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Bioactive procyanidins from dietary sources: The relationship between bioactivity and polymerization degree

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ABSTRACT

Background: Procyanidins, commonly found in plant natural sources, are polymerized forms of flavanols, which are a subclass of flavonoids. They have been reported to exhibit broad benefits to human health and used in the prevention of cancers, cardiovascular diseases, diabetes, etc. Bioactivities of procyanidins depend on many factors including the structures of procyanidins. Differences in composition of the monomers and degree of polymerization (DP) contribute to the variation in procyanidins.

Scope and approach: The basic structures and natural sources of procyanidins have been summarized in detail. Importantly, the structure-activity relationships of procyanidins, especially the relationship between degrees of polymerization and their antioxidant, anticancer, antidiabetic, anti-obesity, and cardioprotective effects as well as their potential mechanisms have been reviewed in detail. Additionally, current challenges in the studies of procyanidins have been discussed.

Key findings and conclusions: Procyanidins are structurally diverse compounds and can be classified as monomeric, oligomeric, or polymeric variants depending on the DP, which plays a role in manifesting various effects that are associated with human health. The diversity and complexity of these chemical compounds and the difficulties encountered in the isolation of plant procyanidins continue to be major challenges. A better understanding of this information may promote the use of procyanidins in improving human health.

Abbreviations: ABCA1, ATP-binding cassette A subfamily A member 1; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; ARE, antioxidative response element; AS, atherosclerosis; CAT, catalase; CVD, cardiovascular diseases; DP, degree of polymerization; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; ELF-EMF, extremely low-frequency electromagnetic fields; ERK1/2, extracellular signal-regulated kinase 1/2; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; GR, glutathione reductase; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione-*S*-transferase; HPLC, high-performance liquid chromatography; iNOS, inducible nitric oxide synthase; IR, insulin resistance; IRE-1α, inositol-requiring enzyme-1α; JNK, c-Jun N-terminal kinase; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MALDI, matrix-assisted laser desorption ionization; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; mDP, mean degree of polymerization; MVD, microvessel density; NMR, nuclear magnetic resonance; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PB1, procyanidin dimer B1; PB2, procyanidin dimer B2; PC1, procyanidin trimer C1; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PHF, paired helical filaments; ROS, reactive oxygen species; SD, sprague dawley; SOD, superoxide dismutase; TFEB, transcription factor EB; UCP, uncoupling protein..

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1. Introduction

Polyphenols are naturally occurring bioactive phytochemicals found in medicinal plants and food (Andriambeloson et al., 1998; Bowser et al., 2017). The bioactivities and potential mechanisms of polyphenols have been widely reported (Catalkaya et al., 2020; Sun et al., 2017; Khan et al., 2020; Liu et al., 2020; Wu et al., 2020; Zhao et al., 2020; Zhou et al., 2020). Proanthocyanidins are one of the most abundantly occurring polyphenols in plants (Bruyne et al., 1999). According to the substitution pattern and the degree of oxidation, proanthocyanidins are mainly classified as propelargonidins, prodelphinidins, and procyanidins; among these groups, procyanidins from plants are most common (Gu et al., 2003).

The benefits of procyanidins have been reported in epidemiological studies (Lamuela-Raventós et al., 2005), therefore, more research groups are interested and have found that procyanidins showed antioxidant (Saito et al., 2009), anticancer (Gopalakrishnan et al., 2018), anti-atherosclerosis (Zhang et al., 2013), hypoglycemic (Kim et al., 2020), hypotensive (Lu et al., 2011), and hypolipidemic activities (Downing et al., 2017). The physiological functions of procyanidins vary depending on their structure, such as the position of the interflavonoid bond and their degree of polymerization (DP) (Abe et al., 2008). Although several studies have been addressed to clarify the structure-activity relationships of procyanidins including plant-based monomers, dimers, and trimers, this relationship has not been studied in a large number of procyanidins because it is difficult to obtain pure compounds with a single DP using currently available research methods. Thus, existing studies on procyanidins are typically centered on compounds that are known to display a various DP. In this review, we have summarized the structures, natural sources of the procyanidins, and the relationship between the DP and biological activities and provided information for better understanding of the mechanisms of the bioactivities of procyanidins.

All available information on this class of compounds was collected from scientific databases. The following electronic databases were used: PubMed, SciFinder, ScienceDirect, Scopus, Web of Science, Wiley, ACS, Springer, and Google Scholar. The search terms used for this review included procyanidins, structure, degree of polymerization, source, activity, pharmacology, mechanism, and toxicity. The search was refined and only articles in English were included in this study. To find relevant studies, papers were primarily screened based on titles and abstracts. Inclusion criteria were *in vitro*, *ex vivo*, and *in vivo* studies on bioactivities or structure-activity relationship of procyanidins, and studies with or without a proposed mechanism of action. Exclusion criteria were articles on synthetic molecules or studies not addressing the current topic.

2. Structures and general information of procyanidins

Procyanidins are also known as condensed tannins and are derived from proanthocyanidins (Quideau et al., 2011). The basic structural unit of procyanidins is the flavane-3-ol. Its basic skeleton consists of the typical C6–C3–C6 phenolic flavonoid ring structure (Fig. 1A). The structural diversities of procyanidins depend on the type of the basic flavan-3-ol unit, the connection mode between units, the spatial configuration, and the modification of the phenyl hydroxyl groups (e.g. esterification or methylation). Procyanidins can be classified according to their DP (Gu et al., 2004), which refers to the number of structural units constituting the procyanidins. The molecular weight and the number of the hydroxyl groups of procyanidins increase exponentially with an increase in the DP, which influences the separation efficiency. The higher the DP, the more difficult the identification, because the number of different potential isomers increases exponentially. The monomers combine to form oligomers, which then undergo further polymerization. Procyanidins are mixtures of oligomers and polymers consisting of the monomers, (+)-catechin and/or (-)-epicatechin (Fig. 1B) (Bittner et al., 2013). Generally, depending on the number of monomers present participating in the polymerization process, procyanidins with low DP were called oligomers, while procyanidins with high DP are called polymers (Esatbeyoglu et al., 2015; Huang et al., 2010; Luo et al., 2018). Dimeric procyanidins are subclassified into types A and B depending on the stereo configuration and the linkage between monomers (Rue et al., 2018). Only one interflavan bond exists between type B procyanidin monomers and they are linked by the C4–C8 or C4–C6 bonds (Fig. 1C and D). Type A procyanidins have two linkages, which include a C4–C8 bond and an additional ether bond (C2–O–C7 or

