C., & Gribaudo, G. (2022). Tackling the future pandemics: Broad-spectrum antiviral agents (BSAAs) based on A-type proanthocyanidins. *Molecules (Basel, Switzerland)*, *27*(23), 8353. https://doi.org/10.3390/molecules27238353

Man, S., Ma, J., Yao, J., Cui, J., Wang, C., Li, Y., Ma, L., & Lu, F. (2017). Systemic perturbations of key metabolites in type 2 diabetic rats treated by polyphenol extracts from *Litchi chinensis* seeds. *Journal of Agricultural and Food Chemistry*, *65*, 7698–7704. https://doi.org/10.1021/acs.jafc.7b02206

Martins, G. R., do Amaral, F. R. L., Brum, F. L., Mohana-Borges, R., de Moura, S. S. T., Ferreira, F. A., Sangenito, L. S., Santos, A. L. S., Figueiredo, N. G., & da Silva, A. S. (2020). Chemical characterization, antioxidant and antimicrobial activities of açaí seed (*Euterpe oleracea* Mart.) extracts containing A-and B-type procyanidins. *Lebensmittel-Wissenschaft & Technologie*, *132*, 109830. https://doi.org/10.1016/j.lwt.2020.109830

Mau, J.-L., Lin, H.-C., & Chen, C.-C. (2002). Antioxidant properties of several medicinal mushrooms. *Journal of Agricultural and Food Chemistry*, *50*, 6072–6077. https://doi.org/10.1021/jf0201273

Mbaoji, F. N., Onwuka, A. M., Onu, S., Peter, I. E., Nweze, J. A., & Okonta, L. E. (2020). Evaluation of methanol-dichloromethane extract of *Stemonocoleus micranthus* Harms (*Fabaceae*) stem bark for anti-inflammatory and immunomodulatory activities. *Evidence-Based Complementary and Alternative Medicine*, *2020*, 1738163. https://doi.org/10.1155/2020/1738163

McRae, J. M., Falconer, R. J., & Kennedy, J. A. (2010). Thermodynamics of grape and wine tannin interaction with polyproline: Implications for red wine astringency. *Journal of Agricultural and Food Chemistry*, *58*(23), 12510–12518. https://doi.org/10.1021/jf1030967

Michalska, A., Wojdyło, A., Honke, J., Ciska, E., & Andlauer, W. (2018). Drying-induced physico-chemical changes in cranberry products. *Food Chemistry*, *240*, 448–455. https://doi.org/10.1016/j.foodchem.2017.07.050

Miranda-Hernández, A. M., Muñiz-Márquez, D. B., Wong-Paz, J. E., Aguilar-Zárate, P., de la Rosa-Hernández, M., Larios-Cruz, R., & Aguilar, C. N. (2019). Characterization by HPLC–ESI–MS^2 of native and oxidized procyanidins from litchi (*Litchi chinensis*) pericarp. *Food Chemistry*, *291*, 126–131. https://doi.org/10.1016/j.foodchem.2019.04.020

Monagas, M., Garrido, I., Lebron-Aguilar, R., Gómez-Cordovés, M. C., Rybarczyk, A., Amarowicz, R., & Bartolome, B. (2009). Comparative flavan-3-ol profile and antioxidant capacity of roasted peanut, hazelnut, and almond skins. *Journal of Agricultural and Food Chemistry*, *57*, 10590–10599. https://doi.org/10.1021/jf901391a

Muñoz-Arrieta, R., Esquivel-Alvarado, D., Alfaro-Viquez, E., Alvarez-Valverde, V., Krueger, C. G., & Reed, J. D. (2021). Nutritional and bioactive composition of Spanish, Valencia, and Virginia type peanut skins. *Journal of Food Composition and Analysis*, *98*, 103816. https://doi.org/10.1016/j.jfca.2021.103816

Mustafa, A. M., Abouelenein, D., Acquaticci, L., Alessandroni, L., Abd-Allah, R. H., Borsetta, G., Sagratini, G., Maggi, F., Vittori, S., & Caprioli, G. (2021). Effect of roasting, boiling, and frying processing on 29 polyphenolics and antioxidant activity in seeds and shells of sweet chestnut (*Castanea sativa* mill.). *Plants*, *10*, 2192. https://doi.org/10.3390/plants10102192

