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Proanthocyanidins: Components, Pharmacokinetics and Biomedical Properties

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Abstract: Proanthocyanidins (PAs) are a group of polyphenols enriched in plant and human food. In recent decades, epidemiological studies have upheld the direct relationship between PA consumption and health benefits; therefore, studies on PAs have become a research hotspot. Although the oral bioavailability of PAs is quite low, pharmacokinetics data revealed that some small molecules and colonic microbial metabolites of PAs could be absorbed and exert their health beneficial effects. The pharmacological effects of PAs mainly include anti-oxidant, anticancer, anti-inflammation, antimicrobial, cardiovascular protection, neuroprotection, and metabolism-regulation behaviors. Moreover, current toxicological studies show that PAs have no observable toxicity to humans. This review summarizes the resources, extraction, structures, pharmacokinetics, pharmacology, and toxicology of PAs and discusses the limitations of current studies. Areas for further research are also proposed.

Keywords: Proanthocyanidins; Resource; Structure; Pharmacokinetics; Pharmacology; Toxicology.

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Introduction

Proanthocyanidins (PAs), or condensed tannins, are a form of flavonoids with natural anti-oxidant qualities. PAs are widely distributed in segmental tissues and overland parts of plants, such as barks, leaves, flowers, fruit, and seed. PAs have a variety of structures, including dimers, trimers, oligomers, or polymers of the flavan-3-ols (flavors) (Feng *et al.*, 2016) and comprise two main subgroups: A- and B-type PAs, which differ in their distribution, structure, and biological activities (Dong *et al.*, 2013). PAs are primarily known for their powerful anti-oxidative properties (Mendoza-Wilson *et al.*, 2014); however, they also show other biological activities, such as anticancer, anti-inflammation, antimicrobial, cardiovascular, and nerve protective properties (Martinez-Micaelo *et al.*, 2012a; Wang *et al.*, 2014; Marin *et al.*, 2015; Salvado *et al.*, 2015; Neilson *et al.*, 2016; Kim and Je, 2017; Smeriglio *et al.*, 2017). Moreover, research indicates no observable toxicological effects of PAs on organisms (Evans *et al.*, 2014; Sano, 2017). Therefore, as natural products, PAs are under a promising prospect in the healthcare field.

Resources

PAs are abundant in edible plants like vegetables, fruit, nuts, and spices (Laboratory, 2004). PA's contents have been determined in common fruit including apricot, cherry, flat peach, peach, plum, and nectarine (Redondo *et al.*, 2017). PAs also exist in non-edible plants, such as ornamental flowers (Kato *et al.*, 2017) and antiparasitic herbs (Payne *et al.*, 2018). In terms of plant species, PAs can be found in an arbor, shrub, and herbaceous plants and are usually found in epidermal tissues and the overland parts of plants. Table 1 shows the PAs classified by planting organs. PA's content varies in different parts of the plant. However, insufficient data are available to compare the order of their contents in different parts. In addition, PAs can be discovered in the vacuole of plant cells or associated with the cell wall and other cellular components (Mateos-Martin *et al.*, 2012b; Dominguez-Rodriguez *et al.*, 2017).

Extraction

Sample Pretreatment Before Extraction

Sample pretreatment aims to achieve the maximum extraction efficiency of PAs by focusing on two factors: particle size and moisture content. The former enhances the contact surface of the sample with the solvent for the recovery of PAs. After being powdered in an electric blender (Nguyen *et al.*, 2017), homogenized in a digital homogenizer (Zhang *et al.*, 2017b), milled with a pestle in a mortar (Brillouet *et al.*, 2017), and crushed (Ho *et al.*, 2017), the samples are sieved to obtain uniform particles and guarantee the extraction efficiency of PAs (Dominguez-Rodriguez *et al.*, 2017). The moisture content might decrease the stability of samples because of some unexpected enzymatic reaction. However, water loss via drying can induce cell contraction, further decreasing the extraction efficiency of the analytes from the cell (Dominguez-Rodriguez *et al.*, 2017). Depending on the different materials used, the drying methods can comprise freeze-drying, hot air drying,

Table 1. Extraction of PAs Form Different Parts of Plants

Plant Part	Resource	Pretreatment	Extract	Purification	Reference
Pistils, stamens, petals, sepals, stems, leaves and roots	*Geranium sylvaticum*	Freeze-dried and homogenized	Acetone/water (7:3, v:v)	Sephadex LH-20 column with water-methanol-acetone mixtures	Tuominen and Karonen (2018)
Bark	*Senna singueana*	Dried and ground, defatted	100% methanol at ambient temperature	(unfound)	Sobeh *et al.* (2017)
	Yyoung hawthorn shoots	Washed with 80% acetone stored for 24 h at 18°C; sonicated for 30 min at −20°C	Water and chloroform (ratio unfound)	1. Supersaturated NaCl solution; 2. Acetate to water 0.5:5 (v/v) 3. Chloroform and hexane	Wyspianska *et al.* (2016)
Leaf	*Alectryon oleifolius*	Dried and ground	Liquid/solid ratio: 20 mL/g; solvent systems: 1/1 (v/v) methanol/chloroform, 4/1 (v/v) methanol/water, and acetone; stirred at room temperature; filtered and concentrated under reduced pressure in a water bath ($\leq$40°C)	(unfound)	Payne *et al.* (2018)
	Cinnamomum longepaniculatum leaves	Dried in the shade for 7 days at 25°C, powdered, and sieved	Temperature:100°C; ethanol concentration: 70%; pH: 5; ultrasonication power: 660 W; ultrasonication time: 44 min; liquid/solid ratio:20 mL/g	(unfound)	Liu *et al.* (2017b)

Table 1. (*Continued*)

Plant Part	Resource	Pretreatment	Extract	Purification	Reference
	Chamaecyparis obtusa var. formosana leaves	Soaked (boiling deionized water for 6 h),filtered under vacuum, concentrated and freeze-dried	Ethyl acetate, n-butanol, and water(ratio unfound)	Sephadex LH-20 gel, TLC	Hsu *et al.* (2018)
	Xao tam phan (*Paramignya trimera*)	Dried; ground; sieved	Liquid/solid ratio: 100 mL/g; Meoh concentration: 100%; pH: 5; microwave power: 360 W; microwave time: 30 min; temperature: 26 ± 1°C;	(unfound)	Nguyen *et al.* (2017)
	Hancornia speciosa (Apocynaceae)	Air-dried at 40°C and ground in mill	Concentration: ethanol: water (70:30 v/v); temperature: room temperature; time: 7 days concentrated under reduced pressure in a rotary evaporator at 40°C; freeze-dried	100% methanol (ultrasonic bath,10 min), centrifuged at 12, 000 × *g*/5 min	Bastos *et al.* (2017)
	Psidium guajava L. leaves	Air-dried at room temperature, powdered	Solid to solvent ratio (1:80 (w/v)); acetone/water ratio (50% (v/v)), temperature of the bath (48°C), time (30 min), and acetic acid percentage (0% (v/v))	(unfound)	Diaz-de-Cerio *et al.* (2017)
	Zanthoxylum Bungeanum Leaves	Dried at ambient temperature in the dark; sieved	Concentration: 60% ethanol solution; time: for 15 min ultrasonic power: 350 W; temperature: 50°C	Aqueous two phase system	He *et al.* (2016a)
	Copaifera langsdorffii- Leaves	Dried and ground	Ethanol: water 7:3 solution	(unfound)	Furtado *et al.* (2015)

Table 1. (*Continued*)

Plant Part	Resource	Pretreatment	Extract	Purification	Reference
Flower	Small-leaved lime flowers (*Tilia cordata Mill.*)	Dried in shade and finely grounded	Acetone: methanol: water (3:1:1, v/v/v); 30 min/5 times sonication	Preparative Sephadex LH-20 column; Toyopearl HW-40F column; Diaion HP-20 column chromatography	Czerwinska *et al.* (2018)
	Flowers of *Magnolia coco*	70% aqueous acetone	Et2O, EtOAc, and n-BuOH (ratio unfound)	Preparative TLC silica gel 60 F254; Toyopearl HW-40 column chromatography	Kato *et al.* (2017)
Fruit	Lychee pericarp	Blended with chilled aqueous ethanol for 3 min and then homogenized at ice bath 10,000 rpm/5 min	Ultra-high-pressure-assisted extraction: a pressure of 295 MPa, a pressure holding time of 13 min, liquid-to-solid ratio of 16:1 70% ethanol, 25 °C	(unfound)	Zhang *et al.* (2017b)
	Apple	(unfound)	Supercritical fluid, freeze-dried	MN Polyamide column Preparative HPLC	Hollands *et al.* (2017)
	Grape pericarp (*Vitis vinifera*)	Frozen in liquid nitrogen; milled with a pestle in a mortar	Acetone/water (70:30, v/v) containing 0.05% (v/v) trifluoroacetic acid liquid: solid (3 mL/g); stirred for 1 h at room temperature in the dark	Toyopearl TSK-HW 50F column	Brillouet *et al.* (2017)

Table 1. (*Continued*)

Plant Part	Resource	Pretreatment	Extract	Purification	Reference
	Elderberry	Crushed; lyophilized; ground	Freeze-dried berries: diatomaceous earth (4:1) extracted with dichloromethane (40°C), followed by 96% EtOH (70°C), 50% EtOH (70°C), water at 50°C and 100°C; performed at (1500 psi/5 minutes heating/ 5 minutes static time) × 60 s	Preparative HPLC	Ho *et al.* (2017)
	Pyracantha fortuneana Fruit	Washed and freeze-dried for 72 h, and ground	70% acetone at room temperature; 3 times; evaporated under vacuum (40°C); petroleum ether and ethyl acetate; freezed-dried	Sephadex LH-20 column (50% methanol, 90% methanol, 70% acetone)	Wei *et al.* (2017)
	Choerospondias axillaris Fruit Peels	Rinsed, freeze-dried (72 h) and ground	Liquid/solid:150 mL/5g; acetone/methanol/water solution (2:2:1); ultrasonic time: 20 min × twice; at ambient temperature; rotary-evaporated under vacuum at 40°C	HP-2MGL resin column (60% acetone); Sephadex LH-20 (35% methanol and acetone/water (60:40, v/v))	Li *et al.* (2016b)
	Cranberry juice	(unfound)	100% ethyl acetate (1:1 ratio) incubated at room temperature for 24 h, filtered and repeated twice; freeze-dried at vacuum	Sephadex LH-20 column (95% (v/v) ethanol, 50% (v/v) aqueous acetone C18 Sep-Pak cartridge	Chang *et al.* (2017)

Table 1. (*Continued*)

Plant Part	Resource	Pretreatment	Extract	Purification	Reference
	Avocado	Washed, freeze-dried, ground	Uultrasonically extracted three times with acetone/water (70:30, v/v) solution at 25°C; add 0.1% ascorbic acid	Sephadex LH-20 column (50% methanol/water and 70% acetone/water)	Chai *et al.* (2015b)
Seeds	U.S. Pecans and Chinese Hickory Nuts	Shelled; frozen in liquid nitrogen; ground; defatted (hexanes/18 h)	$(CH_3)_2CO/H_2O/CH_3COOH$ (ratio unfound)	Sephadex LH-20 column chromatography	Gong and Pegg (2017)
	Lotus Seedpod	(unfound)	Acetone/water (V/V, 7:3) for three times	Sephadex LH-20 column chromatography	Zhang *et al.* (2017a)
	peanut (*Arachis hypogaea*) skin	lyophilized	Acetone: water (60:40), pH 1.5; 70°C; 30 min	Amberlite XAD-2 resin; Sephadex LH-20, TLC	Oldoni *et al.* (2016)
	Cacao bean	Washed, frozen (liquid nitrogen), ground	Defatted three times with n-hexane (solid/liquid 1:5, w/v), 80% aqueous methanol (v/v) and 75% aqueous acetone (v/v), evaporated at 30°C, extractions with an equal volume of chloroform three times	High-speedcounter-current chromatography	Li *et al.* (2016a)
	Iris lactea Pall, var. Chinensis (Fisch.)	Air-dried; powdered	Supercritical carbon dioxide extraction; residue: 80% ethanol (3 × 25 L, each 3 h) at 60°C	Silica gel column chromatography (light petroleum-ethyl acetate gradient (from 5:1 to 0:1); high-speed counter-current chromatography	Lv *et al.* (2015)

Table 1. (*Continued*)

Plant Part	Resource	Pretreatment	Extract	Purification	Reference
	País grape seeds	Rinsed (distiled water at 4 °C), lyophilized, ground in a mill	Solid/liquid (0.01 g/mL, 0.02 g.mL); agitation (150 rpm) for 3 h in the dark; pH and temperature based on the enzyme	(unfound)	Fernandez *et al.* (2015)
	Black soybean seed coats	Stored at 10°C prior to use	70% acetone/0.5% acetic acid solution for 3 h at room temperature	Sepabeads SP700 column, Sephadex LH-20 column, preparative reversed phase HPLC.	Ito *et al.* (2013)

microwave drying, shade drying, sun dry and vacuum drying (Saifullah *et al.*, 2019). Generally, samples from different plants or different parts of plants need different pretreatments. For instance, fresh leaves of *Cinnamomum longepaniculatum* were dried in the shade for 7 days at 25°C and then powdered and sieved (40–60 meshes) (Liu *et al.*, 2017b). *Chamaecyparis obtusa var. formosana (Hayata) Rehder (Cupressaceae)* leaves were soaked in boiling deionized water for 6 h, concentrated, and freeze-dried (Hsu *et al.*, 2018). However, in some particular cases, such as single-factor experiments, all parts of plants are dealt with in the same way (Tuominen and Karonen, 2018).