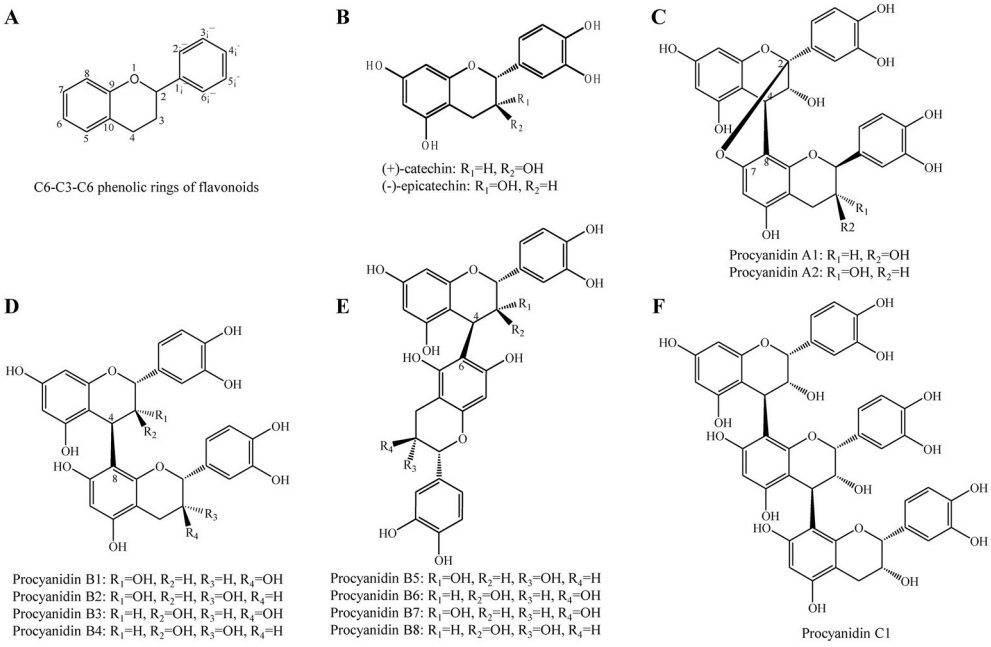

Fig. 1. Structures of oligomeric procyanidins. (A) C6–C3–C6 phenolic rings of flavonoids, (B) Monomer: (+)-catechin and (-)-epicatechin, (C) A-type dimer procyanidins linked with double C4→C8 and C2–O–C7 linkages, (D) B-type dimer procyanidin linked with a single C4→C8, (E) B type dimer procyanidin linked through C4→C6 linkage, (F) Trimer procyanidin C1.

C2–O–C5 linkage) (Fig. 1E) (Tsao, 2010). Fig. 1F shows an example of a trimer procyanidin, called procyanidin C1, which is composed of epicatechin-(C4β-C8)-epicatechin-(C4β-C8)-epicatechin.

The structures of mono- and oligomeric procyanidins are shown in Fig. 1. The number of different isomers of procyanidins increases exponentially when the DP of procyanidins increase. Owing to the lack of effective analytical methods, obtaining pure polymers with a high DP is difficult. Therefore, studies on polymeric procyanidins are limited. Moreover, the separation composition and structures of procyanidins vary between methods (Gu et al., 2002; Labarbe et al., 1999; Sun et al., 1999). Based on the different physiochemical properties of procyanidins, the current methods for their separation and identification mainly include high-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectrometry (LC-MS/MS), matrix-assisted laser desorption ionization (MALDI), and nuclear magnetic resonance (NMR) (Abe et al., 2008; Rue et al., 2018). Furthermore, the characterization of procyanidin oligomers and polymers, such as average molecular weight, composition, and qualification, can be performed by HPLC following thiolysis and phloroglucinolysis (Gardana & Simonetti, 2019; Guyot et al., 2001; Ramirez-Coronel et al., 2004).

3. Sources and distribution of procyanidins

Procyanidins are secondary metabolites commonly found in plants. Fruits, cereals, beans, and nuts are the main sources of procyanidins. Most research is centered on procyanidins and involves procyanidin-rich fruits such as blueberries, strawberries, apples, grapes, kiwis, cranberries, cherries, apricots, and mangoes (Feliciano et al., 2012; Hollands et al., 2018; Luo et al., 2018; Ma et al., 2018; Mannozzi et al., 2018; Nemes et al., 2018; Ramirez et al., 2014; Ruiz et al., 2005; Zhu et al., 2019). Some major cultivated crops such as barley, sorghum, red rice, soybeans, and cocoa are also rich in procyanidins (Esatbeyoglu et al., 2015; Gangopadhyay et al., 2016; Hibi & Yanase, 2019; Wang et al., 2018; Zhao et al., 2018). Nuts such as almonds, hazelnuts, walnuts, pistachios, and peanuts are also important sources of procyanidins (Bansode et al., 2014; Grace et al., 2014; Ojeda-Amador et al., 2019; Schmitzer et al., 2011; Tsujita et al., 2013). Procyanidins are distributed throughout the plant and are found in the seeds, leaves, fruits, flowers, skins, and shells. Moreover, some plant-based processed drinks based such as fruit juices, wine, and beer are also rich in procyanidins (Caton et al., 2010; Longo et al., 2019; Madigan et al., 1994).

Different types of procyanidins are found in plants. Type B procyanidins are abundant in grapes, blueberries, cocoa, sorghum, and apples (Gu et al., 2002, 2003), while plums, avocados, peanuts, curry, cinnamon, and cranberries are identified as potential sources of type A procyanidins (Gu et al., 2003). The total content of procyanidins and the distribution of oligomers and polymers across different plants vary greatly. Cashew and black bean plants contain only monomers and dimers, whereas procyanidins with different DP are widely distributed in most plants (DP up to 33) (Gu et al., 2004). The amounts and DP of procyanidins also vary greatly in different tissues of the same plant. For example, the seeds of grape contain higher concentrations of monomers and oligomers than the skin, but the DP of procyanidins in the skin is much higher than that of seeds (Kennedy & Jones, 2001; Labarbe et al., 1999; Souquet et al., 1996), and is easier to be transferred into wine (Sun et al., 1999). It is reported that the level of monomers, dimers, and trimers in grape is 76.93–133.18 mg/L in wine, 2.30–8.21 mg/g in grape seeds, and 0.14–0.38 mg/g in grape skins, respectively, while the mean degree of polymerization (mDP) is 6.3–13.0 for wine, 6.4–7.3 for grape seeds, and 33.8–85.7 for grape skins, respectively (Monagas et al., 2003)