Nakase, H., Sato, N., Mizuno, N., & Ikawa, Y. (2022). The influence of cytokines on the complex pathology of ulcerative colitis. *Autoimmunity Reviews*, *21*, 103017. https://doi.org/10.1016/j.autrev.2021.103017

Nie, F., Liu, L., Cui, J., Zhao, Y., Zhang, D., Zhou, D., Wu, J., Li, B., Wang, T., & Li, M. (2023). Oligomeric proanthocyanidins: An updated review of their natural sources, synthesis, and potentials. *Antioxidants*, *12*(5), 1004. https://doi.org/10.3390/antiox12051004

Occhipinti, A., Germano, A., & Maffei, M. E. (2016). Prevention of urinary tract infection with Oximacro®, a cranberry extract with a high content of A-type proanthocyanidins: A pre-clinical double-blind controlled study. *Urology Journal*, *13*(2), 2640–2649. https://doi.org/10.22037/uj.v13i2.3190

Oldoni, T. L. C., Melo, P. S., Massarioli, A. P., Moreno, I. A. M., Bezerra, R. M. N., Rosalen, P. L., da Silva, G. V. J., Nascimento, A. M., & Alencar, S. M. (2016). Bioassay-guided isolation of proanthocyanidins with antioxidant activity from peanut (*Arachis hypogaea*) skin by combination of chromatography techniques. *Food Chemistry*, *192*, 306–312. https://doi.org/10.1016/j.foodchem.2015.07.004

Ou, K., & Gu, L. (2014). Absorption and metabolism of proanthocyanidins. *Journal of Functional Foods*, *7*, 43–53. https://doi.org/10.1016/j.jff.2013.08.004

Paone, P., & Cani, P. D. (2020). Mucus barrier, mucins and gut microbiota: The expected slimy partners? *Gut*, *69*(12), 2232–2243. https://doi.org/10.1136/gutjnl-2020-322260corr1

Patanè, G. T., Putaggio, S., Tellone, E., Barreca, D., Ficarra, S., Maffei, C., Calderaro, A., & Laganà, G. (2023). Catechins and proanthocyanidins involvement in metabolic syndrome. *International Journal of Molecular Sciences*, *24*(11), 9228. https://doi.org/10.3390/ijms24119228

Payne, S. E., Flematti, G. R., Reeder, A., Kotze, A. C., Durmic, Z., & Vercoe, P. E. (2018). Procyanidin A2 in the Australian plant *Alectryon oleifolius* has anthelmintic activity against equine cyathostomins in vitro. *Veterinary Parasitology*, *249*, 63–69. https://doi.org/10.1016/j.vetpar.2017.11.008

Peng, J., Li, K., Zhu, W., Deng, X., & Li, C. (2018). Separation and purification of four phenolic compounds from persimmon by high-speed counter-current chromatography. *Journal of Chromatography B*, *1072*, 78–85. https://doi.org/10.1016/j.jchromb.2017.11.010

Petroski, W., & Minich, D. M. (2020). Is there such a thing as "anti-nutrients"? A narrative review of perceived problematic plant compounds. *Nutrients*, *12*(10), 2929. https://doi.org/10.3390/nu12102929

Petry, N., Egli, I., Zeder, C., Walczyk, T., & Hurrell, R. (2010). Polyphenols and phytic acid contribute to the low iron bioavailability from common beans in young women. *The Journal of Nutrition*, *140*(11), 1977–1982. https://doi.org/10.3945/jn.110.125369

Pierre, J. F., Heneghan, A. F., Feliciano, R. P., Shanmuganayagam, D., Roenneburg, D. A., Krueger, C. G., Reed, J. D., & Kudsk, K. A. (2013). Cranberry proanthocyanidins improve the gut mucous layer morphology and function in mice receiving elemental enteral nutrition. *Journal of Parenteral and Enteral Nutrition*, *37*(3), 401–409. https://doi.org/10.1177/0148607112463076

Pinto-Merino, Á., Labrador, J., Zubiaur, P., Alcaraz, R., Herrero, M. J., Montesinos, P., Abad-Santos, F., & Saiz-Rodríguez, M. (2022). Role of pharmacogenetics in the treatment of acute myeloid leukemia: Systematic review and future perspectives. *Pharmaceutics*, *14*, 559. https://doi.org/10.3390/pharmaceutics14030559

Pinzón-Arango, P. A., Liu, Y., & Camesano, T. A. (2009). Role of cranberry on bacterial adhesion forces and implications for *Escherichia coli*–uroepithelial cell attachment. *Journal of Medicinal Food*, *12*, 259–270. https://doi.org/10.1089/jmf.2008.0196