Extraction of PAs From Plants

Numerous extraction methods have been used to extract PAs. The conventional methods are based primarily on the use of organic solvents in solid–lipid extraction and lipid–lipid extraction. In both cases, the materials are homogenized and extracted using a solvent, such as 100% methanol (Sobeh *et al.*, 2017); 100% ethyl acetate (Chang *et al.*, 2017); 70% (Furtado *et al.*, 2015), 75% (Yu *et al.*, 2016b), and 80% (Li *et al.*, 2016a) ethanol; a solution of acetone and water in varying proportions such as 50% (Diaz-de-Cerio *et al.*, 2017), 60% (Oldoni *et al.*, 2016), 70%, and 75% (Campos *et al.*, 2016); and other proportions of organic mixtures (Li *et al.*, 2016b; Gong and Pegg, 2017; Kato *et al.*, 2017; Czerwinska *et al.*, 2018; Hsu *et al.*, 2018). According to recent reports, the optimal solvent to extract PAs has been acetone/water (70:30, v/v) (Ito *et al.*, 2013; Chai *et al.*, 2015a; Cuadrado-Silva *et al.*, 2016; Ramsay *et al.*, 2016; Brillouet *et al.*, 2017; Zhang *et al.*, 2017a; Tuominen and Karonen, 2018). In some experiments, aqueous-organic solvents with an acidic pH have been applied to increase the rate of extraction (Ito *et al.*, 2013; Brillouet *et al.*, 2017). Conventional extraction techniques are simple to operate and have low requirements for instruments and reagents. They also need long extraction time (Bastos *et al.*, 2017), large amounts of organic solvents (Yu *et al.*, 2016b), and might suffer from low reproducibility and selectivity. Therefore, some advanced techniques have been reported recently (Table 1), including ultrasound assisted extraction (UAE) (Chai *et al.*, 2015b; He *et al.*, 2016a; Li *et al.*, 2016b; Liu *et al.*, 2017a; Wyspianska *et al.*, 2017; Czerwinska *et al.*, 2018), microwave-assisted simultaneous distillation and dual extraction (Nguyen *et al.*, 2017), ultra-high-pressure-assisted extraction (Zhang *et al.*, 2017b), supercritical fluid extraction (Lv *et al.*, 2015; Hollands *et al.*, 2017), and enzymatic extraction (Fernandez *et al.*, 2015). Compared with the conventional methods, several key points should be considered when using these advanced extraction methods. For example, in UAE, experimenters must carefully select the extraction temperature, solvent concentration, pH, liquid/solid ratio, ultrasonication power and time. Any changes to the above six factors will lead to altering extraction efficiency.

Purification

The principle for purification is that the solubility of different components of a crude extract in the eluent is changed or the adsorption capacity of the resin is different. For example, Sephadex LH-20 column chromatography filled with hydroxypropylated dextran

gel can get rid of the sugar, pigments like chlorophyll, and most interfering phenolics (Chai *et al.*, 2015b; Wei *et al.*, 2017). A Sephadex LH-20 column has to be pre-equilibrated with water, methanol, ethanol, acetone, or their combinations (Tuominen and Karonen, 2018). In addition, different components are elected using different eluants according to the target product.

Structure

PAs are a type of flavonoid present at high levels in fruit, vegetables, nuts, seeds, flowers, and bark (Feng *et al.*, 2016). Procyanidins (PCs) are oligomeric compounds of PAs, for example polymers of catechin (CC) and epicatechin (EC) are linked between C4 and C8 (or C6) and yield cyanidin when depolymerized under oxidative conditions (Esatbeyoglu *et al.*, 2011; Connor *et al.*, 2014). Flavonoids are polyphenolic compounds with the general structure of a 15-carbon skeleton consisting of two phenyl rings (A and B), and heterocyclic ring (C), which is either an enone, a pyran, or a pyrone (Forbes *et al.*, 2014). Flavonoids have been classified according to their chemical structure and subdivided into five subgroups, which differ by the presence or absence of a carbonyl group at C4, a double bond between carbon atoms C2 and C3, and a hydroxyl group at C3 of ring C (Forbes *et al.*, 2014). These subfamilies are termed anthocyanidins, anthoxanthins (including flavone and flavonol), flavanones, flavanonols, and flavans (including flavan-3-ols (flavanols), flavan-4-ols and flavan-3,4-diols) (Wen *et al.*, 2017). PAs are oligomers or polymers of flavanols, which have a 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton and include CC, gallocatechin (GC), catechin 3-gallate (CG), gallocatechin 3-gallate (GCG), EC, epigallocatechin (EGC), epicatechin 3-gallate (ECG), and epigallocatechin 3-gallate (EGCG) (Ververidis *et al.*, 2007).

Judging by the degree of polymerization, PAs can be divided into oligomers and polymers. Oligomers are formed by 2–10 monomers and are the most active PAs. The classification of oligomers depends on the degree of polymerization, connection modes, and monomer types. With increasing polymerization degree (more than a tetramer), the number of PAs reported decreasing (Nishizuka *et al.*, 2011). Polymers may be constituted by more than 10 monomers.

Degree of Polymerization

Monomers are flavan-3-ols and form the basic structural units of PAs, including CC, EC, and other units, such as EGC (with one more hydroxyl group) or epiafzelechin (with one less hydroxyl group) (Zhang *et al.*, 2015). In addition, plants produce oligomeric PAs coupled with gallic acid (GC) or sugar molecules (Weber *et al.*, 2007).

Dimers, compounds connected by two monomers (most are CC and EC) in a certain way, are subdivided into A-type and B-type PAs according to their connection modes. A-type PA dimers are doubly linked via a C–C bond and a C–O–C bond, such as PC A1, PC A2 (Neto, 2007), geranins A and geranins B (Calzada *et al.*, 1999). B-type PA dimers are bound by a single C–C bond (C4–C6 or C4–C8 inter-flavan bond) between monomers.

C4–C8 linkages form B1 (epicatechin-(4β-8)-catechin), B2 ((−)-epicatechin-(4β-8)-(−)-epicatechin), B3 (catechin-(4α-8)-catechin), B4 (catechin-(4α-8)-epicatechin). C4–C6 linkages form B5 (epicatechin-(4β-6)-epicatechin), B6 (catechin-(4α-6)-catechin), B7 (epicatechin-(4α-6)- catechin), and B8 (catechin-(4α-6)-epicatechin) (de Camargo *et al.*, 2015). Some PA dimers are formed from other structural units, such as epiafzelechin-epicatechin, which contains epiafzelechin (Sadhu *et al.*, 2007) and epigallocatechin-(2β-O-7,4β-8)-epicatechin, which contains epigallocatechin (Ma *et al.*, 2000).

Trimers are compounds composing of three monomers (most are CCs and ECs), and most are connected by two C4–C8 bonds, such as PC C1 and PC C2, both are B-type PA trimers (Weber *et al.*, 2007). Cinnamtannin B1 and aesculitannin C are A-type PA trimers. Cinnamtannin B1 has two C–C bonds and one A-type linkage (Mateos-Martin *et al.*, 2012a), and aesculitannin C has one C–C bond and two A-type linkages (Lin *et al.*, 2002). There are also other trimers such as epicatechin-(2β-O-7,4β-8)-epiafzelechin-(4α-8)-epicatechin (Bicker *et al.*, 2009).

Tetramers have various kinds of connection methods. Cinnamtannin A2 and arecatannin A2 (Takanashi *et al.*, 2017) only contain three single C–C bonds. Epicatechin-(2β-O-7, 4β8)-epicatechin-(4β-8)-catechin-(4α-8)-epicatechin has a C–O–C ether bond and two C–C bonds (Lou *et al.*, 2004). Parameritannin A2 comprises two C–O–C ether bonds (Kamiya *et al.*, 2001). PA tetramers in cranberry have typical structure composed of EC units with one Atype linkage (Neto, 2007). Other tetramers contain other units, such as davallin, which is isolated from ferns and contains EC (Zhang *et al.*, 2015).

Few species of pentamers have been isolated. Structural units of pentamers vary. For example, epiafzelechin-(4β-8)-[epigallocatechin-(4β-8)-]^3-catechin contains both epiafzelechin and EGC. Most PA's pentamers isolated from natural products only have C–C bonds, such as cinnamtannin A3 (Zhang *et al.*, 2015). Few pentamers have a C–O–C bond-like epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(2β-O-7,4β-8)-epicatechin-(4α-8)-catechin. The content of PA pentamers is usually low; however, peanut skins are relatively rich in pentamers (Laboratory, 2004; Lou *et al.*, 2004).

A-Type and B-Type PAs

In addition to the polymerization type, PAs can also be classified according to their connection modes and biological activities. A-type and B-type PAs are the two main subgroups of PAs and differ in their distribution, structure (Fig. 1), and biological activities.

The A-type linkage is a less common feature in PAs, and A-type PAs are doubly linked by a 4β-8 (B-type) and 2β-O-7 inter-flavanoid bonds (Neto, 2007). Dimers of A-type PAs contain PC A1 and A2. PC A1 is an epicatechin-(2β-7,4β-8)-catechin dimer found in peanut (*Arachis hypogaea*) skin (Oldoni *et al.*, 2016), the pericarps of *Litchi chinensis* (Ma *et al.*, 2014), lychee seeds (Xu *et al.*, 2010), *Rhododendron spiciferum* (Bicker *et al.*, 2009), and *Ecdysanthera utilis* (Lin *et al.*, 2002). PC A2 was the first identified A-type PA and was isolated from the shells of the fruits of *Aesculus hippocastanum* (Sharma *et al.*, 2015). PC A2 can be found in chestnut (Facino *et al.*, 1996), cranberry juice concentrate (Koerner *et al.*, 2009), lychee fruit pericarp (Kamiya *et al.*, 2001), peanut (Koerner *et al.*,

2009), and *Cdysanthera utilis* (Lin *et al.*, 2002). Other A-type PAs can be found in *Geranium niveum* (Calzada *et al.*, 1999), cinnamon (Mateos-Martin *et al.*, 2012a), cranberries (Weber *et al.*, 2007), and peanut skins (de Camargo *et al.*, 2015). Geranins A and B are dimers of A-type PAs found in *Geranium niveum* with the structure of epicatechin-afzelechin-(4β-8,2β-O-7)-afzelechin (Geranins A) and epicatechin-catechin-(4β-8,2β-O-7)-afzelechin (Geranins B) (Calzada *et al.*, 1999). Trimers of A-type PAs contain

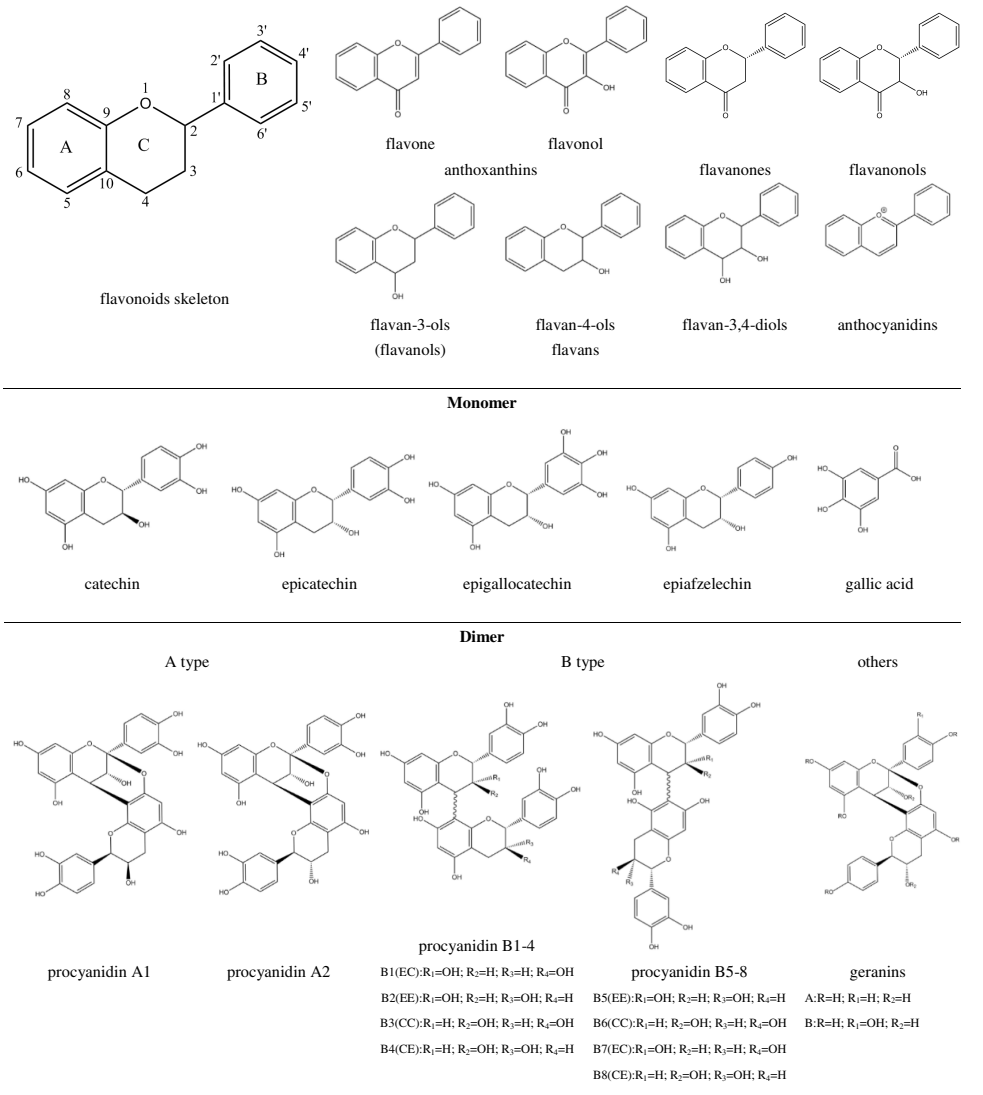

Figure 1. Structures of proanthocyanidins.