4. Bioavailability, biological activities, and action mechanisms of procyanidins

Procyanidins have been widely studied in recent years and their biological activities and mechanisms of action are constantly being elucidated. In previous studies, the positive correlation between procyanidins consumption and reduced risk of diseases, as well as free radical scavenging, anticancer, and anti-inflammatory effects of procyanidins, has been reported, which can be attributed to the presence of a large number of phenyl hydroxyl groups (Gonthier et al., 2003). More importantly, these activities may be related to the structure of the procyanidin moiety and their DP (Sun et al., 1998). Since the DP-activity relationship appears to be system dependent, the correlation between structures and biological activities of procyanidins cannot be broadly summarized (Bitzer et al., 2015). In most cases, the activities of procyanidins are proportional to DP, but some cases show a reverse trend (Andriambeloson et al., 1998). Moreover, in some systems, there appears to be an “optimum DP” above and below which, the procyanidin activity is reduced (Bitzer et al., 2015). Multiple studies have reported the potential underlying mechanisms and the contribution of DP on their beneficial effects (Bak et al., 2016; Oteiza et al., 2018). The small amount of free dimer to tetramer procyanidins are absorbable in rat plasma, reaching the maximum concentration at 1 h after injection (Serra et al., 2010; Shoji et al., 2006). Therefore, the polymers may be passively transported through the epithelium by the paracellular route based on their hydrophilic character, which may maintain their parental structures to preserve biological ability (Appeldoorn et al., 2009). Especially, dimers may contribute to systemic effects of procyanidins, and it has previously been shown that oligomers such as procyanidin A1, A2, and B2 can be absorbed without conjugation or methylation, thereby conserving the biological activity after absorption (Appeldoorn et al., 2009). However, the oligomer absorption rate is less than 10% of monomers. The bioavailability of them depends on their structures, interactions with other food components, activities of gastrointestinal (GI) enzymes and gut microbiota compositions, etc. In general, procyanidins can be either absorbed directly at the GI tract with or without modification, such as sulfation and methylation, and/or reacted into small metabolites by GI enzymes or microbiota, which further exert their beneficial activities in models, such as beta cells, skeletal muscle, and endothelial cells (Oteiza et al., 2018). So far, no concrete conclusions can be drawn about the relationship between DP and activities of procyanidins because of the system-dependency. However, in several studies, some ideas were presented to explain the contribution of DP on the beneficial effects. Under anaerobic conditions, polymeric procyanidins can be degraded to low molecular weight metabolites by human fecal microflora within 48 h (Gonthier et al., 2003). Procyanidins showed high stability under gastric and duodenal digestion conditions, and most procyanidins reached the colon in an intact form and were degraded by gut microbiota to play a role in disease prevention (Ou & Gu, 2014; Serra et al., 2010; Tao et al., 2019). However, in some studies, the potential underlying mechanisms that involved high molecular weight polymeric procyanidins that had a direct effect without degradation were shown. For example, polymers are most effective for preserving membrane integrity and preventing loss of gut barrier function compared with mono- and oligomeric procyanidins from cocoa, thereby reducing epithelial inflammatory cytokine secretion, including interleukin-8, which is closely associated with inflammatory bowel disease and colon cancer (Bitzer et al., 2015). Moreover, no conjugation or methylation of oligomeric procyanidins were observed *in vivo*, to conserve biological activity, this might partly compensate the lower absorption compared with monomeric procyanidins (Appeldoorn et al., 2009; Shoji et al., 2006). Furthermore, the synergistic effect indicated that the bioavailability of oligomeric procyanidins might be underestimated (Appeldoorn et al., 2009). Therefore, increasing the bioavailability of procyanidins *in vivo* may be required to maximize the benefits of procyanidins. Here, we summarized the relationship between the DP and bioactivities of procyanidins and described the activities and their potential mechanisms of action in detail according to the disease types (Table 1).

Table 1
Biological activities and related mechanisms of procyanidins.

Bioactivity	Compound	Plant sources	Model	Mechanism	Reference
Antioxidant and scavenging free radicals	Procyanidins	*Vitis vinifera* seed	Healthy human	Spare liposoluble vitamin E and reduce DNA oxidative damage	Simonetti et al. (2002)
	Procyanidins	Lotus seedpod	ELF-EMF induced oxidative stress injury in ICR mice	Increase activities of SOD, CAT, GSH-Px, GR and GST and decrease MDA activity	Luo et al. (2016)
	Procyanidins	Wild grape seed (*Vitisa murensis*)	Ethanol-induced SD rat models	Regulate antioxidant enzymes and alcohol metabolism systems via MAPK pathways	Bak et al. (2016)
	Procyanidin B2	–	Human umbilical vein endothelial cells (HUVEC)	Improve the bioactivity of nitric oxide and inhibit NADPH oxidase	Steffen et al. (2008)
	Procyanidin B1	Lotus seed skin	High fat diet-induced mice and HepG2 cells	Enhance Nrf 2 nuclear translocation, Nrf 2–ARE binding and ARE transcriptional activity	(Li et al., 2018)
Anti-cancer	Procyanidins	Grape seed	In A431 cell xenografts mouse model	Decrease the levels of PI3K, inhibit the constitutive activation of NF-κB/p65	Meeran and Katiyar (2008)
	Procyanidins	Apple	Colon tumor rat model and human metastatic colon carcinoma cells	Inhibit activity of protein kinase C, enhance ERK1/2 and JNK expression, and down-regulate activation of caspase-3	Gossé et al. (2005)
	Procyanidin B2	–	Hodgkin's lymphoma (H-RS) cells	Inhibit the expression of NF-κB-driven genes, including inflammatory cytokines and anti-apoptotic proteins, inhibit the binding of NF-κB to DNA	Mackenzie et al. (2008)
		e			
Anti-atherosclerosis	Procyanidins Procyanidin B2	Cocoa	Human aortic VSMC	Inhibit expression of pro-MMP-2 in VSMC and membrane type-1 (MT1)-MMP activity	Lee et al. (2008)
	Procyanidins	*Litchi pericarp*	ApoE knockout mice fed by high fat diet	Reduce excess NO production, iNOS expression, and oxidative stress through NADPH oxidase-dependent mechanisms	Rong et al. (2017)
	Procyanidins	Apple	Atherogenic diet-induced rabbit model	Increase ABCA1 expression	Wang et al. (2017)
Vasodilation improvement	Procyanidin B2	–	NOS inhibitor-induced rat hypertension model	Downregulate of Ang II type 1 receptor and NADPH oxidase subunit	Ding et al. (2018)
	Procyanidins Trimer C1	–	Rat aortic endothelial cells	Induce NO production via large-conductance Ca^{2+}-activated K^+ and PI3K/Akt pathways	Byun et al. (2012)
	Procyanidin B2	–	Human umbilical vein endothelial cells	Suppresses activation of NLRP3 inflammasome, production of ROS and transcriptional activity of AP-1	Yang et al. (2014)
Diabetes prevention	A-type and B-type oligomeric procyanidins	A-type from litchi pericarp B-type from lotus seedpod	STZ-induced diabetic mice fed with high fat diet	Improve glucose homeostasis by increasing the expression of GLUT, insulin receptor α protein in liver and muscle tissues, activate glucose metabolism-related enzymes	Li, Wang, et al. (2016)
	Dimer to tetramer procyanidins	Black soybean seed coat	ICR mice given glucose orally	Activate insulin and AMPK signaling pathways and promote GLUT4 in muscle	Yamashita et al. (2016)
	Catechins	Cocoa	INS-1 832/13 β-cells and primary rat islets	Improve the redox state of β cells, leading to Nrf 2 nuclear migration and up-regulate expressions of mitochondrial respiration, increase insulin secretion	Rowley et al. (2017)
	B-type procyanidins	*Astilbe thunbergii*	GK/Slc rats administered starch, sucrose, or glucose orally	Inhibit pancreaticα-amylase	Kato et al. (2017)
	(-)-Epicatechin		High-fructose induced metabolic syndrome rat model	Mitigates IR by modulating redox signaling and ER stress	Bettaieb et al. (2014)
Anti-obesity	Procyanidins	Bayberry leaves (*Myrica rubra* Sieb.et Zucc.)	High fat diet-induced obese rat	Up-regulate the expression of SIRT1 and BMP4 and the brown fat level, down-regulate C/EBP-α expression	Zhou et al. (2017)
	Procyanidins	Cacao liquor	High fat diet induced C57BL/6 mice	Activate AMPKα signaling pathway, up-regulate uncoupling protein expression and adiponectin secretion	Yamashita et al. (2012)
	Oligomeric procyanidins	Apple	Mice orally administered corn oil and human administered diet containing fat (40 g)	Inhibit pancreatic lipase and triglyceride absorption	Sugiyama et al. (2007)
	Highly polymeric procyanidins	Apple	High fat/high sucrose diet induced C57BL/6J mice	Attenuate weight gain and inflammation, decrease *Firmicutes/Bacteroidetes* ratio in gut microbiota	Masumoto et al. (2016)
	Procyanidin B2	–	High fat-cholesterol diet induced male rabbits	Improve *Bacteroidetes/Akkermansia* ratio in gut microbiota	Xing et al. (2019)
Prevention of Alzheimer's disease	Procyanidins	Apple	PC-12 cells	Suppress amyloid *β*-protein aggregation	Toda et al. (2011)
	Polyphenolic	Grape seed	JNPL3 transgenic mice	Interferes tau aggregation	Santa-Maria et al. (2012)
	Polyphenolic extract	Grape seed	The ultrastructure of paired helical filaments (PHFs) isolated from Alzheimer's disease brain	Disrupt and disintegrate the ultrastructure of native PHFs found in AD brain	Ksiezak-Reding et al. (2012)
Insomnia improvement	Procyanidins B2	Lotus seedpod	Chlorophenylalanine induced insomniac rat	Regulate NO/ADMA/DDAH pathway by inhibiting oxidative stress	Xiao et al. (2019)
Anti-virus	Catechin procyanidin B2	-	Feline calicivirus (FCV–F9) Murine norovirus (MNV-1)	Alters capsid structure by binding to human norovirus-like particles, decreases infectivity of human norovirus	Liu et al. (2018)
	Procyanidins	Larch bark	*Staphylococcus aureus (S. Aureus)*		Li et al. (2017)