Prior, R. L., Lazarus, S. A., Cao, G., Muccitelli, H., & Hammerstone, J. F. (2001). Identification of procyanidins and anthocyanins in blueberries and cranberries (*Vaccinium spp.*) using high-performance liquid chromatography/mass spectrometry. *Journal of Agricultural and Food Chemistry*, *49*(3), 1270–1276. https://doi.org/10.1021/jf001211q

Putnik, P., Kresoja, Ž., Bosiljkov, T., Jambrak, A. R., Barba, F. J., Lorenzo, J. M., Roohinejad, S., Granato, D., Žuntar, I., & Kovačević, D. B. (2019). Comparing the effects of thermal and non-thermal technologies on pomegranate juice quality: A review. *Food Chemistry*, *279*, 150–161. https://doi.org/10.1016/j.foodchem.2018.11.131

Qi, Q., Chu, M., Yu, X., Xie, Y., Li, Y., Du, Y., Liu, X., Zhang, Z., Shi, J., & Yan, N. (2022). Anthocyanins and proanthocyanidins: Chemical structures, food sources, bioactivities, and product development. *Food Reviews International*, *39*(7), 1–29. https://doi.org/10.1080/87559129.2022.2029479

Rasmussen, S. E., Frederiksen, H., Struntze Krogholm, K., & Poulsen, L. (2005). Dietary proanthocyanidins: Occurrence, dietary intake, bioavailability, and protection against cardiovascular disease. *Molecular Nutrition & Food Research*, *49*(2), 159–174. https://doi.org/10.1002/mnfr.200400082

Rauf, A., Imran, M., Abu-Izneid, T., Patel, S., Pan, X., Naz, S., Silva, A. S., Saeed, F., & Suleria, H. A. R. (2019). Proanthocyanidins: A comprehensive review. *Biomedicine & Pharmacotherapy*, *116*, 108999.

Redondo-Castillejo, R., Garcimartín, A., Hernández-Martín, M., López-Oliva, M. E., Bocanegra, A., Macho-González, A., Bastida, S., Benedí, J., & Sánchez-Muniz, F. J. (2023). Proanthocyanidins: Impact on gut microbiota and intestinal action mechanisms in the prevention and treatment of metabolic syndrome. *International Journal of Molecular Sciences*, *24*(6), 5369. https://doi.org/10.3390/ijms24065369

ReFaey, K., Tripathi, S., Grewal, S. S., Bhargav, A. G., Quinones, D. J., Chaichana, K. L., Antwi, S. O., Cooper, L. T., Meyer, F. B., Dronca, R. S., Diasio, R. B., & Quinones-Hinojosa, A. (2021). Cancer mortality rates increasing vs cardiovascular disease mortality decreasing in the world: Future implications. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, *5*(3), 645–653. https://doi.org/10.1016/j.mayocpiqo.2021.05.005

Remy-Tanneau, S., Le Guernevé, C., Meudec, E., & Cheynier, V. (2003). Characterization of a colorless anthocyanin– flavan-3-ol dimer containing both carbon– carbon and ether interflavanoid linkages by NMR and mass spectrometry. *Journal of Agricultural and Food Chemistry*, *51*(12), 3592–3597. https://doi.org/10.1021/jf021227b

Renard, C. M. G. C., Baron, A., Guyot, S., & Drilleau, J.-F. (2001). Interactions between apple cell walls and native apple polyphenols: Quantification and some consequences. *International Journal of Biological Macromolecules*, *29*, 115–125. https://doi.org/10.1016/S0141-8130(01)00155-6

Renard, C. M. G. C., Dupont, N., & Guillermin, P. (2007). Concentrations and characteristics of procyanidins and other phenolics in apples during fruit growth. *Phytochemistry*, *68*(8), 1128–1138. https://doi.org/10.1016/j.phytochem.2007.02.012

Rodríguez-Pérez, C., Quirantes-Piné, R., Contreras, M. d. M., Uberos, J., Fernández-Gutiérrez, A., & Segura-Carretero, A. (2015). Assessment of the stability of proanthocyanidins and other phenolic compounds in cranberry syrup after gamma-irradiation treatment and during storage. *Food Chemistry*, *174*, 392–399. https://doi.org/10.1016/j.foodchem.2014.11.061