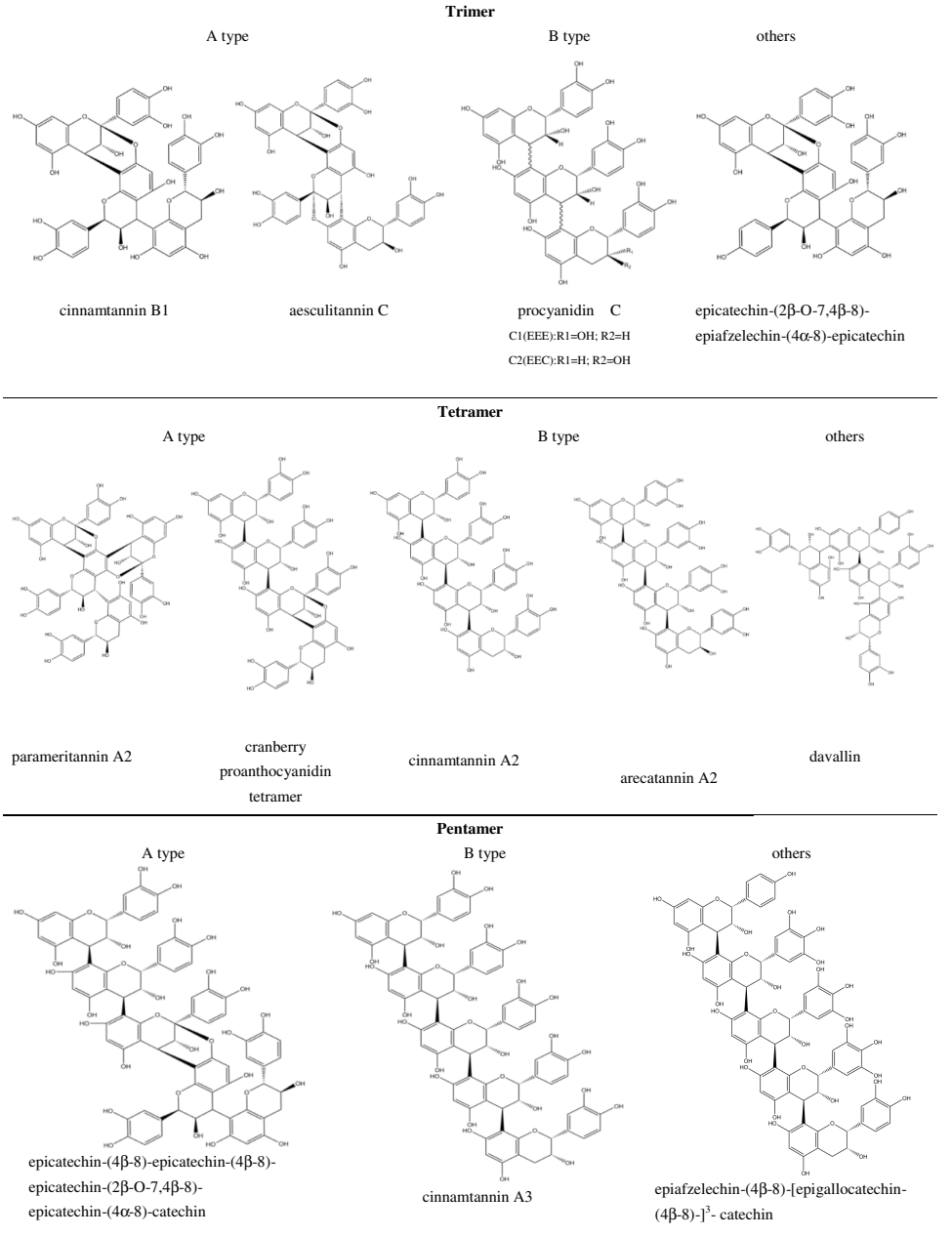

Figure 1. (*Continued*)

cinnamtannin B1 and aesculitannin C. Cinnamtannin B1 is a condensed tannin found in *Cinnamomum verum* (Mateos-Martin *et al.*, 2012a). Tetramers of A-type PAs contain arecatannin A2, and a kind of tetramer found in cranberry composed of EC units with one A-type linkage (Neto, 2007).

B-type PAs are widespread in many plant foods and are commonly isolated from apple, cocoa, and grape seed (Feng *et al.*, 2016). B-type PAs have single inter-flavan linkages among their monomers. Dimeric B-type PAs have the molecular formula $C_{30}H_{26}O_{12}$ and C4–C6 or C4–C8 inter-flavan bonds. PC B1–B4 are characterized by a C4–C8 linkage and are the most common B-type dimers (Feng *et al.*, 2016). PC B5–B8 are occasionally seen and are formed by a C4–C6 linkage (de Camargo *et al.*, 2015). B-type PAs trimers only contain C4–C8 linkages and termed PC C1 (epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin) and PC C2 (catechin-(4α-8)-catechin-(4α-8)-catechin) (Feng *et al.*, 2016). Cinnamtannin A2 is tetramer of B-type PAs and only contains three single C–C bonds (Zhang *et al.*, 2015) (Fig. 1).

Linkage types of the inter-flavan bonds affect their bioactivities, and different subtypes of B-type PAs have certain special characteristics. PC B1 is more potent at scavenging O_2^- than PC A2 (Dong *et al.*, 2013). Esterification of PC B2 by GC improves its free radical scavenging ability (Lin *et al.*, 2002). PC B2 inhibits the formation of the advanced glycation end-products pentosidine, carboxymethyllysine, and methylglyoxal (Kondo *et al.*, 2000). PC B3 is a hair-growth stimulant (Kamiya *et al.*, 2001). PC B2 and B5 inhibit rat erythrocyte hemolysis potently (Dong *et al.*, 2013). PC C2 promotes hair-growth *in vitro* and induces anagen *in vivo* (Neto, 2007). It can enhance tumor necrosis factor alpha (TNF-α) secretion in a dose- and time-dependent manner (Ma *et al.*, 2000).

Besides, A-type PAs and B-type PAs can be transformed into each other under certain conditions. A-types can be converted from the oxidation of their accompanying B-type analogs (Sharma *et al.*, 2015). PC B1 can be converted into PC A1 by radical oxidation using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radicals under neutral conditions (Kondo *et al.*, 2000). In plants, the transformation of B-type PCs to A-types might involve an enzyme catalyzed oxidation reaction (Sharma *et al.*, 2015).

Pharmacokinetics

The pharmacokinetics process is a key issue linking PAs and health effects, which include hydrolysis, absorption, metabolism, distribution, and excretion (Fig. 2).

Hydrolysis

In vitro studies. Spencer *et al.* found that PC oligomers (trimer to hexamer) are hydrolyzed into a mixture of EC monomers and dimers under conditions similar to those found in the human stomach (Spencer *et al.*, 2000). Similarly, after the co-incubation of PC dimer B2 and dimer B5 in simulated gastric juice, EC was observed (Zhu *et al.*, 2002; Kahle *et al.*, 2011). However, there are conflicting observations: When PC oligomers were incubated in gastric juice at pH 7.4, the decomposition of PAs was scarcely observed (Zhu *et al.*, 2002),

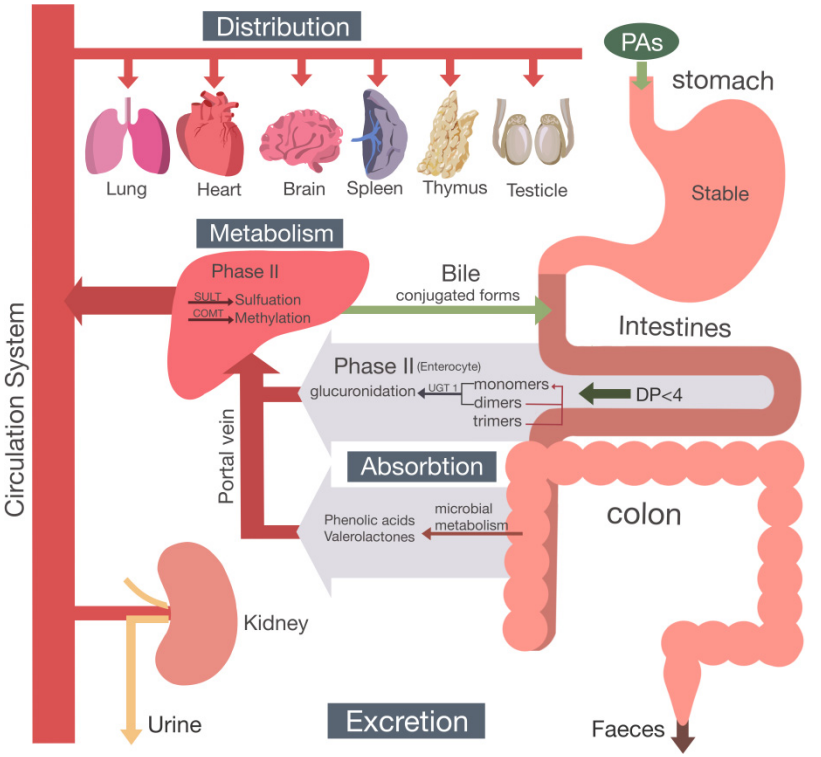

Figure 2. The absorption, metabolism, distribution, and excretion of PAs. After oral administration, PAs are first absorbed and metabolized in the small intestine and then further metabolized in the liver; however, the absorption correlates negatively with the polymerization degree. The unabsorbed remainder is fermented by colonic microbiota, resulting in a wide range of metabolites. These metabolites then enter into blood and reach other organs, where they exhibit their pharmacological effects, ultimately being excreted through urine and feces.

indicating that the pH value may be a critical factor for the degradation of PAs during gastric digestion (Zhu *et al.*, 2002). In addition, it is believed that during digestion, high molecular weight PAs could form complexes with proteins, starch, and digestive enzymes, resulting in the formation of less digestible complexes (Smeriglio *et al.*, 2017).

In vivo studies. Experiments on human stomach digestion of PCs were carried out with cocoa beverage, which demonstrated that PC polymers and flavanol monomers were remarkably stable in the stomach environment *in vivo* (Zhu *et al.*, 2002). A similar study was carried out with Grape seed procyanidin extract (GSPE) in rats, which revealed high stability of PCs under gastric and duodenal digestion conditions (Serra *et al.*, 2010).

Absorption

According to the "rule of five" (Zhang *et al.*, 2016), it was supposed that the high degree of polymerization of PAs caused poor absorption and low permeability, which might be because their molecular weight and sum of OH groups were more than 500 and 5, respectively (Zhang

et al., 2016). In other words, PA monomers and dimers could be absorbed *in vivo*, but the oral bioavailability of polymers is limited in the digestive tract, which has been confirmed by many studies (Zumdick *et al.*, 2012; Hemmersbach *et al.*, 2013).

In vitro studies. Dimeric PCs were found to have a slight permeation in cultured intestinal Caco-2 cells (Zumdick *et al.*, 2012; Hemmersbach *et al.*, 2013). However, for PCs with a higher degree of polymerization, the permeation coefficients gradually decreased (Zumdick *et al.*, 2012). Ou *et al.* (2014) investigated the transportation of A-type PCs in Caco-2 cells, and the result showed that A-type PCs could be transported at low rates. In addition, although monomeric CC and PCs are usually less permeable through Caco-2 cells, their intestinal microbiota metabolites could pass through the membrane of monolayer Caco-2 cells, indicating the potential role of intestinal microbiota metabolites in exerting pharmacological effects (Wang *et al.*, 2013).

In vivo studies. After the oral administration of GSE, CC, and EC to rats, monomers, dimers, and trimers of PCs were detected in the plasma, suggesting that PCs monomers, dimers, and trimers could be directly absorbed (Serra *et al.*, 2010). Appeldoorn *et al.* (2009) reported that PC dimers A1 and A2 could be absorbed from the small intestine of rats and better absorbed than dimer B2. In addition, when rats were fed with purified PC B2, and PC B2 could be detected in plasma and urine (Stoupi *et al.*, 2010), fed rats with PC B2 at doses of 10.5 mg/kg and 21 mg/kg, the maximum plasma concentrations (C_{max}) of PC B2 were 1.38 μg/ml and 2.6 μg/ml, respectively (Stoupi *et al.*, 2010), which suggest that the maximum concentration of PC B2 in plasma is dose-dependent. Similar experiments have been conducted in pigs. After oral application of a single dose of 10 mg PC B4 /kg body weight, intact PC B4 appeared in plasma and urine within 48 h (Bittner *et al.*, 2014). Comparing the two experiments: Single doses of PC B2 and B4 were given to rats and pigs at 10.5 mg/kg and 10 mg/kg, the C_{max} of PC B2 (rat) and B4 (pig) in plasma were 1.38 μg/ml and 2.13 ng/ml, respectively. Compared with PC B4 the higher C_{max} of the intact PC B2 might be attributed to the PCs' chemical characteristics and experimental species differences (Stoupi *et al.*, 2010; Bittner *et al.*, 2014). There have likewise been some human trials. After the consumption of GSE and cocoa, PC B1 and B2 were detected in serum and plasma, respectively (Holt *et al.*, 2002; Sano *et al.*, 2003), suggesting that PA dimers B1 and B2 could be absorbed by the human intestinal tract. In another human trial, after ingestion of a single dose of 1 mg EC and PC B1/kg body weight, EC and its methylated metabolites, as well as PC B1 and its metabolites, were detected in the plasma within the 8 h, but no dimeric or oligomeric PCs were detected in plasma after ingestion of a single dose of polymeric PC, indicating that polymeric PC could not be absorbed by humans directly (Wiese *et al.*, 2015).

Metabolism

Metabolism in the Small Intestine and Liver

Most PAs are circulated in their conjugated forms *in vivo*. Baba *et al.* (2002) found that PC B2 is partially degraded to EC, and EC is conjugated and/or methylated in rats. This finding was confirmed by Bittner *et al.* (2014): After oral administration of PC B4, EC,

3′-O-methyl-EC, and 4′-O-methyl-EC could be found at higher concentration than PC B4 in the plasma of pigs. Furthermore, glucuronidated conjugates of these metabolites were also detected, indicating that PC B4 could be degraded to monomeric subunitsand then further metabolized to methylated and glucuronidated conjugates in pigs (Bittner *et al.*, 2014). A similar experiment was conducted in humans: After the ingestion of EC, free and conjugated EC was determined in plasma and urine within 8 h following enzymatic treatment, EC, 3′-O-methyl-EC, and 4′-O-methyl-EC were detected in samples (Wiese *et al.*, 2015). After PC B1 ingestion, the conjugated forms of methyl-O-PC B1 were detected in the plasma and urine within 8 h; Therefore, EC and PC B1 could be absorbed and metabolized to conjugated and methylated metabolites in human bodies (Wiese *et al.*, 2015). Furthermore, pharmacokinetic data revealed that the plasma kinetics area under the curve (AUC) showed significant higher values for the monomeric metabolites than for intact dimer PCs (Bittner *et al.*, 2014; Wiese *et al.*, 2015); therefore, we could speculate that PA monomeric metabolites might play an important role in the pharmacological action of PAs.

It has been reported that methylation and glucuronidation of PCs and EC mainly happen in the liver and small intestine (Zhang *et al.*, 2016). The small intestine is the main site for glucuronidation, which occurs in the luminal part of the endoplasmic reticulum via the superfamily of uridine 50-diphosphate glucuronosyltransferases (UGTs) (Monagas *et al.*, 2010). UGT1 is responsible for the glucuronidation of flavonoids particularly (Cheng *et al.*, 1999). Sulfation and methylation mainly occur in the liver through cytosol sulfotransferases (SULT) and catechol-O-methyltransferase (COMT) (Monagas *et al.*, 2010). It is also reported that a high concentration of PA dimers could inhibit the activity of COMT via a competitive mechanism or by dimer–protein interactions (Spencer *et al.*, 2001). For further metabolism, part of the monomeric or dimeric flavan-3-ols is absorbed into the blood in the small intestine, while the other part is transported back to the liver and undergoes phase II metabolism, producing glucuronide, sulfate, and/or methylated metabolites, which are then recycled back to the small intestines via bile excretion in conjugated forms (Monagas *et al.*, 2010).