(*continued on next page*)

Table 1 (*continued*)

Bioactivity	Compound	Plant sources	Model	Mechanism	Reference
				Damage integrity and permeability of cell wall and cell membrane, affect protein synthesis and bind to DNA	
Pain relief	Procyanidins	Grape seed	Monosodium urate induced CD-1 mice *in vivo* and RAW 264.7 cells *in vitro*	Attenuate gout pain and suppress ankle swelling; inhibit NLRP3 inflammasome and increase of IL-1β	Liu et al. (2017)
Neuroprotection	Procyanidin B2	-	High-glucose-cultured dorsal root ganglion (DRG) neuron	Improve oxidative stress, neuronal regeneration, and the cell viability of DRG neurons, inhibit neuronal apoptosis via PI3K/Akt signaling pathway	Zhang et al. (2018)

5. Antioxidant and free radical scavenging activity

Free radicals are normal products of many metabolic pathways, but excess free radicals promote lipofuscin formation, mitochondrial DNA mutation, cell apoptosis, and reduction of protein synthesis, which in turn could cause cancer, Parkinson's disease, and various cardiovascular diseases (Kehrer & Klotz, 2015). Through endogenous and exogenous mechanisms, procyanidins exhibit strong antioxidant and free radical scavenging activity owing to their unique molecular stereostructure and the presence of a large number of phenyl hydroxyl groups in their molecular structure (Fig. 2). An epidemiological study showed that procyanidins administered to healthy volunteers at a dose of 110 mg/day for 30 days, exerted antioxidant effects by sparing the fat-soluble vitamin E and reducing DNA oxidative damage when compared with the volunteers in the placebo group (Simonetti et al., 2002). Experiments in mice show that lotus-seedpod procyanidins can effectively prevent oxidative stress injury induced by exposure to extremely low-frequency electromagnetic fields (ELF-EMF) and significantly enhance superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GSH-Px), and glutathione-*S*-transferase (GST) activity, and thus reduce lipid peroxidation (Luo et al., 2016). Interestingly, procyanidins from wild grape seed regulate the antioxidant enzymes and alcohol metabolism in Sprague Dawley (SD) rats by means of the mitogen-activated protein kinase