Russo, T. A., & Johnson, J. R. (2003). Medical and economic impact of extraintestinal infections due to *Escherichia coli*: Focus on an increasingly important endemic problem. *Microbes and Infection*, *5*, 449–456. https://doi.org/10.1016/S1286-4579(03)00049-2

Sadler, C. R., Grassby, T., Hart, K., Raats, M., Sokolović, M., & Timotijevic, L. (2021). Processed food classification: Conceptualisation and challenges. *Trends in Food Science and Technology*, *112*, 149–162. https://doi.org/10.1016/j.tifs.2021.02.059

Sánchez-Rubio, F., Fernández-Santos, M. R., Castro-Vázquez, L., García-Álvarez, O., Maroto-Morales, A., Soler, A. J., Martínez-Pastor, F., & Garde, J. J. (2018). Cinnamtannin B-1, a novel antioxidant for sperm in red deer. *Animal Reproduction Science*, *195*, 44–52. https://doi.org/10.1016/j.anireprosci.2018.05.004

Severo, C., Anjos, I., Souza, V. G. L., Canejo, J. P., Bronze, M. R., Fernando, A. L., Coelhoso, I., Bettencourt, A. F., & Ribeiro, I. A. C. (2021). Development of cranberry extract films for the enhancement of food packaging antimicrobial properties. *Food Packaging and Shelf Life*, *28*, 100646. https://doi.org/10.1016/j.fpsl.2021.100646

Sheikh, Y., Chanu, M. B., Mondal, G., Manna, P., Chattoraj, A., Deka, D. C., Talukdar, N. C., & Borah, J. C. (2019). Procyanidin A2, an anti-diabetic condensed tannin extracted from *Wendlandia glabrata*, reduces elevated G-6-Pase and mRNA levels in diabetic mice and increases glucose uptake in CC_1 hepatocytes and C_1C1_2 myoblast cells. *RSC Advances*, *9*, 17211–17219. https://doi.org/10.1039/c9ra02397f

Shu, B., Wang, J., Wu, G., Cao, X., Huang, F., Dong, L., Zhang, R., Liu, H., & Su, D. (2022). Newly generated and increased bound phenolic in lychee pulp during heat-pump drying detected by UPLC–ESI-triple-TOF-MS/MS. *Journal of the Science of Food and Agriculture*, *102*, 1381–1390. https://doi.org/10.1002/jsfa.11470

Sieniawska, E., Ortan, A., Fierascu, I., & Fierascu, R. C. (2019). Procyanidins in food. *Handbook of Dietary Phytochemicals*, *38*, 1–40. https://doi.org/10.1007/978-981-13-1745-3_43-1

Silva, G. V. D., Machado, B. A. S., Oliveira, W. P. D., Silva, C. F. G. D., Quadros, C. P. D., Druzian, J. I., Ferreira, E. D. S., & Umsza-Guez, M. A. (2020). Effect of drying methods on bioactive compounds and antioxidant capacity in grape skin residues from the new hybrid variety “BRS Magna”. *Molecules (Basel, Switzerland)*, *25*, 3701. https://doi.org/10.3390/molecules25163701

Singla, M., & Sit, N. (2021). Application of ultrasound in combination with other technologies in food processing: A review. *Ultrasonics Sonochemistry*, *73*, 105506. https://doi.org/10.1016/j.ultsonch.2021.105506

Su, D., Wang, Z., Dong, L., Huang, F., Zhang, R., Jia, X., Wu, G., & Zhang, M. (2019). Impact of thermal processing and storage temperature on the phenolic profile and antioxidant activity of different varieties of lychee juice. *Lebensmittel-Wissenschaft & Technologie*, *116*, 108578. https://doi.org/10.1016/j.lwt.2019.108578

Sui, Y., Li, X., Li, S., Xie, B., & Sun, Z. (2016). Characterization and preparation of oligomeric procyanidins from *Litchi chinensis* pericarp. *Fitoterapia*, *112*, 168–174. https://doi.org/10.1016/j.fitote.2016.06.001

Sui, Y., Shi, J., Cai, S., Xiong, T., Xie, B., Sun, Z., & Mei, X. (2021). Metabolites of procyanidins from *Litchi chinensis* pericarp with xanthine oxidase inhibitory effect and antioxidant activity. *Frontiers in Nutrition*, *8*, 676346. https://doi.org/10.3389/fnut.2021.676346