Metabolism by the Colonic Microbiota

It has been estimated that only 5% of the dietary polyphenols are absorbed in the small intestine, and over 90% of the intake could not be absorbed in the small intestine and remains at a high concentration in the colon (Clifford, 2004). Many reports provided evidence that parental PAs are extensively metabolized by the colonic microbiota (Tomas-Barberan *et al.*, 2019). The human colonic microbiota is a large and complex microbial community with an extensive metabolic repertoire, which complement the activity of mammalian enzymes in the liver and gut mucosa; therefore, the colonic microbiota makes an important contribution to human metabolism (Rowland *et al.*, 2018). The potential bioactivities of PAs might be attributed to their colonic degradation products, including phenolic acids and valerolactones (Choy and Waterhouse, 2014). After feeding rats with *cinnamon* bark, Mateos-Martin *et al.* (2012c) detected 30 microbial-derived PA metabolites, including 3- and 4-hydroxyphenylpropionic acid and phenolic acids derived from

further transformations in the liver, such as ferulic acid, and some other metabolites derived from PA fermentation, such as 3-hydroxyphenylacetic acid and 3, 4-dihydroxyphenylacetic acid. Similarly, Gonthier *et al.* (2003) reported that the principal microbial metabolites: 3-hydroxyphenylpropionic acid, 3-hydroxybenzoic acid, and 3-hydroxyhippuric acid were detected in the urine of rats fed with red wine polyphenols. Later, they compared the metabolism of PC dimer B3, trimer C2, and a polymer isolated from *willow tree catkins* to that of the CC monomer in rats. Sixteen metabolites of microbial origin were detected and identified as phenylvaleric, phenylpropionic, phenylacetic, and benzoic acid derivatives (Gonthier *et al.*, 2003). The total yields significantly decreased from the CC monomer ($10.6 \pm 1.1\%$) to the PC dimer ($6.5 \pm 0.2\%$), trimer ($0.7 \pm 0.1\%$), and polymer ($0.5 \pm 0.1\%$), indicating that the degree of PC polymerization has a major impact on the limited metabolism by the intestinal microbiota compared with that of CC (Gonthier *et al.*, 2003). This finding was confirmed by Goodrich *et al.* (2015): After feeding rats with GSE, the concentration of monomers was statistically lower at 6 h in the distal colon, while for dimers and oligomers, the concentrations present in the distal colon at 3 h and 6 h were not statistically different, showing that the colonic microbiota find it harder to degrade dimers and oligomers than monomers. In addition, they also reported that larger metabolites, such as 1-(3′, 4′-dihydroxyphenyl)-3-(2″, 4″,6″-trihydroxyphenyl) propan-2-ol, and those in the valerolactone group, are produced early and then continue to be degraded throughout the colon (Goodrich *et al.*, 2015). Smaller metabolites, such as phenyl alkyl acids, reached their maximum concentrations at later time points, followed by benzoic acid derivatives and some other metabolites with larger AUCs, which were regarded as ultimate metabolites (Goodrich *et al.*, 2015). However, in the pig gut, the microbial metabolites are different: an increasing trend was observed only for hippuric acid, but not for phenolic acids, after administering GSE to pigs (Rzeppa *et al.*, 2012). A similar phenomenon was declared by Bittner *et al.* (2014) in an investigation of the metabolism of PC B4 in pigs. These different results might result from the low dose of GSE and PC B4 or there might have been interference of phenolic acids and PCs in the control diet.

Human colon microbial metabolism of PAs was investigated both *in vitro* and *in vivo*. In an *in vitro* study, EC, CC, PC B2, PC A2, partially purified apple (exclusively B-type PCs), and cranberry PCs (predominantly A-type PCs) were incubated with the human microbiota, and gas chromatography (GC)-mass spectrometry (MS) analysis showed that the common metabolites of all six substrates were benzoic acid, 2-phenylacetic acid, 3-phenylpropionic acid, 2-(3-hydroxyphenyl) acetic acid, 2-(4-hydroxyphenyl) acetic acid, 3-(3-hydroxyphenyl)propionic acid, and hydroxyphenylvaleric acid (Ou *et al.*, 2014). 5-(3, 4-dihydroxyphenyl)-valerolactones and 5-(3- hydroxyphenyl)-valerolactones were identified as the microbial metabolites of EC, CC, PC B2, and apple PCs but not of PC A2 or cranberry PC (Ou *et al.*, 2014). In addition, the time taken for PC A2 degradation was much longer than that for PC B2, indicating that the A-type is more resistant to microbial catabolism compared with that of the B-type (Ou *et al.*, 2014) and that accessibility of PCs to microbiota decreases when PCs have a higher degree of polymerization (Ou *et al.*, 2014). Urpi-Sarda *et al.* (2009) studied the human colon microbial metabolism of PC *in vivo*: A significant increase in the urinary excretion of vanillic, 3, 4-dihydroxyphenylacetic,

3-hydroxyphenylacetic acids, particularly (3,4-dihydroxyphenyl)-valerolactone, was detected. Similarly, ferulic acid, vanillic acid, and (4-hydroxyphenyl) acetic acid levels significantly increased in the plasma and urine after the ingestion of EC and PC B1 by humans (Wiese *et al.*, 2015). However, they also reported no correlation between the intake of flavan-3-ols and the occurrence of phenolic acids in blood and urine or the phenolic compound profiles in feces (Wiese *et al.*, 2015), which might have been caused by the comparably low dose of PCs ingested by the participants.

Distribution

To identify the metabolic target and understand how PCs act in human bodies, researchers need to study the distribution of PC metabolites in tissues. However, information continues to be lacking in this aspect. As noted above, PCs are first absorbed and metabolized in the small intestine and then metabolized in the liver (Serra *et al.*, 2010; Zhang *et al.*, 2016). The rest is fermented by the colonic microbiota (Clifford, 2004), resulting in a wide range of metabolites. These metabolites then enter into the blood and reach other organs. Urpi-Sarda *et al.* (2010) studied the distribution of EC metabolites in rats fed with a cocoa diet for 3 weeks, glucuronide derivatives of EC and methyl-EC were detected in the thymus, testicles, liver, lymphatic nodes, and spleen. The EC metabolites that accumulated in the lymphoid tissues correlated well with previous findings (Ramiro-Puig *et al.*, 2007), demonstrating that PAs could regulate immune function. High concentrations of EC metabolites in the testicles suggested that the testes might be an important site of oxidation (Orozco *et al.*, 2003). In another study, 2 h after the acute intake of *hazelnut* extract, the presence of CC-glucuronide, methyl-CC-glucuronide, and methyl-CC-sulfate in the thymus, lung, kidney, spleen, and testicles was observed in rats (Serra *et al.*, 2011). In addition, free forms of CC and EC were not detected in either the plasma or tissues, except in the lung (Serra *et al.*, 2011). By contrast, the free forms of PC dimers and trimers were only quantified in the plasma, but not in the tissues, which indicated that PCs with a low grade of polymerization could be absorbed in rats but did not accumulate in tissues (Serra *et al.*, 2011). Regarding colonic metabolites, protocatechuic acid was found in most tissues except the testicles, and a wide range of simple aromatic acids was detected in the kidney and heart (Serra *et al.*, 2011), which might have been related to their excretion in urine and potential health effects in cardiovascular protection (Fraga *et al.*, 2010). The disposition of PC metabolites in the brain was also observed (Serra *et al.*, 2013), proving that PC metabolites have the capacity to cross the blood–brain barrier and could provide neuroprotection (Narita *et al.*, 2011). Previous studies also showed the difference between the nature of the tissular metabolites and the blood metabolites, which might reflect the specific uptake or elimination of some tissular metabolites or might result from intracellular metabolism (Manach *et al.*, 2004).

Excretion

Stoupi *et al.* (2010) studied the excretion of the [^{14}C] PA dimer B2 in male rats: After oral administration of ^{14}C-labeled PA dimer B2, 58% of ^{14}C containing metabolites were

excreted in the urine, and almost all of the rest (41%) was excreted in the feces. While after intravenous administration, 76% of the dose was excreted via urine and 28% was excreted in feces, indicating that urine is the main excretion pathway of PCs and their metabolites, and that excretion might be affected by the route of administration. Bile excretion is a different pathway during the process of metabolism (Choy and Waterhouse, 2014). As for the specific metabolites of each excretory pathway, PC monomers, dimers, and the methylated and conjugated metabolites, were detected in urine in both rats and pigs after the ingestion of PC B2 and PC B4, respectively (Bittner *et al.*, 2014; Wiese *et al.*, 2015). Urinary excretion of colonic microbial flora metabolites, such as vanillic, 3, 4-dihydroxyphenylacetic, and 3-hydroxyphenylacetic acids was observed in human subjects (Urpi-Sarda *et al.*, 2009). With regard to excretion via feces, non-metabolized PC B2, its microbial breakdown products, PC B2 metabolites excreted in bile, and PC B2 metabolites effluxed from enterocytes were regarded as the radioactive component of feces after consumption of ^{14}C-labeled PC dimer B2 (Choy and Waterhouse, 2014). Besides, the main metabolites in bile are glucuronide, sulfate, and/or methylated metabolites of monomeric or dimeric flavan-3-ols, as part of the metabolites in enterohepatic recirculation (Monagas *et al.*, 2010).

Pharmacology

Anti-oxidant Activities

In chemistry, a free radical is an atom, molecule, or ion that has an unpaired valence electron. Oxygen-centered free radicals are known as reactive oxygen species (ROS). ROS are generated by normal metabolic processes or exogenous factors and agents and can lead to oxidative damage of human cells, causing diseases such as cancer, cardiovascular disease, osteoporosis, and degenerative diseases (Chai *et al.*, 2012). PAs are polyphenol anti-oxidants with high anti-oxidant activities and play a key role in the defense against damage caused by excessive free radicals. The mechanisms of the anti-oxidant activity of PAs include:

Inhibition of enzyme activities. PA A2 demonstrated potent xanthine oxidase inhibitory activity *in vitro* (Sheu *et al.*, 2016). Japanese quince (*Chaenomeles japonica*) fruit flavanol preparation (JQFFP), which is rich in PC monomers and oligomers, inhibits the activity of matrix metalloproteinase-2 (MMP-2) and cyclooxygenase (COX-1 and COX-2) (Owczarek *et al.*, 2017). PAs also inhibit the activity of lipoxygenase and enzymes participating in enzymatic peroxidation, such as phospholipase A2 (PLA2) (Jimenez-Aspee *et al.*, 2017). Besides, many flavonoid compound inactivate enzymes via chelation (Kurek-Gorecka *et al.*, 2013).

Scavenging of free radicals. PAs scavenge free radicals through three distinct mechanisms: Hydrogen atom transfer, single electron transfer–proton transfer (SET-PT), and sequential proton-loss electron-transfer (SPLET) (Foti *et al.*, 2008; Mendoza-Wilson *et al.*, 2014). Different mechanisms dominate in different solvents (Vagánek *et al.*, 2014).

Regulation of gene expression and signaling pathways. PAs suppressed the expression of COX-2 and nuclear factor-κB (NF-κB) (Owczarek *et al.*, 2017). NRF2 is a major

anti-oxidant transcription factor, and the KEAP1-NRF2 signaling pathway is one of the most important endogenous anti-oxidative stress pathways. PAs can antagonize oxidative damage by activating the NRF2 signaling pathway (Choi *et al.*, 2016), and can protect rat myoblast H9C2 cells against hypoxia/reoxygenation-induced oxidative stress and endoplasmic reticulum stress injury via the Janus kinase/signal transducer and activator of transcription (JAK2/STAT3) signaling pathway (Yu *et al.*, 2016a).

Synergistic action with other anti-oxidants. GSPE increased the levels of superoxide dismutase (SOD) and cut the levels of malondialdehyde in a hypoxia-induced pulmonary hypertension (HPH) rat model (Jin *et al.*, 2016).

Stabilization of biological membranes. Flavonoids can stabilize biological membranes, becoming more resistant to oxidation by decreasing their permeability (Kurek-Gorecka *et al.*, 2013).

Structures associated with anti-oxidative properties. PAs' potent anti-oxidative properties are closely related to their structure, such as the monomer compositions, linkages types of the inter-flavan bonds, and the degree of polymerization of their structure.

During PAs' reaction with free radicals, phenoxyl radicals are created and stabilized by the effect of the aromatic ring resonance, and this process is affected by the substituent groups on rings and the chemical bonds between atoms (Kurek-Gorecka *et al.*, 2013).

By synthesizing monomers and their derivatives, scientists have discovered many substituent groups and their positional effects that affect anti-oxidant activities (Table 2) (Fine, 2000; Gulcin, 2012; Kurek-Gorecka *et al.*, 2013; Campos *et al.*, 2016; Feng *et al.*, 2016).

Table 2. Substituent Groups and Their Positional Effects on the Anti-oxidant Activity of PAs

Substituent Group	Positional Effects	Reference
Galloyl group	The anti-oxidant abilities: A-type EGCG dimer > A-type ECG dimer > A-type EC dimer.	Feng *et al.* (2016)
	Esterification of EC and PA B2 by GC increased their free radical scavenging ability.	Fine (2000)
Hydroxyl groups	The anti-oxidant activity of PAs is ascribed to the presence of free hydroxyl groups in the molecule and increases concomitantly with the number of hydroxyl groups.	Campos *et al.* (2016)
	Hydroxyl groups in the B ring are donors of electrons and nitrogen for radicals. Hydroxyl groups near C-3 and C-5 carbons in the presence of 4-oxo groups in the A and C rings generate the maximum free radical scavenging effects.	Kurek-Gorecka *et al.* (2013)
Ortho-dihydroxy (catechol) group	The ortho-dihydroxy in the B ring displays significant ability to "scavenge" oxygen (ROS) and nitrogen radicals (RNS) to ensure the high stability of the created phenoxyl radical.	Kurek-Gorecka *et al.* (2013)
Carbonyl group	The presence of a carbonyl group enhanced anti-oxidant activity. The anti-oxidant activity also increases when the carbonyl group is separated from the aromatic ring.	Gulcin (2012)

Table 2. (*Continued*)

Substituent Group	Positional Effects	Reference
Hydrogen	Hydrogen of C2 at ring C scavenges DPPH and hydroxyl radicals, and the anti-oxidant abilities of B-type EC dimers > A-type EC dimers.	Feng *et al.* (2016)
Oxo group	The presence of the 4-oxo group in the C ring increased the free radical scavenging ability.	Kurek-Gorecka *et al.* (2013)
Methoxy group	One or two methoxy substitutions substantially increased the anti-oxidative properties of monophenols.	Gulcin (2012)

For chemical bonds, the double bond between the C2 and C3 carbon is the reason for the dislocation of an electron in the B ring, which increases their free radical scavenging ability (Kurek-Gorecka *et al.*, 2013).