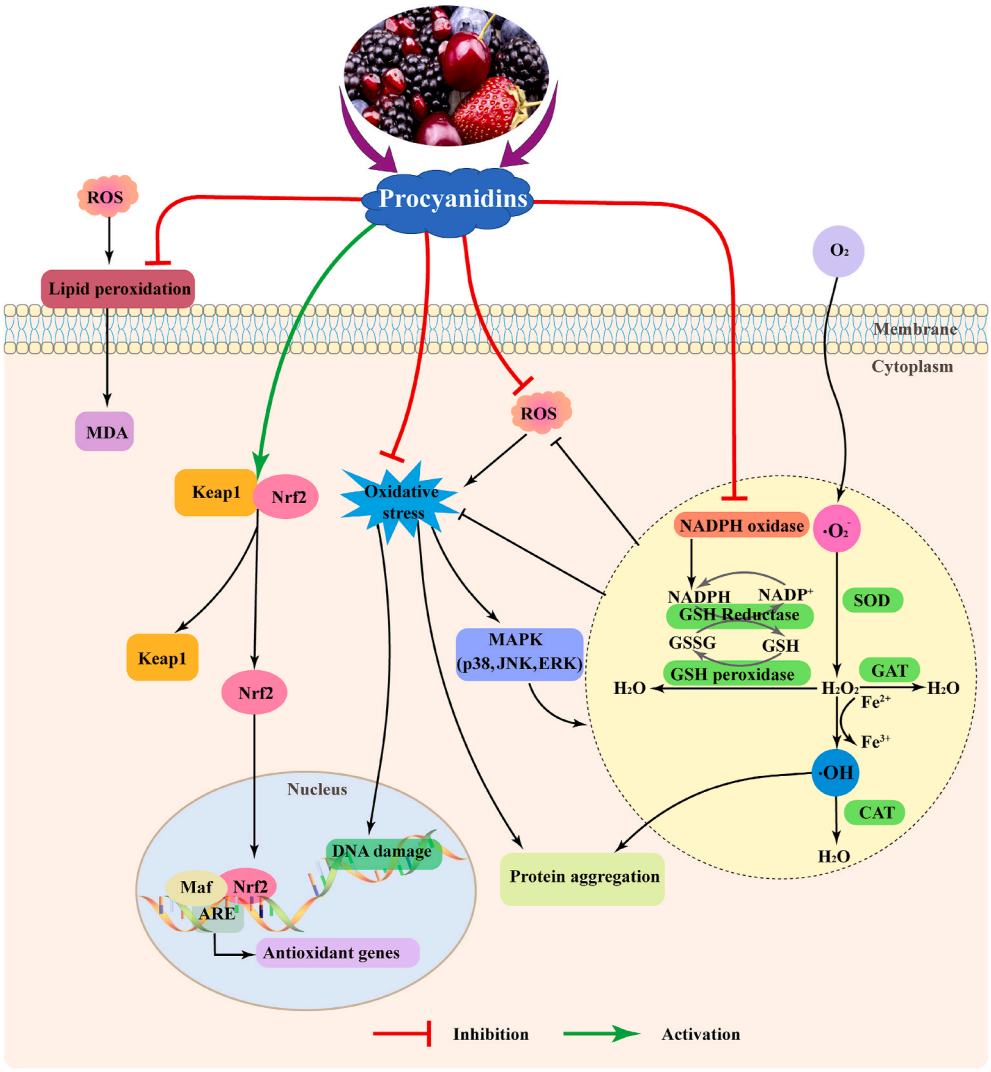

Fig. 2. Proposed mechanisms of antioxidation by procyanidins.

(MAPK) pathway, which reduces the levels of aspartate transaminase, alanine transaminase, and alcohol in serum induced by ethanol, indicating a hepatoprotective effect (Bak et al., 2016). A study reports that procyanidin dimer B2 (PB2) not only scavenges superoxide anion radicals but also inhibits NADPH oxidase in human umbilical vein endothelial cells (Steffen et al., 2008). The antioxidant and free radical scavenging mechanisms of procyanidins have been studied using procyanidin mixtures in previous studies (Huang, 2010; Kaur et al., 2006). Current studies focus on the evaluation of simple monomers/oligomers. PB2 protects neurons from the process of oxidative stress, nitrosation, and excitotoxic stress by the removal of oxygen and nitrogen species (Sutcliffe et al., 2017). PB2 also alleviates free fatty acid-induced hepatic steatosis and promotes lipid degradation by regulating the transcription factor EB (TFEB)-mediated lysosomal pathway and redox state (Su et al., 2018). Moreover, the procyanidin B1 (PB1) significantly enhances the expression of the antioxidant protein by activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidative response element (ARE) *in vitro* (Li et al., 2018).

The structures and DP of procyanidins are closely related to their capacity of antioxidation and free radical scavenging. For example, the scavenging ability for 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals of A-type oligomeric procyanidins from the pericarp of *Litchi chinensis* is as follows: epicatechin < dimer < trimer (Li et al., 2012). The antioxidant activity of mangosteen pericarp tannins increases when the mDP is 2.71–9.27, but decreases when it is 16.80 (Zhou et al., 2011). On the other hand, certain highly polymerized tannins containing several hydroxyl groups are found to be more potent as antioxidants than monomeric phenolics (Hagerman et al., 1998). Moreover, the antioxidant effects of purified catechin monomer and procyanidins (dimer to hexamer) from cocoa were investigated in two different systems. The results show that procyanidins with higher molecular weights are most efficacious when oxidation is initiated in the lipid domains, probably because these molecules insert into the lipid membrane and show a better protection against oxidative stress in both, hydrophobic and hydrophilic domains. However, monomers, dimers, and trimers are most effective as antioxidants when liposomes begin to oxidize in the aqueous phase (Lotito et al., 2000). No differences are observed between monomer, dimers, and trimers from wild berries of *Vaccinium* species in their free radical scavenging or antioxidant activities during the oxidation of methyl linoleate emulsion (Määttä-Riihinen et al., 2005), indicating that the DP of procyanidins affects differently on antioxidant abilities depending on the test system, sources, and types of procyanidins. It should be pointed out that the results of *in vitro* study correlated in part with the *in vivo* studies. However, the *in vitro* systems do not consider or mimic the digestion and absorption of procyanidins. Therefore, that they have flaws for evaluating the bioactivities of procyanidins, especially with a high DP (DP > 3). Although procyanidins with a high DP can have a direct effect according to literature mentioned above (Appeldoorn et al., 2009; Bitzer et al., 2015; Gonthier et al., 2003; Oteiza et al., 2018; Ou & Gu, 2014; Serra et al., 2010), most procyanidins are barely absorbed directly. Therefore, *in vitro* studies using procyanidins with a high DP cannot fully contribute and should be less contribution to estimate the relationship between bioactivities and the DP of procyanidins. It would be preferred to design experiments based on the GI tract system, which may be related to intestinal/mucin models and/or the microbiome. Modification and small metabolites of procyanidins as well as the bioavailability of procyanidins should also be evaluated.

6. Anticancer activity

Numerous studies have shown that procyanidins prevent or inhibit the growth of various cancer types, including colon cancer, breast cancer, and endometrial cancer (Rossi et al., 2013; Theodoratou et al., 2007). Importantly, human studies have been shown a statistically significant decreased risk of colon cancer with the intake of procyanidins (Theodoratou et al., 2007). Similarly, in an Italian case-control study, it was confirmed that high consumption of procyanidins reduced the risk of hormone-related cancer, including endometrial cancer (Rossi et al., 2013). Particularly, procyanidins with a high DP > 3 from bean soups, chocolate, pulses, and grapes were more inversely associated with the risk of endometrial cancer in normal-weight women compared to other class of flavonoids. A certain amount of pure procyanidins is needed for *in vivo* studies. However, this is difficult to prepare. Therefore, the potential mechanisms of either using crude procyanidin extract in an *in vivo* system or using pure procyanidin components *in vitro* systems were studied. In one human pilot study, it was demonstrated that treatment with a smaller size of oligomeric procyanidins for 3 months significantly decreased the bronchial Ki-67 proliferative labeling index as well as serum levels of miR-19a, −19b, and −106b, indicating that procyanidins are antineoplastic agents against lung cancer (Mao et al., 2019; Xue et al., 2018). PB1 has been reported to suppress the growth of liver cancer via inhibiting the Kv10.1 channel in a xenograft mouse model (Na et al., 2020). Moreover, the protection of anti-tumor immune responses by procyanidins may also contribute to their anti-tumor activities (Zhang et al., 2017). Procyanidins achieve this anti-tumor effect not only by virtue of their antioxidant properties, but also via inducing apoptosis and inhibiting tumor cell proliferation through regulation of inflammatory pathways (David et al., 2019) (Fig. 3). Polyphenols from apples contain oligomers/polymers without monomers, significantly reduced the number of preneoplastic lesions, hyperproliferative crypts, and aberrant crypts in a colon tumor rat model (Gossé et al., 2005). The molecular mechanism probably involves the inhibition of protein kinase C activity to enhance the expression of extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun *N*-terminal kinase (JNK), down-regulation of polyamine biosynthesis, and activation of caspase-3 by procyanidins (Gossé et al., 2005). In addition, grape seed procyanidins inhibit tumor cell proliferation in xenograft mouse models, and the underlying mechanisms involve PI3K and MAPK-signaling pathways, and the inhibition of NF-κB/p65 activation (Meeran & Katiyar, 2008). In addition, PB2 interacted with NF-κB protein in Hodgkin's lymphoma cells *in vitro* and inhibited the binding of NF-κB to DNA (Mackenzie et al., 2008). The plausible mechanism of action can be attributed to the inhibition of the expression of NF-κB-driven genes, including cytokines (IL-6, TNF-α, and RANTES) and anti-apoptotic proteins (Bcl-xL, Bcl-2, XIAP, and cFLIP) by the procyanidins (Mackenzie et al., 2008). Grape seed procyanidins inhibit tumor growth *in vivo* and *in vitro* by increasing the protein levels of the cycle-dependent kinase inhibitor Cip1/p21 and decreasing the levels of cyclins and CDKs associated with the G1 phase of HT29 and LoVo human colon cancer cells (Kaur et al., 2006).