Sun, J., Chu, Y.-F., Wu, X., & Liu, R. H. (2002). Antioxidant and antiproliferative activities of common fruits. *Journal of Agricultural and Food Chemistry*, *50*, 7449–7454. https://doi.org/10.1021/jf0207530

Sun, J., Jiang, Y., Shi, J., Wei, X., Xue, S. J., Shi, J., & Yi, C. (2010). Antioxidant activities and contents of polyphenol oxidase substrates from pericarp tissues of litchi fruit. *Food Chemistry*, *119*, 753–757. https://doi.org/10.1016/j.foodchem.2009.07.025

Tanaka, T., Betkekar, V. V., Ohmori, K., Suzuki, K., & Shigemori, H. (2021). Evaluation of amyloid polypeptide aggregation inhibition and disaggregation activity of A-type procyanidins. *Pharmaceuticals*, *14*, 1118. https://doi.org/10.3390/ph14111118

Tang, Y., Xiong, R., Wu, A.-G., Yu, C.-L., Zhao, Y., Qiu, W.-Q., Wang, X.-L., Teng, J.-F., Liu, J., & Chen, H.-X. (2018). Polyphenols derived from lychee seed suppress Aβ (1-42)-induced neuroinflammation. *International Journal of Molecular Sciences*, *19*, 2109. https://doi.org/10.3390/ijms19072109

Tao, W., Pan, H., Jiang, H., Wang, M., & Ye, X. (2022). Extraction and identification of proanthocyanidins from the leaves of persimmon and loquat. *Food Chemistry*, *372*, 130780. https://doi.org/10.1016/j.foodchem.2021.130780

Tao, W., Zhang, Y., Shen, X., Cao, Y., Shi, J., Ye, X., & Chen, S. (2019). Rethinking the mechanism of the health benefits of proanthocyanidins: Absorption, metabolism, and interaction with gut microbiota. *Comprehensive Reviews in Food Science and Food Safety*, *18*(4), 971–985. https://doi.org/10.1111/1541-4337.12444

Terlizzi, M. E., Occhipinti, A., Luganini, A., Maffei, M. E., & Gribaudo, G. (2016). Inhibition of herpes simplex type 1 and type 2 infections by Oximacro®, a cranberry extract with a high content of A-type proanthocyanidins (PACs-A). *Antiviral Research*, *132*, 154–164. https://doi.org/10.1016/j.antiviral.2016.06.006

Thakur, R., Pristijono, P., Scarlett, C. J., Bowyer, M., Singh, S. P., & Vuong, Q. V. (2019). Starch-based films: Major factors affecting their properties. *International Journal of Biological Macromolecules*, *132*, 1079–1089. https://doi.org/10.1016/j.ijbiomac.2019.03.190

Timmermann, C. A. G., Mølck, S. S., Kadawathagedara, M., Bjerregaard, A. A., Törnqvist, M., Brantsæter, A. L., & Pedersen, M. (2021). A review of dietary intake of acrylamide in humans. *Toxics*, *9*, 155. https://doi.org/10.3390/toxics9070155

Unusan, N. (2020). Proanthocyanidins in grape seeds: An updated review of their health benefits and potential uses in the food industry. *Journal of Functional Foods*, *67*, 103861. https://doi.org/10.1016/j.jff.2020.103861

Vasudevan, S., Thamil Selvan, G., Bhaskaran, S., Hari, N., & Solomon, A. P. (2020). Reciprocal cooperation of type A procyanidin and nitrofurantoin against multi-drug resistant (MDR) UPEC: A pH-dependent study. *Frontiers in Cellular and Infection Microbiology*, *10*, 421. https://doi.org/10.3389/fcimb.2020.00421

Vinson, J. A., Bose, P., Proch, J., Al Kharrat, H., & Samman, N. (2008). Cranberries and cranberry products: Powerful in vitro, ex vivo, and in vivo sources of antioxidants. *Journal of Agricultural and Food Chemistry*, *56*, 5884–5891. https://doi.org/10.1021/jf073309b

Wang, L., Lin, X., Zhang, J., Zhang, W., Hu, X., Li, W., Li, C., & Liu, S. (2019). Extraction methods for the releasing of bound phenolics from *Rubus idaeus* L. leaves and seeds. *Industrial Crops and Products*, *135*, 1–9. https://doi.org/10.1016/j.indcrop.2019.04.003