Linkage types of the inter-flavan bonds also affect anti-oxidative properties. A-type and B-type PAs have different inter-flavan bonds among their monomers, and under the same conditions, their anti-oxidant effects are very different. B-type dimers showed higher radical scavenging potency than A-type ones with the same subunits in aqueous systems. However, in tissue or lipid systems, A-type dimers showed similar or even higher anti-oxidant potency than B-type ones (Dong *et al.*, 2013). This might be due to the interaction between the bonds and the solvent. Moreover, there are two kinds of single linkages, C4–C8 or C4–C6, among the eight types of B-type PAs dimers. Fine (2000) found that PC B1–B4 have greater free radical scavenging activities than PA B5–B8.

The degree of polymerization and the conformation affect the anti-oxidative properties. Chai *et al.* (2012) suggested that the degree of polymerization could enhance or reduce the activity of PCs. The ability of PCs to scavenge free radicals tended to increase with the degree of polymerization (monomer < dimer < trimer) (Mendoza-Wilson *et al.*, 2014), and the anti-oxidant activities also increased with the polymerization degree (Li *et al.*, 2016a). However, the degree of polymerization of PCs apparently was not decisive; the most important structural factors were the conformation, the position, and type of subunits (Mendoza-Wilson *et al.*, 2014). PAs with a lower molecular weight (MW) were more efficient than those with a higher MW when acting as superoxide and hydroxyl radical scavengers and xanthine oxidase inhibitors (Arimboor and Arumughan, 2012).

In addition, the solvent also influences the anti-oxidant activity of PAs. Solvents can cause thermodynamic changes in the gas chromatography of OH groups and modify the effect of various structural features of flavonoids (Cao *et al.*, 2018). For example, the presence of acetone might increase the anti-oxidant activity of PAs (Cao *et al.*, 2018). Meanwhile, scientists have considered the effects of illumination on PAs. Liang *et al.* (2016) confirmed that CC was unstable under blue light illumination but was stable under green and red light. Furthermore, no illumination effect on the anti-oxidant function of PAs has been reported, which needs further study.

The anti-oxidant effect of PAs is the most studied bioactivity and the basis of various biological effects. Both the molecular mechanism and the structure–activity relationship (SAR) have been studied in depth, but the relationship with other biological effects still needs further exploring.

Anticancer Activities

Cancers or malignant tumors are a group of diseases defined by the uncontrollable growth of transformed cells, and their capabilities of invasion and metastasis (Cui, 2019). PAs have shown anticancer activity in many experiments, including *in vitro* and animal experiments *in vivo*. The major effects of PAs on tumors include chemical or enzymatic inactivation, mediation of pro-inflammatory activities, cell cycle arrest, cell migration inhibition, and apoptosis induction of tumor cells.

Chemical or enzymatic inactivation. PAs can inhibit the growth and proliferation of some kinds of tumor cells through the inactivation of certain enzymes. PC B3 inhibited histone acetyltransferase among the CC derivatives and suppressed p300-mediated androgen receptor (AR) acetylation, thus inhibiting prostate cancer cell growth (Choi *et al.*, 2011). DNA methyltransferases (DNMTs) are key enzymes for epigenetic modification. PC B2, as an epigenetic modulator, precisely targets DNMTs and reverses the silencing of tumor suppressor genes (Shilpi *et al.*, 2015).

Mediation of pro-inflammatory activities. Inflammation is involved in the reconstruction of the tumor microenvironment (TME) by regulating the homeostasis of tumor tissue. PAs can mediate pro-inflammatory activities by modulating the expression and secretion of cytokines and enzymes, by regulating the related gene expression and signaling pathways. PAs reduced the production of inflammatory cytokines by reducing the production of IL-6, TNF-α (Kresty *et al.*, 2015), and prostaglandin E2 (PGE2) (Saldanha *et al.*, 2016) increasing the expression of NRF2 and its target anti-oxidant genes encoding superoxide dismutase and catalase (Liu *et al.*, 2016). PCs significantly increased the production of prostacyclin and 15-hydroxy eicosatetraenoic acid (15-HETE) (Mao *et al.*, 2016). PAs can also regulate the expression of related genes and signaling pathways mainly by acting on the NF-κB and mitogen-activated protein kinase (MAPK) pathways. JQFFP inhibited the expression of COX-2 and NF-κB in human adenocarcinoma SW-480 cells (Owczarek *et al.*, 2017). Dimeric PC B2 inhibited the expression and secretion of cytokines in a concentration-dependent manner by inhibiting NF-κB-DNA binding and its downstream gene expression in Hodgkin/Reed-Sternberg (H–RS) cells (Mackenzie *et al.*, 2008). Besides, more anti-inflammatory mechanisms of PAs are described as follows:

Effects on apoptosis. Cells undergo apoptosis via three major pathways: The extrinsic/death receptor pathway, the intrinsic/mitochondrial pathway, and the endoplasmic reticulum pathway. All of these pathways involve associated apoptotic proteins. Pro-apoptotic proteins are classified into caspases and BCL2 family. The caspase family consist of 14 known proteins according to their structure and function, and the BCL2 family are localized to the outer membrane of the mitochondria to modulate the release of cytochrome c (Abotaleb *et al.*, 2018; Su *et al.*, 2019). The BCL2 family induces apoptosis via

multi-domain BAX/BAK or BH3 only families, which include PUMA, NOXA, BAD, BIM, SMAC/DIABLO, HRTA/OMI, and ARTS. PUMA and NOXA are produced as a result of DNA damage and transcription of p53 (Aubrey *et al.*, 2017), and BAD is induced by nutrition deprivation and growth signals (Indran *et al.*, 2011). Anti-apoptotic proteins include members of the BCL2 family and BIR domain family. Anti-apoptotic proteins of the BCL2 family include BCL-XL, BCLB, BCLW, MCL1, BF1, and DIVA/BOO. These proteins can bind, interact, and sequester the pro-apoptotic BAX and BAK to preserve mitochondrial membrane integrity (Wong, 2011; Kale *et al.*, 2018). BIR domain-containing anti-apoptotic proteins include N-IAP, c-IAP 1, c-IAP 2, and X-IAP (Fig. 3) (Wong, 2011).

The extrinsic/death receptor pathway. Death receptors, a group of cell surface markers, transmit apoptosis signals through a series of signal transduction processes after binding with the corresponding ligand. This pathway is carried out by the formation of a multi-protein Death Inducing Signaling Complex (DISC) that recruits and activates a pro-caspase and could lead to downstream activation of the intrinsic pathway by inducing mitochondrial stress and direct activation of executioner caspases (Creagh, 2014; Yang, 2015). For example, PAs could induce cell apoptosis through the Fas-mediated apoptotic pathway in human breast adenocarcinoma MCF-7 cells (Kuo *et al.*, 2004) and human non-small cell lung cancer A549 cells (Kuo *et al.*, 2005). The Fas ligand binds the FASR receptor to form DISC where caspase-8 is activated (Creagh, 2014). However, there have been no report of

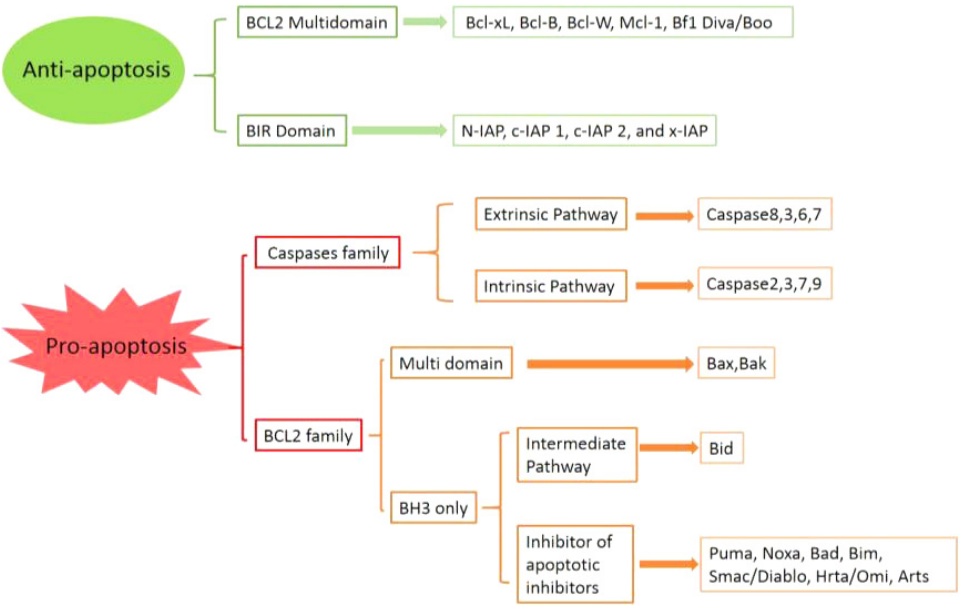

Figure 3. The classification of apoptotic proteins. Pro-apoptotic proteins are classified into caspases and the BCL2 family. The BCL2 family induces apoptosis via multi-domain BAX/BAK or the BH3 only family. Anti-apoptotic proteins include members of the BCL2 family and the BIR domain family.

PAs promoting tumor cell apoptosis through other apoptotic receptors like TNF-α or DR2, suggesting that further studies are necessary.

The endoplasmic reticulum pathway. PAs inhibit endoplasmic reticulum stress-induced apoptosis to protect normal cells against cytotoxicity, such as in cisplatin-induced nephrotoxicity (Gao *et al.*, 2014) and in the skeletal muscle of low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats (Ye *et al.*, 2013). Yu *et al.* (2016a) found that PA could activate the JAK2/STAT3 signaling pathway and then down-regulate the levels of CCAAT/enhancer binding protein homologous protein (CHOP) and caspase-12 in rat myoblast H9C2 cells. PAs can also partially reverse calcium overload and the abnormal activities of anti-oxidant enzymes to reduce mitochondrial stress (Ye *et al.*, 2013).

The intrinsic/mitochondrial pathway. There are many proteins in the mitochondrial outer membrane and cytoplasm, like the BCL2 family, which regulate apoptosis through mitochondrial permeability. Anti-apoptotic proteins BCL2 and BCL-XL inhibit cytochrome C release. Pro-apoptotic proteins of the BCL2 family like BAD, BID, BAX, and BIM promote cytochrome C release (Zhang *et al.*, 2020). Cytochrome C binds to an adaptor protein, apoptotic protease activating factor-1 (APAF-1) and forms an activated complex with procaspase-9, which activates it via cleavage, and the activities of other executioner caspases lead to the degradation of cellular components for apoptosis (Creagh, 2014). PAs directly activate or inhibit many key proteins in the pathway or up- or down-regulate the expression of related genes. PAs up-regulate pro-apoptotic genes, such as *BAX*, *BAK*, *PARP* (encoding poly ADP-ribose polymerase) (Kresty *et al.*, 2015), *BID*, *BAD*, *TP53* (Chen *et al.*, 2018), *CDKN2A* (p16), *CDKN12A*(p21) (Wei *et al.*, 2018), *CASP8*, *CASP9* (Taparia and Khanna, 2016b), and *CASP3* (Wei *et al.*, 2018). PAs also down-regulate the expression of anti-apoptotic genes like *BCL2* (Chung *et al.*, 2012), *BCL2L1* (Bcl-xL) (Taparia and Khanna, 2016b), *XIAP*, and *CFLAR* (cFLIP) (Mackenzie *et al.*, 2008); cell growth-related genes like *AKT* and *PI3K* (Taparia and Khanna, 2016b); and other survival-related genes (Liu *et al.*, 2016). Interestingly, PAs reduce the mitochondrial membrane potential (Taparia and Khanna, 2016b) and induce apoptosis via the mitochondrial pathway through intracellular ROS accumulation (Chen *et al.*, 2018), which seems to contradict the function of procyanidins in scavenging free radicals, thus further research is needed (Fig. 4).