Multiple studies have reported that procyanidins with different DP have varying anticancer effects, although these results are sometimes contradictory. The oligomeric and polymeric procyanidins from apples, rather than the monomeric and dimeric procyanidins, showed more potent anti-proliferative activities (Pierini et al., 2008). Moreover, the antiproliferative effect of procyanidins from grapes and pine bark in HT 29 colon cancer cells increases with an increase in saccharification and DP from monomers to oligomers (DP = 2–3) (Lizarraga et al., 2007). However, the cellular antioxidant activity of procyanidins isolated from *C. axilleum* peels decreases with an increase in DP (Li, Sui, et al., 2016). Interestingly, procyanidins isolated from apples dramatically suppress the melanin production in melanoma cells and the inhibitory ability of the procyanidins is reported as follows: tetramer < pentamer < trimer (Shoji et al., 2005).

7. Prevention of cardiovascular diseases

Cardiovascular disease (CVD) is a collective term for several diseases of the circulatory system. At present, the primary and secondary prevention of CVD mainly relies on a healthy diet including increasing the intake of plant-based foods. Studies have shown that dietary plants provide a large number of phytochemicals, especially procyanidins and flavonoids, which reduce the risk of CVD (Deka & Vita, 2011; Ding et al.,

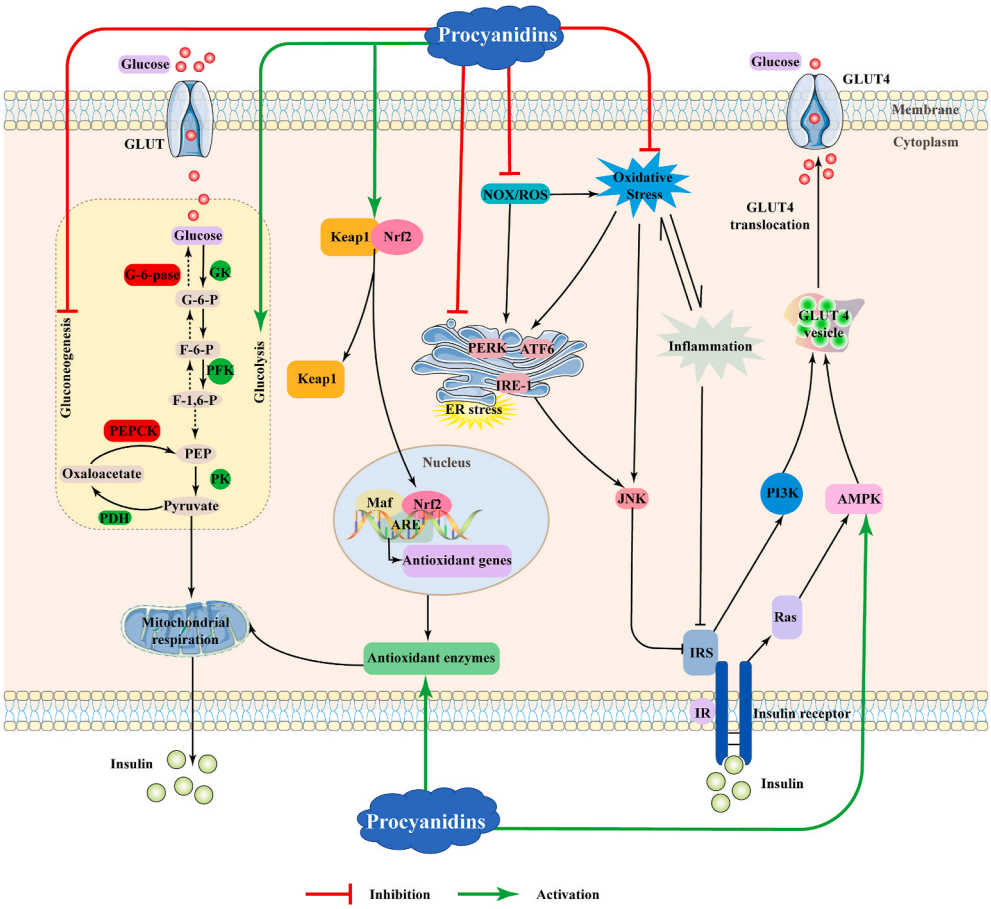

Fig. 3. Proposed anti-cancer mechanisms of procyanidins.

2006; Mukamal et al., 2002). Moreover, procyanidins alleviate CVD-related metabolic syndromes such as atherosclerosis, hypertension, endothelium-dependent vasomotor function, and myocardial ischemia-reperfusion injury in the cardiovascular system (Fig. 4).

7.1. *Anti-atherosclerotic activity*

Atherosclerosis (AS), a main pathological basis of cardiovascular disease (CVD), is considered an inflammatory disease that is characterized by endothelial dysfunction, fatty deposits, build-up and oxidation of LDL, and maturation of the atherosclerosis lesion (Santhakumar et al., 2018). A number of studies have shown that procyanidins can reverse AS through different mechanisms. Clinical trials have shown that administration of tablets containing a high content of procyanidins from grape seeds for 12 weeks reduced oxidized LDL levels to alleviate the occurrence of AS (Sano et al., 2007). The procyanidin fraction of Cocoa and PB2 also exert chemical protection against CVD and AS by inhibiting the thrombin-induced pro-MMP-2 activation and expression (Lee et al., 2008). In addition, procyanidins not only attenuate oxidative stress through NADPH oxidase-dependent mechanism, but also improve the formation of atherosclerotic plaques by reducing the overproduction of nitric oxide (NO) and the expression of inducible nitric oxide synthase (iNOS) in high fat diet induced-apolipoprotein E () knockout (ApoE) mice (Rong et al., 2017; Zhou et al., 2018). Furthermore, apple procyanidins reversed AS by activating ATP-binding cassette A subfamily A member 1 (ABCA 1) in a cholesterol-induced AS rabbit model (Wang et al., 2017).