Wang, M., Chen, J., Chen, S., Ye, X., & Liu, D. (2021). Inhibition effect of three common proanthocyanidins from grape seeds, peanut skins and pine barks on maize starch retrogradation. *Carbohydrate Polymers*, *252*, 117172. https://doi.org/10.1016/j.carbpol.2020.117172

Wang, Q.-Q., Gao, H., Yuan, R., Han, S., Li, X.-X., Tang, M., Dong, B., Li, J.-X., Zhao, L.-C., & Feng, J. (2020). Procyanidin A2, a polyphenolic compound, exerts anti-inflammatory and anti-oxidative activity in lipopolysaccharide-stimulated RAW264.7 cells. *PLoS ONE*, *15*(8), e0237017. https://doi.org/10.1371/journal.pone.0237017

Wang, S., Li, C., Copeland, L., Niu, Q., & Wang, S. (2015). Starch retrogradation: A comprehensive review. *Comprehensive Reviews in Food Science and Food Safety*, *14*, 568–585. https://doi.org/10.1111/1541-4337.12143

Wang, T., Guo, N., Wang, S.-X., Kou, P., Zhao, C.-J., & Fu, Y.-J. (2018). Ultrasound-negative pressure cavitation extraction of phenolic compounds from blueberry leaves and evaluation of its DPPH radical scavenging activity. *Food and Bioproducts Processing*, *108*, 69–80. https://doi.org/10.1016/j.fbp.2018.01.003

Wang, X., Zhang, A., Miao, J., Sun, H., Yan, G., Wu, F., & Wang, X. (2018). Gut microbiota as important modulator of metabolism in health and disease. *RSC Advances*, *8*(74), 42380–42389. https://doi.org/10.1039/c8ra08094a

Wang, Z., Wu, G., Shu, B., Huang, F., Dong, L., Zhang, R., & Su, D. (2020). Comparison of the phenolic profiles and physicochemical properties of different varieties of thermally processed canned lychee pulp. *RSC Advances*, *10*, 6743–6751. https://doi.org/10.1039/C9RA08393F

Wei, M., Chai, W., Yang, Q., Wang, R., & Peng, Y. (2017). Novel insights into the inhibitory effect and mechanism of proanthocyanidins from *Pyracantha fortuneana* fruit on α-glucosidase. *Journal of Food Science*, *82*(10), 2260–2268. https://doi.org/10.1111/1750-3841.13816

Wilcock, A., Pun, M., Khanona, J., & Aung, M. (2004). Consumer attitudes, knowledge and behaviour: A review of food safety issues. *Trends in Food Science and Technology*, *15*(2), 56–66. https://doi.org/10.1016/j.tifs.2003.08.004

Wojnicz, D., Sycz, Z., Walkowski, S., Gabrielska, J., Aleksandra, W., Alicja, K., Anna, S.-Ł., & Hendrich, A. B. (2012). Study on the influence of cranberry extract Żuravit S·O·S® on the properties of uropathogenic *Escherichia coli* strains, their ability to form biofilm and its antioxidant properties. *Phytomedicine*, *19*(6), 506–514. https://doi.org/10.1016/j.phymed.2011.12.013

Xi, Y., Zeng, X., Pu, Y., Li, X., Che, H., Ma, Y., & Jiang, W. (2023). The synergistic effect of dietary cholesterol with fruit tannins in forming kidney stones. *Food Innovation and Advances*, *2*(2), 163–170. https://doi.org/10.48130/FIA-2023-0019

Xiao, H., Lin, Q., Liu, G. Q., Wu, Y., Wu, W., & Fu, X. (2013). Inhibitory effects of green tea polyphenols on the retrogradation of starches from different botanical sources. *Food and Bioprocess Technology*, *6*(8), 2177–2181. https://doi.org/10.1007/s11947-011-0739-8

Xie, C., Wang, K., Liu, X., Liu, G., Hu, Z., & Zhao, L. (2023). Characterization and bioactivity of A-type procyanidins from litchi fruitlets at different degrees of development. *Food Chemistry*, *405*(30), 134855. https://www.sciencedirect.com/science/article/pii/S0308814622028175 https://doi.org/10.1016/j.foodchem.2022.134855

Xu, M., Lv, C., Wang, H., Lu, Q., Ye, M., Zhu, X., & Liu, R. (2022). Peanut skin extract ameliorates high-fat diet-induced atherosclerosis by regulating lipid metabolism, inflammation reaction and gut microbiota in ApoE$^{-/-}$ mice. *Food Research International*, *154*, 111014. https://doi.org/10.1016/j.foodres.2022.111014