Effects on cell cycle distribution. Cell cycle arrest can inhibit cell proliferation and is considered a potential method to treat cancer. The cell cycle includes the G1, S, G2, and M phases and is strictly controlled by cyclins and the cyclin-dependent kinases (CDKs) (Chen *et al.*, 2017; Liao *et al.*, 2019). Different members of these regulatory partners function at different phases. For example, cyclin A-CDK2 mainly functions in the S phase; cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 regulate the transition from the G1 to the S phase; and cyclin B-CDK1 regulates progression from the G2 to the M phase (Lim and Kaldis, 2013). Cell cycle progression is monitored by checkpoints, which include the G1, G2/M, and metaphase checkpoints (Barnum and O'Connell, 2014). In addition, CDK inhibitors (CKIs) suppress CDK functions to regulate cell cycle progression (Besson *et al.*, 2008) and include two families: CDK interacting protein/kinase inhibitory protein

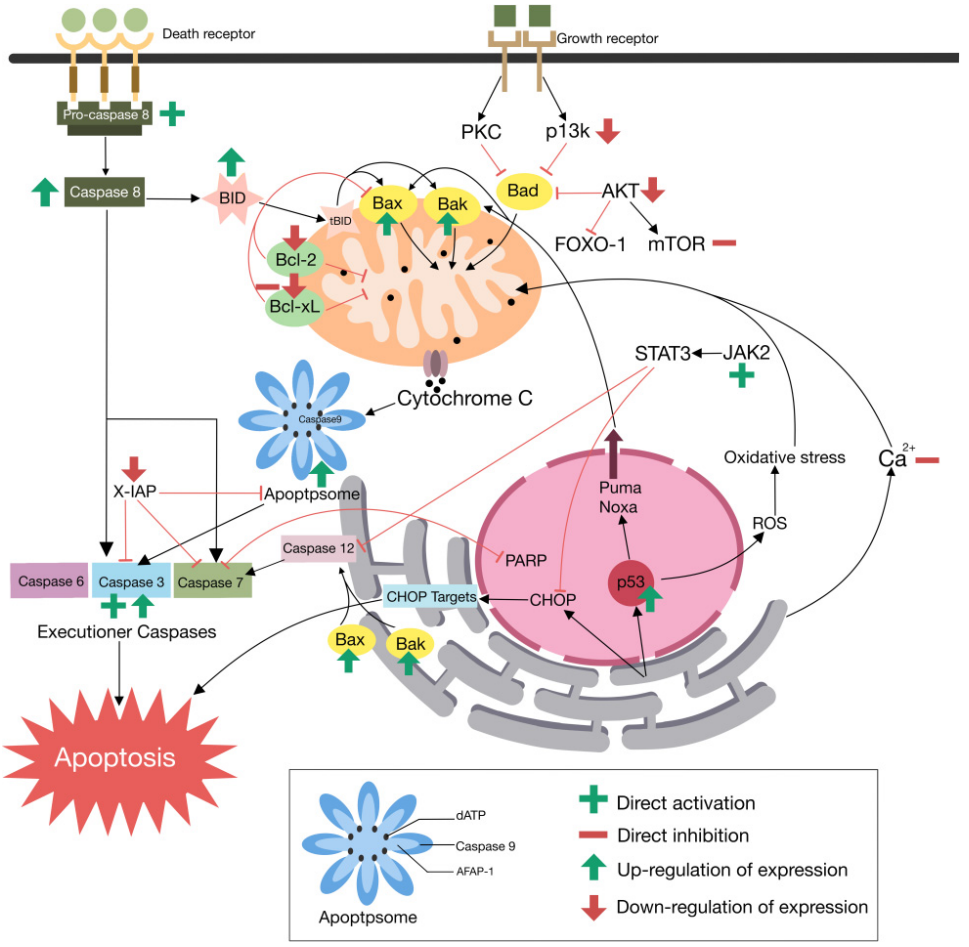

Figure 4. The mechanism of PAs' effects on apoptosis. Diagrams of the intrinsic/mitochondrial pathway, the extrinsic/death receptor pathway, the endoplasmic reticulum pathway, and the role of some apoptotic proteins and pro-apoptotic proteins including caspases family (caspase 3, 6, 7, 8, 9 and 12) and BCL2 family (BAX, BAK, BAD, PUMA, and NOXA), anti-apoptotic proteins including BCL2, BCLl-XL, and X-IAP. Black arrows indicate activation and red lines indicate inhibition. Symbols next to each element indicate the effects of PAs: Direct activation, direct inhibition, up-regulation of expression, and down-regulation of expression.

(CIP/KIP) and inhibitor of kinase 4/alternative reading frame (INK4a/ARF). The CIP/KIP family includes p21, p27, and p57, which suppress CDK2 activity (Abukhdeir and Park, 2008; Besson *et al.*, 2008). The INK4a/ARF family includes INK4A (p16), INK4B (p15), INK4C (p18), and INK4D (p19) (Besson *et al.*, 2008; Li *et al.*, 2011), which inhibit the activities of CDK4 and CDK6 (Abukhdeir and Park, 2008; Besson *et al.*, 2008; Li *et al.*, 2011). PAs can arrest the cell cycle at different phases *in vitro*, such as at the G0/G1 phase (Liu *et al.*, 2016), the G1 phase (Fraga *et al.*, 2010), the G1/S phase (Chai *et al.*, 2015a), the S phase (Mackenzie *et al.*, 2008), and the G2/M phase (Feng *et al.*, 2016). PAs mainly

regulate the protein levels of CDK and cyclins involved in cell cycle progression. For example, PAs suppress the expression of CyclinD1, CDK4 in bladder cancer BIU87 cells (Liu *et al.*, 2016); CyclinD1, CDK4, CDK2, CDK6, and Cyclin A in preadipocytes (Wei *et al.*, 2018); or increase the p53-independent expression of p21 in BxPC-3 cells (Chung *et al.*, 2012) and colon cancer cells (Pierini *et al.*, 2008) to arrest cells at the G0/G1 to S phase. PAs also decreased expressions of CyclinB1 in BxPC-3 cells (Chung *et al.*, 2012) to arrest cells at the G2/M phase.

Pierini *et al.* (2008) found that it is not the flavan-3-ol compositions of the PA fraction that determine the phase in which the cell cycle is arrested, but the tissue specific or cell type specific response (Pierini *et al.*, 2008). GSPE induced preadipocytes (Liu *et al.*, 2016) to arrest at the G0/G1 phase, while BIU87 cells (bladder cancer cells) (Liu *et al.*, 2016), BxPC-3 cells (Chung *et al.*, 2012), oral squamous cell carcinoma 25(SCC-25) cells (Chatelain *et al.*, 2011), and pulmonary artery smooth muscle cells (PASMCs) (Jin *et al.*, 2016) arrested at the G1 phase. *Pinus massoniana* Bark Extract (PMBE) induced HeLa cells (human cervical carcinoma cells) and HepG2 (human hepatoma cell) cells to arrest at the G2/M phase, while BEL-7402 (human hepatoma cell) and LoVo (human colorectal cancer cells) cells arrested at the G1/S phase (Feng *et al.*, 2016). Cocoa PCrich extract arrested human ovarian cancer cells OAW42 and OVCAR3 cells in the sub-G1/G0 (hypodiploid) phase but also arrested OVCAR3 cells in the S phase (Taparia and Khanna, 2016a) (Fig. 5).

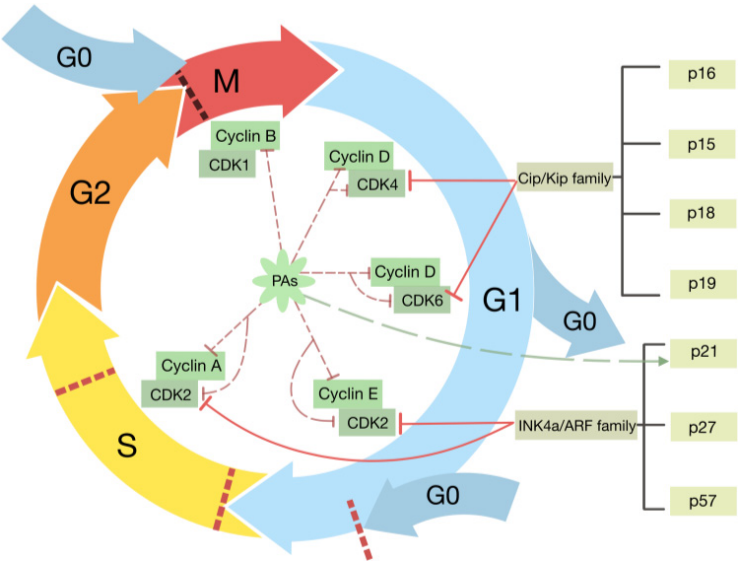

Figure 5. Mechanisms of PAs arresting cell cycle. Cell cycle includes the G1, S, G2, and M phases and is strictly controlled by cyclins and CDKs. Different members of these regulatory partners function at different phases. CDK inhibitors include the CIP/KIP family and the INK4a/ARF family, which suppress different CDKs. PAs can down-regulate the protein levels of CDK and cyclins (dotted red lines) and up-regulate levels of CDK inhibitors (green arrow).

Antimigration. Invasion and metastasis are two principal malignant characteristics of cancer cells (Hsiao *et al.*, 2018). PAs inhibit metastasis mainly by down-regulating the expression of genes and molecules related to angiogenesis and metastatic progression. PAs in PMBE strongly inhibited HeLa cell migration (Wu *et al.*, 2011) by down-regulating the expression of cathepsin B (Li *et al.*, 2016c). Members of the MMP family are involved in cell migration. JQFFP could inhibit MMP9 expression and showed antimetastatic activities in colon cancer SW-480 cells (Owczarek *et al.*, 2017). PC from natural cocoa down-regulated pro-MMP2 and reduced active MMP2 levels in epithelial ovarian carcinoma cell lines (Taparia and Khanna, 2016a). In addition, PC decreased the expression levels of vascular endothelial growth factor (VEGF) in human breast cancer MDAMB-231 cells and decreased angiogenesis (Lewandowska *et al.*, 2013). PC A2 inhibited platelet-derived growth factor type BB (PDGF-BB)-induced proliferation and migration in vascular smooth muscle cells (VSMCs) through the kinase insert domain receptor (KDR, a VEGF receptor) and via the JAK2/STAT-3/cPLA2 signaling pathways (Zhang *et al.*, 2018).

PAs have unique anticancer mechanisms in different conditions of tumorigenesis and their anticancer effects are influenced by many factors. For example, the cell lines used in experiments can show different sensitivities (Lee, 2017). Furthermore, most experiments used naturally extracted PAs, which are affected by the mixed action of PAs with diverse structures and degrees of polymerization. Therefore, some scientists synthesized oligomeric PAs to explore the relationship between their structure and the anticancer effects and found that both the substituent group and the degree of polymerization influenced the anticancer effects.

Among many substituent groups, hydroxyl and methoxy groups have significant effects. All flavones and many flavonoids with phenolic hydroxyl groups showed anticarcinogenic properties (Feng *et al.*, 2016), and the position of the hydroxy group on the B ring is important in flavonols: The 4′-hydroxy derivative was more potent than the 2′-hydroxy derivative (Estevez-Sarmiento *et al.*, 2018). For methoxy groups, the 3-methoxy is essential for cytotoxicity against tumor cells (Estevez-Sarmiento *et al.*, 2018). In addition, oligomers and polymers of flavan-3-ol have a stronger antiproliferative effects on cells than monomers and dimers (Lee, 2017). Furthermore, compared with the monomer and trimer, the hexamer (Hex) was the most vigorous at reducing colorectal cancer (CRC) cell viability (Choy *et al.*, 2016). However, there are a few opposing views, Ma *et al.* (2018) reported that the most effective PCs with antiproliferative activity was mainly PC B3, a B-type PA dimer. Therefore, the effect of the degree of polymerization requires more study.

The anticancer effect of PAs is a new research hotspot in recent years. Due to the complex mechanism of cancer, the anticancer mechanisms of PAs found are also extremely complicated and lack a clear structure–activity relationship. PAs-based anticancer drugs may emerge if structure–activity relationships can be clarified and specific structural modifications will be completed in the future.

Anti-Inflammation

The potential anti-inflammatory effect of PAs has been explored in numerous studies. Rodriguez-Ramiro *et al.* (2013) reported that cocoa polyphenols could prevent

inflammation in the colon of azoxymethane-treated rats and in TNF-α-stimulated Caco-2 cells. In addition, significant decreases in the plasma levels of inflammatory factors, such as TNF-a, IL-6 and MCP-1, companied with amelioration of macrophage infiltration in epididymal fat and liver tissues, were observed in mice after supplementation with GSPE (Liu *et al.*, 2017a). Furthermore, PAs from *Serjania schiedeana* could ameliorate joint inflammation observably (Salinas-Sanchez *et al.*, 2017). Numerous studies have investigated the mechanisms of anti-inflammatory effects of PAs, with most attention paid to the following pathways.

Inhibition of cyclooxygenase (COX) and lipoxygenase (LOX). COX and LOX are considered pivotal enzymes in inflammation and are involved in the metabolism of arachidonic acid into several inflammatory mediators, such as prostanoids and leukotrienes (LTs), which play important roles in both physiological and pathophysiological inflammation (Martinez-Micaelo *et al.*, 2012a). Studies showed that PAs could inhibit whole process of the expression of *COX2* gene, including *COX2* gene transcription (Hou *et al.*, 2007), COX 2 protein expression (Zhang *et al.*, 2006), and COX 2 enzyme activity (Martinez-Micaelo *et al.*, 2012b), which was consistent with the decrease in PG secretion in inflammation. In addition, PAs could also inhibit the secretion of LTs (Schramm *et al.*, 2001) and activities of human recombinant 5-LOX (Sies *et al.*, 2005), contributing to a decrease in LT levels. The decrease in PG and LT levels result in an attenuated inflammatory response.

Modulation of cytokine secretion. PCs can down-regulate the expression and secretion of pro-inflammatory cytokines, including IL-1β, IL-2, IL-6, IL-8, TNF-α, and INF-γ and up- regulate the secretion of anti-inflammatory cytokines such as IL-10, IL-4, and TGF-β (Martinez-Micaelo *et al.*, 2012a).

Regulation of the NF-κB pathway. The NF-κB pathway has long been considered as a prototypical pro-inflammatory signaling pathway, largely based on the role of NF-κB in the expression of pro-inflammatory genes, including those encoding cytokines, chemokines, and adhesion molecules (Lawrence, 2009; Kim *et al.*, 2019). Lee *et al.* (2017) reported that GSP could suppress the activation of NF-κB by inhibiting IκBα phosphorylation in lipopolysaccharide (LPS)-stimulated human hepatic stellate cells, which was confirmed by Jiang *et al.* (2015), both *in vivo* and *in vitro*, revealing that PCs could ameliorate the inflammatory response by inhibiting the activation of NF-κB and subsequently suppressing the expression of pro-inflammatory genes.

Phosphorylation regulation via mitogen-activated protein kinase (MAPK) pathways. MAPK signaling pathways, including extracellular signal-regulated kinase (ERK), c-Jun NH2-terminal kinase (JNK), and p38, are involved in activating a variety of transcription factors including NF-κB and activator protein-1 (AP-1) (Limtrakul *et al.*, 2016; Liu *et al.*, 2019). Mitogens, growth factors, and stress and inflammatory stimuli are activators of the ERK, JNK, and p38 cascades (Martinez-Micaelo *et al.*, 2012a). A PA-rich red rice extract demonstrated inhibitory effects on the phosphorylation of p38, JNK, and ERK1/2 induced by LPS in mice (Limtrakul *et al.*, 2016). A similar effect was observed in hematopoietic stem cells subjected to GSP pretreatment (Lee *et al.*, 2017).

Moreover, PAs could inhibit the expression of inducible NO synthase and further decrease NO synthesis (El-Shitany and Eid, 2017; Lee *et al.*, 2017), which might be another method to reduce MAPK-related inflammation. In addition, the inhibitory effect of PA on allergic inflammation has been reported. Lee *et al.* (2012) found that GSPE could attenuate allergic inflammation in murine models of asthma. Coleman and Shaw (2017) proposed that PA-rich extracts could inhibit the production of eotaxin-1 (CCL-11) and eotaxin-3 (CCL-26) in human alveolar epithelial cells and reduce the infiltration of eosinophil cells in the lungs. Furthermore, GSPE could suppress the Th2 immune response and decrease the expression of IL-5, IL-13, and IL-4, leading to subtle infiltration of eosinophil cells and a decrease in IgE secretion (Lee *et al.*, 2012).