7.2. *Vasodilation improvement*

Hypertension is a high-risk factor in CVD resulting in high morbidity and mortality (Horowitz et al., 2015). Studies have shown that the low molecular weight procyanidins from grape seeds reduce hypertension in spontaneously hypertensive rats, and the mechanism may be related to increase the bioavailability of endothelial NO, thereby improving endothelial dysfunction (Belcaro et al., 2013; Draijer et al., 2015; Quiñones et al., 2013, 2014). A similar mechanism in reducing hypertension induced by a nitric oxide synthase inhibitor is encountered in the PB2-treated hypertensive nephropathy rat model (Ding et al., 2018). Procyanidin trimer C1 (PC1) promoted NO production in aortic endothelial cells of rats via hyperpolarization and the PI3K/Akt pathway *in vivo* (Byun et al., 2012). However, (-)-epicatechins improved vascular oxidation and inflammation caused by chronic nitric oxide deficiency in rats, but was not efficacious in attenuating hypertension (Gómez-Guzmán et al., 2011). Moreover, our group found that PB2 inhibits NLRP3 inflammasome activation via suppression of AP-1 pathway in human endothelial cells, indicating the potential anti-inflammatory and anti-cardiovascular bioactivity of PB2 (Yang et al., 2014).

8. Prevention of insulin resistance and diabetes

Diabetes is mainly caused by insufficient insulin secretion and insulin resistance (IR) and is often accompanied by serious complications and multiple organ dysfunctions during the progress of the disease. Procyanidins from the diet prevent the development and progression of diabetes through different mechanisms, including regulation of protein expression in the glucose delivery system, increasing glycolysis, and inhibiting gluconeogenesis in liver and skeletal muscles to improve

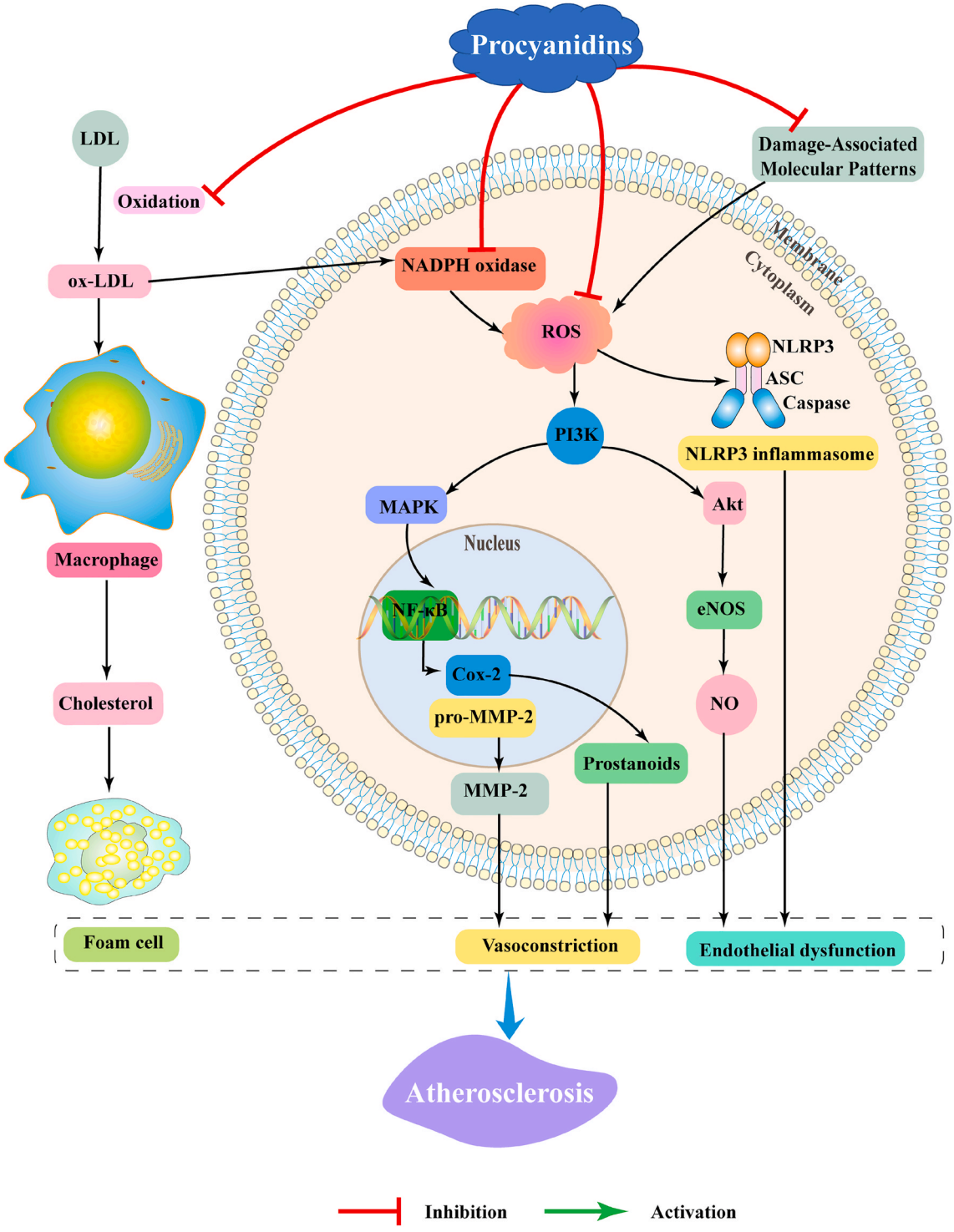

Fig. 4. Schematic representation of mechanisms on prevention of cardiovascular diseases by procyanidins.

glucose balance (Fig. 5)(Xiao, 2020). Studies have shown that type A oligomeric procyanidins from litchi pericarp and type B oligomeric procyanidins from lotus seedpod improve glucose homeostasis in diabetic mice by increasing the expression of glucose transporter (GLUT) and insulin receptor α protein in liver and muscle tissues, and activating a series of enzymes related to glucose metabolism (Li, Sui, et al., 2016). Similarly, after long-term dietary administration of high fat-induced obesity and type 2 diabetes mouse model, oligomeric cocoa procyanidins have been shown to be the most effective components in improving weight gain, fat mass, glucose tolerance, and insulin resistance compared with monomeric or polymeric procyanidins. The potential underlying mechanisms of poorly absorbed oligomeric procyanidins in the gut may act to further inhibit the absorption of macronutrients, increase the secretion of glucagon-like peptide-1 (GLP-1), which drives insulin secretion, and inhibit metabolic endotoxemia (Dorenkott et al., 2014). Thus, oligo- and polymeric procyanidins may exert anti-diabetes activities by stimulating glycogen synthesis and glucose uptake in skeletal muscle (Bowser et al., 2017). The purified dimeric, trimeric, and tetrameric procyanidins from the seed coat of black soybeans when administered to ICR mice show significant improvement in