Xu, Q., Chen, Z., Zhu, B., Wang, G., Jia, Q., Li, Y., & Wu, X. (2020). A-type cinnamon procyanidin oligomers protect against 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced neurotoxicity in mice through inhibiting the P38 mitogen-activated protein kinase/P53/BCL-2 associated x protein signaling pathway. *The Journal of Nutrition*, *150*, 1731–1737. https://doi.org/10.1093/jn/nxaa128

Xu, X., Xie, H., Wang, Y., & Wei, X. (2010). A-type proanthocyanidins from lychee seeds and their antioxidant and antiviral activities. *Journal of Agricultural and Food Chemistry*, *58*(22), 11667–11672. https://doi.org/10.1021/jf1033202

Yan, F., Chen, L., Chen, W., Zhao, L., Lu, Q., & Liu, R. (2021). Protective effect of procyanidin A-type dimers against H_2O_2-induced oxidative stress in prostate DU145 cells through the MAPKs signaling pathway. *Life Sciences*, *266*, 118908. https://doi.org/10.1016/j.lfs.2020.118908

Yan, F., Zhao, L., Chen, W., Lu, Q., Tang, C., Wang, C., & Liu, R. (2020). Comparison of the inhibitory effects of procyanidins with different structures and their digestion products against acrylamide-induced cytotoxicity in IPEC-J2 cells. *Journal of Functional Foods*, *72*, 104073. https://doi.org/10.1016/j.jff.2020.104073

Yan, Z., Zhong, Y., Duan, Y., Chen, Q., & Li, F. (2020). Antioxidant mechanism of tea polyphenols and its impact on health benefits. *Animal Nutrition*, *6*(2), 115–123. https://doi.org/10.1016/j.aninu.2020.01.001

Yang, H., Tuo, X., Wang, L., Tundis, R., Portillo, M. P., Simal-Gandara, J., Yu, Y., Zou, L., Xiao, J., & Deng, J. (2021). Bioactive procyanidins from dietary sources: The relationship between bioactivity and polymerization degree. *Trends in Food Science & Technology*, *111*, 114–127. https://doi.org/10.1016/j.tifs.2021.02.063

Yang, K., & Chan, C. B. (2017). Proposed mechanisms of the effects of proanthocyanidins on glucose homeostasis. *Nutrition Reviews*, *75*(8), 642–657. https://doi.org/10.1093/nutrit/nux028

Yang, S., Zhang, Y., Li, W., You, B., Yu, J., Huang, X., & Yang, R. (2021). Gut microbiota composition affects procyanidin A2-attenuated atherosclerosis in ApoE$^{-/-}$mice by modulating the bioavailability of its microbial metabolites. *Journal of Agricultural and Food Chemistry*, *69*, 6989–6999. https://doi.org/10.1021/acs.jafc.1c00430

Ye, H., Luo, L., Wang, J., Jiang, K., Yue, T., & Yang, H. (2022). Highly galloylated and A-type prodelphinidins and procyanidins in persimmon (*Diospyros kaki* L.) peel. *Food Chemistry*, *378*, 131972. https://doi.org/10.1016/j.foodchem.2021.131972

You, Y., Li, N., Han, X., Guo, J., Zhao, Y., Liu, G., Huang, W., & Zhan, J. (2018). Influence of different sterilization treatments on the color and anthocyanin contents of mulberry juice during refrigerated storage. *Innovative Food Science & Emerging Technologies*, *48*, 1–10. https://doi.org/10.1016/j.ifset.2018.05.007

Yu, J., Ahmedna, M., Goktepe, I., & Dai, J. (2006). Peanut skin procyanidins: Composition and antioxidant activities as affected by processing. *Journal of Food Composition and Analysis*, *19*, 364–371. https://doi.org/10.1016/j.jfca.2005.08.003

Yu, Y., Chen, P., Li, X., Shen, S., & Li, K. (2022). Persimmon proanthocyanidins with different degrees of polymerization possess distinct activities in models of high fat diet induced obesity. *Nutrients*, *14*(18), 3718. https://doi.org/10.3390/nu14183718

Zang, X., Shang, M., Xu, F., Liang, J., Wang, X., Mikage, M., & Cai, S. (2013). A-type proanthocyanidins from the stems of *Ephedra sinica* (*Ephedraceae*) and their antimicrobial activities. *Molecules (Basel, Switzerland)*, *18*(5), 5172–5189. https://doi.org/10.3390/molecules18055172