Antimicrobial Activity

PAs cannot only inhibit bacterial infection but also have an inhibitory effect on fungi, viruses, and parasites (Marin *et al.*, 2015), revealing the important role of PAs in preventing and treating infectious diseases.

Antibacterial activity. Many clinical trials have shown that cranberry juice and its derivatives are useful mainly because of the anti-adhesive properties of Cranberry PAs, which have an important effect in the prophylaxis of recurrent urinary tract infection (UTI) (Micali *et al.*, 2014a). Antibiofilm properties of Cranberry PAs on *Pseudomonas aeruginosa* were also observed (Ulrey *et al.*, 2014), indicating that PAs might be a useful therapy against biofilm-mediated infections caused by *P. aeruginosa*. In addition, EGCG, the main CC of tea polyphenols, has broad antibacterial properties. For example, it can inhibit infection by *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Helicobacter pylori*, and certain other gram-positive and gram-negative bacteria, directly or indirectly (Hu *et al.*, 2002; Cui *et al.*, 2012; Steinmann *et al.*, 2013). These compounds seem to affect bacterial growth via several mechanisms, such as inhibition of extracellular enzymes, deprivation of microbial essential substrates, disintegration of bacterial outer membrane with cytoplasm leakage, or by direct action on microbial metabolism (Smeriglio *et al.*, 2017). Besides, damaging the cell walls, decreasing the heat resistance of bacterial spores, and assisting in the action of antibacterial substances, were also discussed in some reports (Sakanaka *et al.*, 2000; Hu *et al.*, 2002; Cui *et al.*, 2012).

Antiviral activity. *In vitro* studies showed that some compounds of tea polyphenols, including PC B2 and EGCG, exhibited inhibitory activity against influenza A and B viruses (Yang *et al.*, 2014b), mainly by binding to the glycoproteins of the viral envelope to block hemagglutinin domains, which, in turn, inhibited virus particle agglutination and prevented influenza virions adsorbing and entering host cells (Yang *et al.*, 2014b). The inhibitory effect of EGCG on the hepatitis C virus has also been reported, in which it inhibits the entry of hepatitis C virus and its replication in hepatocytes (Calland *et al.*, 2012; Wang *et al.*, 2017). In addition, green tea EGCG has antiviral effects against HIV-1 infection by inhibiting gp120 binding to human CD4+ T cells (Williamson *et al.*, 2006) and blocking the life cycle of HIV-1 (Yamaguchi *et al.*, 2002).

Table 3. The Relationship between Chemical Structure and PAs' Antimicrobial Activity Effects

Bioactivities	Class	Structure	Example	Reference
Antibacterial activity	Monomer compositions	O-galloyl group	A 3-O-galloyl group is crucial for pronounced inhibition of bacterial Vibrio cholerae neuraminidase (VCNA) by flavan-3-ols.	Quosdorf *et al.* (2017)
		Hydroxyl group	Procyanidin A1, B3, C4 and cinnamtannin D1 showed pronounced anti-oxidant activities and the activities are enhanced as the amount of OH groups in procyanidins increased.	Wang *et al.* (2015)
	Linkages types of inter-flavan bonds	C2–O–C7/C2–O–C5 bond or C4–C8/C4–C6 bonds	A-type PAs show stronger anti-adhesion activity than B-type PAs, thus suggesting that A-type linkage may be responsible for abridged bacterial adherence to uroepithelial cells.	Micali *et al.* (2014b)
	Degree of polymerization (DP)		Cranberry A-type proanthocyanidins (PACs) oligomers specific DP may be effective in disrupting the assembly of cariogenic biofilms.	Ikai *et al.* (2013)
Antiviral activity	Monomer compositions	Hydroxyl group	The phenolic hydroxyl group of EGC in the B ring play an important role in the anti-influenza A virus activity.	Yang *et al.* (2014a)
		Virus-proline-PAs complexes	The formation of virus-proline-PAs complexes probably mediates the blockage or alteration of capsid protein binding determinants and reduces antigen capture.	Lipson *et al.* (2012)
		Methyl group	The methyl group located on the B ring of isorhamnetin may contribute to its strong antiviral potency against influenza virus in comparison with other flavonoids.	Dayem *et al.* (2015)
		Galloyl group	Galloylation of the procyanidin core structure was shown to be a prerequisite for anti-influenza A viruses activity	Derksen *et al.* (2014)
	Degree of polymerization		The antiviral activity of feline calicivirus (FCV-F9): procyanidin extract (polymeric polyphenols) > procyanidin B2 > monomeric catechin hydrate.	Liu *et al.* (2018)
Antifungal activity	Linkages types of inter-flavan bonds	C2–O–C7/C2–O–C5 bond or C4–C8/C4–C6 bonds	PAs with B-type linkages proved active against 14 fungal strains and increase the activity of bifonazole and ketoconazole.	Karioti *et al.* (2011)

Antifungal activity. Luiz *et al.* (2015) first reported that PA polymeric tannins from *Stryphnodendron adstringens* have active antibiofilm activity on *Candida albicansin vitro*. Similar research was also carried out *in vivo*, showing that PAs from *Stryphnodendron adstringens* could efficiently control vaginal infection by *C. albicans* and *C. glabrata* in mice (de Freitas *et al.*, 2018). In addition, EGCG was found to have a higher antifungal activity against dermatophytes than conventional antifungal agents, such as amphotericin B, itraconazole, and miconazole (Park *et al.*, 2011), suggesting that EGCG might be an effective antifungal therapy in dermatophytosis.

Antiparasitic activity. Previous studies showed that EGCG could inhibit the binding of isolates of *Plasmodium falciparum* to the Intercellular Adhesion Molecule-1 (ICAM-1) in cellular receptor, which is related to cerebral malaria (Patil *et al.*, 2011). An *in vivo* study also suggested that EGCG inhibits the growth of *Trypanosoma cruzi* and increases the survival rates of acute Chagas' disease (Guida *et al.*, 2007); however, the mechanisms remain unknown.

Summarily, these previous studies showed that antimicrobial activity effects of PAs are affected by their chemical structure (Table 3).

Cardiovascular-Protective Activity

Epidemiological studies suggest that PAs have significant cardiovascular-protective properties (Wang *et al.*, 2014; Kim and Je, 2017). Further research showed that PAs play an important role in preventing atherosclerosis, balancing blood pressure, and regulating lipid metabolism (Smeriglio *et al.*, 2017).

Anti-atherosclerosis. It has been reported that oxidized low-density lipoprotein (oxLDL) plays a crucial role in early progression of atherosclerosis, via its effect in eliciting endothelial dysfunction and macrophage activation (Hort *et al.*, 2012; Lin *et al.*, 2018). PAs have inhibitory effects against human LDL oxidation *in vitro* (Hort *et al.*, 2012), which was confirmed later in a human study. After consumption of cocoa extract, a significant decrease in the oxLDL concentration was observed in plasma (Ibero-Baraibar *et al.*, 2014). In addition, the differentiation of monocytes to macrophages, another key event in the progression of atherosclerosis, was inhibited by oligomeric PAs both *in vivo* and *in vitro* (Mohana *et al.*, 2015). Rong *et al.* (2017) found that litchi pericarp PCs extract (LPPC) significantly reduced the atherosclerotic lesion size in apolipoprotein E-knockout mice, mainly by inducing the expression of inducible nitric oxide synthase (iNOS) and the production of NO, thereby improving endothelial function.

Antihypertension. Hypertension, as the major risk factor for cardiovascular diseases, correlates with endothelial dysfunction (Hugel *et al.*, 2016). Pons *et al.* (2017) reported that increased blood pressure (BP) was attenuated significantly after chronic administration of low molecular weight GSPE in cafeteria diet-fed rats. This was consistent with their previous research, in which after a single oral administration of a GSE, decreased systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed in rats with metabolic syndrome, via mechanisms involving a change in endothelium-derived NO availability (Pons *et al.*, 2016). In addition, in a clinical trial, grape-wine extract was found

to substantially reduce 24-h ambulatory systolic/diastolic BPs and decrease the levels of vasoconstrictor endothelin-1 (Draijer *et al.*, 2015). However, grape juice extract alone was found to have no effect on BP, indicating that CCs and PCs, which are relatively less abundant in grape juice extract, but are rich in grape-wine extract, are likely to be the main flavonoid classes contributing to this BP lowering effect (Draijer *et al.*, 2015).

Antihyperlipidemia. Serum cholesterol and triglyceride are controllable cardiovascular disease (CVD)-associated risk factors, and hypercholesterolemia and hypertriglyceridemia play an important role in the occurrence and development of CVD (Blade *et al.*, 2016; Bae *et al.*, 2018). A recent study demonstrated that oligomeric PCs from GSE exert a hypocholesterolemic effect in pigs, mainly by increasing biliary excretion and reducing micellar solubility (Quifer-Rada *et al.*, 2016). Downing *et al.* (2015) reported that GSPE significantly ameliorated hypertriglyceridemia induced by fructose, via enhancing fecal bile acid and cholesterol excretion, and inhibiting hepatic lipogenesis. Subsequent studies showed that these effects are achieved by influencing the expression of related genes. For example, GSPE induced hepatic bile acid biosynthetic gene expression, especially that encoding cholesterol 7α-hydroxylase (CYP7A1), to increase the synthesis of bile acid (Heidker *et al.*, 2016). GSPE also decreased intestinal apical sodium-dependent bile acid transporter (*ASBT*) gene expression to block the reuptake of bile acid (Heidker *et al.*, 2016). Moreover, GSPE could also attenuate the expression of hepatic lipogenic genes induced by cholestyramine to decrease lipogenesis (Heidker *et al.*, 2016). Other mechanisms of PAs effects, such as inducing reverse cholesterol transportation and inhibiting intestinal lipid absorption, have likewise been discussed (Downing *et al.*, 2017).

Anti-arrhythmia. Cardiac arrhythmias are abnormalities or perturbations in the normal activation or beating of the heart myocardium (Fu, 2015). PAs and PAs-enriched extracts have been demonstrated to have anti-arrhythmic effects in animal models. Liang *et al.* (2009) found that GSPE treatment significantly reduced the incidence of ventricular fibrillation (VF) in reperfusion rabbit hearts, which might be mediated by inhibiting the degradation of connexin 43 and enhancing gap junction conductance. In addition, oligomer PCs were found to significantly reduce the incidence of reperfusion-induced VF and decrease the release of lactate dehydrogenase (LDH) in isolated rat hearts (Makdessi *et al.*, 2006), which was confirmed *in vivo* by Zhao *et al.* (2010), who also reported that increased expression of Na^+/K^+ ATPase α1 subunit was the potential mechanism, which might be caused by a decrease in free radical generation induced by GSPE.

Metabolism Regulation

PAs and PA-rich plant extracts were reported to have an important role in the treatment of certain metabolic diseases, such as obesity, diabetes, and other metabolic disorders (Salvado *et al.*, 2015; Akaberi and Hosseinzadeh, 2016; Yang and Chan, 2017).

Effect on obesity. A study following 124,086 US men and women for up to 24 years showed that a higher intake of foods rich in flavonols, flavan-3-ols, anthocyanins, and flavonoid polymers might contribute to weight maintenance in adulthood, and could help to refine dietary recommendations for the prevention of obesity and its potential consequences

(Bertoia *et al.*, 2016). More animal studies have been performed, treating hamsters in both high-fat and standard diet with GSPE, in which a significant decrease in body weight gain was observed, and the weight of all the white adipose tissue (WAT) deposits, especially retroperitoneal WAT, decreased significantly (Caimari *et al.*, 2013). When mice were fed a high-fat diet supplemented with either a cocoa flavanol extract or a flavanol fraction enriched with monomeric, oligomeric, or polymeric PCs for 12 weeks, the weight of mice decreased in all groups, and the oligomer-rich fraction proved to be most effective in preventing weight gain (Dorenkott *et al.*, 2014). A previous study showed that the corresponding mechanism might be that PAs could inhibit intestinal lipase and amylase and then reduce the absorption of lipids and glucose in the small intestine (Dorenkott *et al.*, 2014). Further research suggested that PAs could potentiate hypothalamic leptin /STAT3 signaling and POMC gene expression to decrease food intake (Ibars *et al.*, 2017). Moreover, a recent study demonstrated that PAs could suppress fat accumulation by down-regulating the expression of lipogenic and adipogenic genes via inhibiting both SREBP-1c and PPARγ, as well as up-regulating the lipolysis cascade via promoting the expression of PPARβ/δ-dependent fatty acid oxidative genes through activating *Prkaa*1 gene expression in adipose tissue (Ali *et al.*, 2015). These mechanisms indicated that PAs exert their anti-obesity effect mainly by reducing energy intake and increasing energy expenditure. In addition, some recent studies reported that the effects of PAs on obesity are associated with gut microbial species (Masumoto *et al.*, 2016; Liu *et al.*, 2017a); however, additional studies are needed to understand the specific mechanism.

Effect on type 2 diabetes. A meta-analysis of relevant studies showed that higher intakes of total flavonoids and their subclasses (anthocyanidins, flavan-3-ols, flavonols, and isoflavones) were associated with lower risk of type 2 diabetes mellitus (Xu *et al.*, 2018). Obesity is an important risk factor for diabetes; therefore, the anti-obesity effect of PAs indicated their potential role in the treatment of diabetes (Alkhalidy *et al.*, 2018). However, there are some unique mechanisms. PAs were found to exert their antihyperglycemic effect mainly by stimulating glucose uptake into insulin-sensitive tissues (Salvado *et al.*, 2015). For example, PAs upregulate the expression of glucose transporter-4 (GLUT4) gene in adipose tissue and muscle, and modulates GLUT4 translocation into the plasma membrane to induce glucose uptake (Salvado *et al.*, 2015). PAs also target hepatic glycolytic and gluconeogenic enzymes to reduce glucose production (Salvado *et al.*, 2015). In addition, PAs have a direct role in modulating several pancreatic β-cell functions, such as prevention of oxidative stress, enhancement of insulin secretion, and promotion of β-cell survival (Yang and Chan, 2017).

Neuroprotective Activities

Strathearn *et al.* (2014) found that PAs significantly alleviated dopaminergic neuron death and neurite loss in a rotenone-treated primary cultured cell model of Parkinson's disease. Amelioration of mitochondrial dysfunction and interference with microglial activation were considered as the potential mechanisms (Strathearn *et al.*, 2014). Similarly, PAs were also reported to markedly reduce rotenone-induced oxidative stress in human

neuroblastoma SH-SY5Y cells (Ma *et al.*, 2018). In addition, PAs markedly enhanced cell viability against rotenone neurotoxicity and considerably blocked rotenone-induced activation of caspase-9, caspase-3, and the cleavage of PARP, which are wellknown biochemical features of apoptosis (Ma *et al.*, 2018). The result also demonstrated that PAs exert their anti-apoptotic effect by suppressing the p38, JNK, and ERK signaling pathways (Ma *et al.*, 2018). He *et al.* (2016b) found that PAs notably decreased the proportion of neuronal apoptosis in the hippocampal CA1 region and increased synaptic density in a mouse model of Alzheimer's disease. The level of activated astrocytes and microglia expression in the hippocampus was also reduced, revealing that PAs may be a candidate to treat Alzheimer's disease (He *et al.*, 2016b). Besides, some phenolic acids, such as GC and ferulic acid, which are metabolites of PAs produced by the gut microbiota, were found to have neuroprotective activities, such as an antidepressant-like effect and an ischemia/reperfusion injury protective effect (Szwajgier *et al.*, 2017).

Toxicology

*In vitro studies.*Segal *et al.* (2018) evaluated the mutagenicity of Oligopin®, a French maritime pine bark extract rich in procyanidolic oligomers (OPC). The results indicated that Oligopin® was non-genotoxic in both bacterial and human lymphocytes assays (Segal *et al.*, 2018). Similarly, the mutagenicity of a PC-rich extract from grape seeds and skins (GSSE) was also evaluated. The bacterial reverse mutation test showed that the extract was weakly mutagenic at a dose of 5 mg/plate, while cultures treated with 19.5 μg/mL and 9.7 μg/mL of GSSE did not show significant mutagenicity compared with that of the negative controls (Lluis *et al.*, 2011). In addition, Enzogenol®, a pine bark extract containing more than 80% PAs was confirmed to have no mutagenic effect with 5000 μg/plate in bacterial reverse mutation tests (Frevel *et al.*, 2012).

In vivo studies. An acute toxicity test showed the lethal dose 50 (LD50) of GSSE was expected to be more than 5000 mg/kg in female Wistar rats (Lluis *et al.*, 2011). The systemic toxicity of Oligopin® was evaluated by acute and 90-day repeated dose oral toxicity studies using Sprague Dawley rats. The result indicated that Oligopin® was not acutely toxic via oral administration at up to 2000 mg/kg and was well tolerated following repeated oral administration to Sprague Dawley rats, with a no-observed-adverse-effect-level (NOAEL) of 1000 mg/kg/day (Segal *et al.*, 2018). Rats and Beagle dogs were used as models to evaluate the systemic toxicity of Enzogenol®. The results indicated that the maximum tolerated dose (MTD) in rats was greater than 2500 mg/kg body weight, and the NOAEL in rats was 2500 mg/kg/day under 14-day treatment. For dogs, the MTD was considered to be 1250 mg/kg/day, and the NOAEL on repeated oral administration (14-days) was 750 mg/kg/day (Frevel *et al.*, 2012).

Adverse reports on human subjects. A study carried out in healthy Japanese subjects suggested that GSE is generally safe and well tolerated when taken orally at doses of up to 2500 mg per day for 4 weeks (Sano, 2017). Moreover, Enzogenol® consumption at 480 mg/day for 6 months and 960 mg/day for 5 weeks showed no adverse effects on liver and kidney function, hematology, and other events (Frevel *et al.*, 2012). In another study,

Table 4. Completed Clinical Trials of PAs Provided by U.S. National Institutes of Health (https://clinicaltrials.gov)

NCT Number	Title	Gender	Conclusion	Ref.
NCT03451682	Effects of Procyanidine on Semen Parameters and DNA Fragmentation Index During Cryopreservation of Abnormal Human Semen Samples	Male 18–50 Years	Not found	
NCT03414164	*In Vitro* Effects of Procyanidine on Semen Parameter and DFI	Male 18–50 Years	Not found	
NCT00318019	Effect of OPC Factor on Energy Levels	All 45–65 Years	OPC Factor™ increased energy levels	LaRiccia *et al.* (2008)
NCT03214276	Effects of Polyphenols Supplementation on Cycling Endurance	Male 25–45 Years	Not found	
NCT03135314	Cocoa Flavanol Intake and Exercise in Hypoxia	Male 18–36 Years	Cocoa Flavanol had beneficial effects on endothelial function and prefrontal oxygenation	Decroix *et al.* (2018)
NCT03194620	Absorption, Metabolism and Excretion of Dietary Polyphenolic Bioactives in Humans	Male 25–60 Years	Not found	
NCT01969994	Absorption, Metabolism, and Excretion of (-)-[2-14C] Epicatechin in Humans	Male 18–50 years	(1) EC is well absorbed and fully metabolized and then excreted in urine (2) Metabolism of EC has species-dependent differences (3) The metabolites are the main functional components	Ottaviani *et al.* (2016)
NCT01483508	Absorption and Metabolism of Dietary Cocoa Procyanidins in Humans	All 18–70 Years	Dietary procyanidins have no effect on systemic pool of flavanols	Ottaviani *et al.* (2012)
NCT01847053	Bioavailability Study of Cinnamon in Healthy Subjects	Male 18–40 Years	Not found	
NCT01687114	Urinary Proanthocyanidin-A2 as a Biomarker of Compliance to Intake of Cranberry Products	Female 20–40 Years	Not found	
NCT00740077	Bioavailability of Flavonoids and Phenolic Acids From Cranberry Juice Cocktail in Healthy Older Adults	All 50–70 Years	Phenolic compounds in cranberry juice are bioavailable and exert anti-oxidant action	McKay *et al.* (2015)

Table 4. (*Continued*)

NCT Number	Title	Gender	Conclusion	Ref.
NCT03145987	Effects of a Food Supplement on Cognitive and Neuropsychological Functioning in Older Adults.	All 55–75 Years	Not found	
NCT02764749	Cranberry (Poly)Phenol Consumption on Vascular Function	Male 18–35 Years	Not found	
NCT02734901	Effects of Acute Red Raspberry Consumption on Vascular Function in Healthy Individuals	Male 18–40 Years	Not found	
NCT02728466	Effects of Cocoa Procyanidins on Vascular Function	Male 18–35 Years	Not found	
NCT02515929	Prospective Double-Blind Randomized Controlled Clinical Trial in the Gingivitis Prevention With OPCs	All 18–50 Years	Not found	
NCT02039648	The Influence of Rumex Acetosa L on the Intraoral Colonization With Porphyromonas Gingivalis	All > 18 Years	Not found	
NCT02408289	The Randomized Controlled Cocoa-Appetite Trial	Male 18–35 Years	Epicatechin helped to control food intake.	Greenberg *et al.* (2016)
NCT02333461	Evaluation of Botanicals for Mechanisms Related to Appetite and Fat Metabolism	All 18–70 Years	Dietary grape extact attenuated postprandial hypertriglyceridemia via inhibition of intestinal DGAT1 enzyme activity	Velliquette *et al.* (2015)
NCT02063477	Effect of Oligopin® on Blood Pressure	All > 18 Years	Oligopin® improved the lipid cardiovascular profile	Valls *et al.* (2016)
NCT00568152	Effect of Apple Flavanols on Risk of Cardiovascular Disease	All 19–64 Years	Apple puree attenuated platelet reactivity and increases plasma concentrations of nitric oxide metabolites	Gasper *et al.* (2014)
NCT02013856	The Effects of Apple Derived Flavanols on Cardiovascular Disease Risk (FLAVASCULAR Study)	All > 50 Years	Not found	

Table 4. (*Continued*)

NCT Number	Title	Gender	Conclusion	Ref.
NCT01010841	Trial of Two Dietary Programs on Cardiometabolic Risk Factors in Subjects with Metabolic Syndrome	Female 20–75 Years	Not found	
NCT00742287	Cardiovascular Effects of Oligomeric Procyanidins (OPCs) in Smokers	Male 30–60 Years	Monomeric and oligomeric flavanols improved overall vascular health	Weseler *et al.* (2011)
NCT01707615	Beneficial Effects of Grape Seed Proanthocyanidin Extract on Progression of Atherosclerotic Plaques in Clinical Use	All 43–75 Years	GSPE inhibited the progression of mean maximum carotid intima-media thickness and reduced carotid plaque size.	Cao *et al.* (2015)
NCT00713167	The Efficacy of Red Grape Seed Extract on Lipid Profile and Oxidized Low-Density Lipoprotein (OX-LDL)	All 21–64 Years	Red grape seed extract improved lipid profiles and decreased oxidized low-density lipoprotein	Razavi *et al.* (2013)
NCT01688154	Ability of Grape Seed Proanthocyanidins to Reduce Postprandial Triglycerides in Humans	All 20–40 Years	Not found	
NCT01681394	Effect of a Polyphenol-rich Cocoa Extract on Peripheral Blood Mononuclear Cells Gene Expression	Male 20–35 Years	Not found	
NCT01099150	Dark Chocolate and Platelet Function in Humans	All 18–70 Years	Dark chocolate and white chocolate improved postprandial platelet function	Ostertag *et al.* (2013)
NCT01669317	Mechanisms Underlying the Sleep Promoting Effect of Cherry Juice Standardized to Its Proanthocyanidin Content	All > 65 Years	Not found	
NCT01398150	Cranberry Enhances Human Immune Function and Reduces Illness	All 18–50 Years	Cranberry beverage modified the *ex vivo* proliferation of γδ-T cells and reduced symptoms associated with colds and influenza	Nantz *et al.* (2013)
NCT01346774	Preventing Urinary Tract Infection Post-Surgery	Female > 18 Years	Cranberry extract capsules reduced the rate of UTI	Foxman *et al.* (2015)

Table 4. (*Continued*)

NCT Number	Title	Gender	Conclusion	Ref.
NCT01691430	A Trial of Cranberry Capsules for Urinary Tract Infection Prevention in Nursing Home Residents	Female > 65 Years	Cranberry capsules had no effect in treating bacteriuria and pyuria	Juthani-Mehta *et al.* (2016; Datta *et al.* (2018)
NCT02087735	Measurement of Urinary Catabolites of PACs as Biomarkers of Consumption of Cranberry Extracts	Female 18–40 Years	Not found	
NCT01219595	Cranberry Proanthocyanidins for Modification of Intestinal *E. Coli* Flora and Prevention of Urinary Tract Infections in UTI-Susceptible Women	Female 18–65 Years	Not found	
NCT00100893	IH636 Grape Seed Extract in Preventing Breast Cancer in Postmenopausal Women at Risk of Developing Breast Cancer	Female 40–75 Years	Not found	

whole grape exact was administered for 6 weeks to 14 pre-hypertensive, overweight, and/or pre-diabetic subjects, and no statistically significant differences were found between the placebo control and whole grape exact-treated subjects with respect to biometrics, vital signs, hematology (complete blood count), liver function, kidney function, and electrolytes (Evans *et al.*, 2014).

The study of the toxicity of PAs is an indispensable step for their clinical application. However, compared with other aspects, fewer studies on toxicity of PAs have been performed and most of them are *in vitro* and *in vivo* animal studies. Moreover, the available clinical trials are mostly small sample trials, so the conclusions need further validation. Therefore, larger, well-designed, placebo-controlled studies are supposed to further evaluate the toxicological effects of PAs in humans.

Human Clinical Trials

Although many *in vitro* cell model and *in vivo* animal model studies have been carried out, which help us identify the potential health effects of PAs and their specific mechanisms, human clinic trials are the most valuable studies, and to date, there are only 36 related complete human clinical trials on proanthocyanidins (www.clinicaltrials.gov) (Table 4).

Conclusions and Perspectives

The importance of consuming fruit and vegetables to achieve better health is widely accepted. Therefore, PAs, which are abundant in our daily diet and in natural products, have received significant research attention. Papers issued in the last few decades have provided a thorough understanding of PAs in terms of their resources, extraction, structure, pharmacokinetics, pharmacology, and toxicology.

After oral administration, PAs are first absorbed and metabolized in the small intestine and then in the liver; however, their absorption correlates negatively with their polymerization degree. PAs that not be absorbed are fermented by colonic microbiota, resulting in a wide range of metabolites, which then enter into the blood and reach other organs where they exhibit their pharmacological effects (Zhang *et al.*, 2016).

The potential pharmacological effects of PAs, including anti-oxidation, anticancer, anti-inflammation, antimicrobial, cardiovascular-protection, neuroprotection, and metabolism regulation, have been confirmed by epidemiological and clinical data (Martinez-Micaelo *et al.*, 2012a; Wang *et al.*, 2014; Marin *et al.*, 2015; Salvado *et al.*, 2015; Neilson *et al.*, 2016; Kim and Je, 2017; Smeriglio *et al.*, 2017)). Mechanisms by which PAs exert these effects have also been investigated thoroughly, mainly via cell models *in vitro*, animal studies *in vivo*, and human clinical studies. Structures of PAs determine their ability to affect electron transport, which is correlated with the anti-oxidant capacity (Kurek-Gorecka *et al.*, 2013). Besides, PAs were also found to interact with proteins (Dorenkott *et al.*, 2014), affect gene expression (Martinez-Micaelo *et al.*, 2012a), and subsequently alter cell metabolism to exert additional pharmacological effects (Martinez-Micaelo *et al.*, 2012a).

Current toxicological tests showed that PAs have no obvious mutagenicity and systemic toxicity, both *in vitro* and *in vivo* (Sano, 2017); however, data are still limited in this aspect.

However, although research on PAs has made marked progress, there are still some issues worthwhile more attention and further research. First, science standards are lacking in the study of PAs; therefore, studies with different materials, for example, purified PAs and PA extracts, or different models with diverse designs, often leading to controversial results (Lin *et al.*, 2002; Lou *et al.*, 2004). Second, the limitations of *in vitro* and animal studies should be reviewed thoroughly. These results can be used to identify some of the mechanisms; however, they cannot be equated directly with the effects on the human body. Third, studies on the effect of PA extracts should exclude the effect of other components in the extract and some PA-related components in the diet. Fourth, the research target should not focus on just one component and one-point target, more rational and complete experimental designs are needed in order to obtain more systematic data. In this aspect, Network Pharmacology (Li *et al.*, 2014; Boezio *et al.*, 2017) and Big Data analysis (Quinney, 2019) might represent the right research direction. Fifth, larger samples, longer time, well designed, and placebo-controlled clinical trials should be conducted to confirm the safety and health benefits of PAs on the human body. The deeper mechanisms should be studied in humans to promote the better use of PAs.

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