Zeng, Y., Zhou, W., Yu, J., Zhao, L., Wang, K., Hu, Z., & Liu, X. (2023). By-products of fruit and vegetables: Antioxidant properties of extractable and non-extractable phenolic compounds. *Antioxidants*, *12*(2), 1–26. https://doi.org/10.3390/antiox12020418

Zhang, H., Lang, W., Liu, X., Bai, J., Jia, Q., & Shi, Q. (2022). Procyanidin A1 alleviates DSS-induced ulcerative colitis via regulating AMPK/mTOR/p70S6K-mediated autophagy. *Journal of Physiology and Biochemistry*, *78*, 1–15. https://doi.org/10.1007/s13105-021-00854-5

Zhang, L., Wang, Y., Li, D., Ho, C.-T., Li, J., & Wan, X. (2016). The absorption, distribution, metabolism and excretion of procyanidins. *Food & Function*, *7*(3), 1273–1281. https://doi.org/10.1039/c5fo01244a

Zhang, Y., Li, D., Qiao, J., Ni, Y., Liu, P., & Huang, D. (2022). Structure, degree of polymerization, and starch hydrolase inhibition activities of bird cherry (*Prunus padus*) proanthocyanidins. *Food Chemistry*, *385*, 132588. https://doi.org/10.1016/j.foodchem.2022.132588

Zhang, Y.-Y., Li, X.-L., Li, T.-Y., Li, M.-Y., Huang, R.-M., Li, W., & Yang, R.-L. (2018). 3-(4-Hydroxyphenyl) propionic acid, a major microbial metabolite of procyanidin A2, shows similar suppression of macrophage foam cell formation as its parent molecule. *RSC Advances*, *8*, 6242–6250. https://doi.org/10.1039/C7RA13729J

Zhao, L., Wang, K., Wang, K., Zhu, J., & Hu, Z. (2020). Nutrient components, health benefits, and safety of litchi (*Litchi chinensis* Sonn.): A review. *Comprehensive Reviews in Food Science and Food Safety*, *19*(4), 2139–2163. https://doi.org/10.1111/1541-4337.12590

Zhao, L., Wen, L., Lu, Q., & Liu, R. (2020). Interaction mechanism between α-glucosidase and A-type trimer procyanidin revealed by integrated spectroscopic analysis techniques. *International Journal of Biological Macromolecules*, *143*, 173–180. https://doi.org/10.1016/j.ijbiomac.2019.12.021

Zhao, L., Yan, F., Lu, Q., Tang, C., Wang, X., & Liu, R. (2022). UPLC-Q-TOF-MS and NMR identification of structurally different A-type procyanidins from peanut skin and their inhibitory effect on acrylamide. *Journal of the Science of Food and Agriculture*, *102*, 7062–7071. https://doi.org/10.1002/jsfa.12067

Zhao, Y., Wu, X., Yu, L., & Chen, P. (2017). Retention of polyphenols in blueberries (*Vaccinium corymbosum*) after different cooking methods, using UHPLC–DAD–MS based metabolomics. *Journal of Food Composition and Analysis*, *56*, 55–66. https://doi.org/10.1016/j.jfca.2016.12.003

Zhou, H.-C., Lin, Y.-M., Li, Y.-Y., Li, M., Wei, S.-D., Chai, W.-M., & Tam, N. F. (2011). Antioxidant properties of polymeric proanthocyanidins from fruit stones and pericarps of *Litchi chinensis*

Sonn. *Food Research International*, *44*(2), 613–620. https://doi.org/10.1016/j.foodres.2010.12.016

Zhou, L., Wang, W., Huang, J., Ding, Y., Pan, Z., Zhao, Y., Zhang, R., Hu, B., & Zeng, X. (2016). In vitro extraction and fermentation of polyphenols from grape seeds (*Vitis vinifera*) by human intestinal microbiota. *Food & Function*, *7*(4), 1959–1967. https://doi.org/10.1039/c6fo00032k

Zhou, W., Zhao, L., Wang, K., Renard, C. M. G. C., Le Bourvellec, C., Hu, Z., & Liu, X. (2023). Plant leaf proanthocyanidins: From agricultural production by-products to potential bioactive molecules. *Critical Reviews in Food Science and Nutrition*, *1*, 1–39. https://doi.org/10.1080/10408398.2023.2244079

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