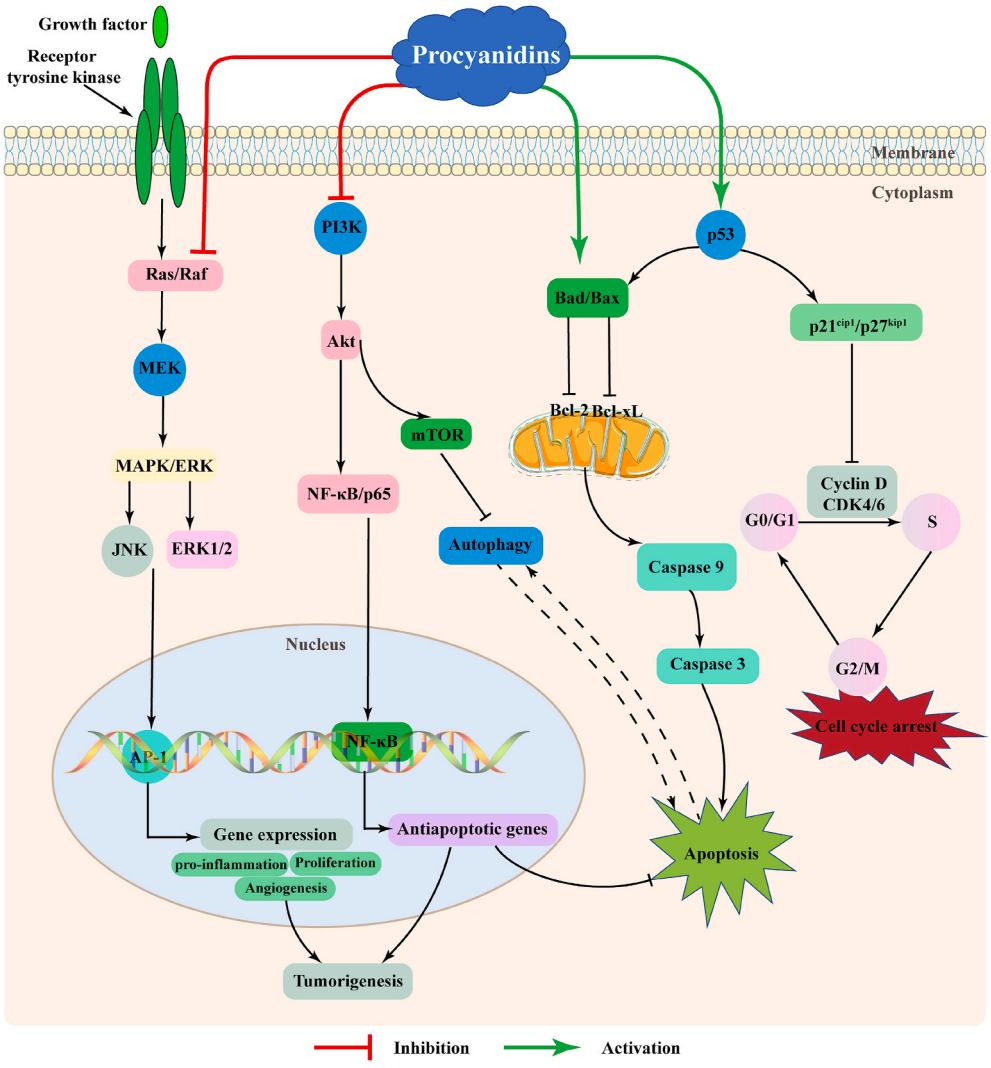

Fig. 5. Proposed anti-diabetes mechanisms of procyanidins.

hyperglycemia by activating the insulin and AMPK signaling pathways and promoting the transport of glucose transporter 4 (GLUT4) in the muscle (Yamashita et al., 2016). Moreover, catechins improve the redox state of the pancreatic β-cells, bring about Nrf2 nuclear migration, upregulate the gene expression that is critical in mitochondrial respiration, increase insulin secretion, and ultimately improve β-cell function in primary islets in rat model (Rowley et al., 2017). Grape seed procyanidins modulate apoptosis and proliferation of β-cells, improve IR, and counteract insulin synthesis in rats (Cedó et al., 2013). In addition, highly condensed procyanidins from *Astilbe thunbergii* potently inhibit pancreatic α-amylase and significantly reduce postprandial hyperglycemia in type 2 diabetic rats (Kato et al., 2017). Studies have also shown that (-)-epicatechin mitigated high-fructose-induced IR by reducing endoplasmic reticulum stress in rat liver and adipose tissue, downregulated JNK phosphorylation in rat liver, hepatocytes and adipocytes, and decreased the expression of protein kinase R-like ER kinase (PERK) and inositol-requiring enzyme-1α (IRE-1α) protein (Bettaieb et al., 2014).

9. *Anti-obesity activity*

Obesity is a metabolic condition with a high probability of developing into the metabolic syndrome in which cholesterol, lipid, and glucose levels increase, thus leading to diabetes and heart diseases. Procyanidins exert anti-obesity effects through different molecular mechanisms (Fig. 6). The extract of procyanidins from bayberry leaves can alleviate high fat diet-induced obesity (Zhou et al., 2017). The anti-obesity effect of procyanidins is possibly due to the upregulation of SIRT1 expression, thereby inducing PPAR-γ deacetylation. It also exerts its effect by downregulating the expression of C/EBP-α, upregulating the expression of BMP 4, and increasing the level of brown fat (Zhou et al., 2017). Cacao liquor is rich in procyanidins and exerts anti-obesity effects by activating the AMPKα signaling pathway, upregulating the expression of uncoupling proteins (UCP) in skeletal muscle and adipose tissue, and increasing adiponectin secretion in white adipose tissue in high fat diet-induced obese C57BL/6 mice (Yamashita et al., 2012). Apple polyphenol extract that is rich in procyanidins exhibits anti-obesity effects by inhibiting pancreatic lipase *in vitro* and triglyceride absorption *in vivo* (Sugiyama et al., 2007). However, other investigated polyphenols found in apple polyphenol (e.g. chalcones, catechins, and phenol carboxylic acids) exhibit weak inhibitory activity on pancreatic lipase (Sugiyama et al., 2007). As the DP increases, the anti-obesity activity of procyanidins increases from dimers to pentamers. In addition, intestinal microbes are also a major causative factor of obesity. Treatment with non-absorbable high-polymer apple procyanidins prevents the increase in body weight and visceral fat. These activities are related to the changes induced in the gut microflora including the ratio of microbes/bacteria to the ratio of head colon/bacteria and its regulation of endogenous metabolites (Masumoto et al., 2016). It also reduces inflammation and intestinal permeability via regulation of the

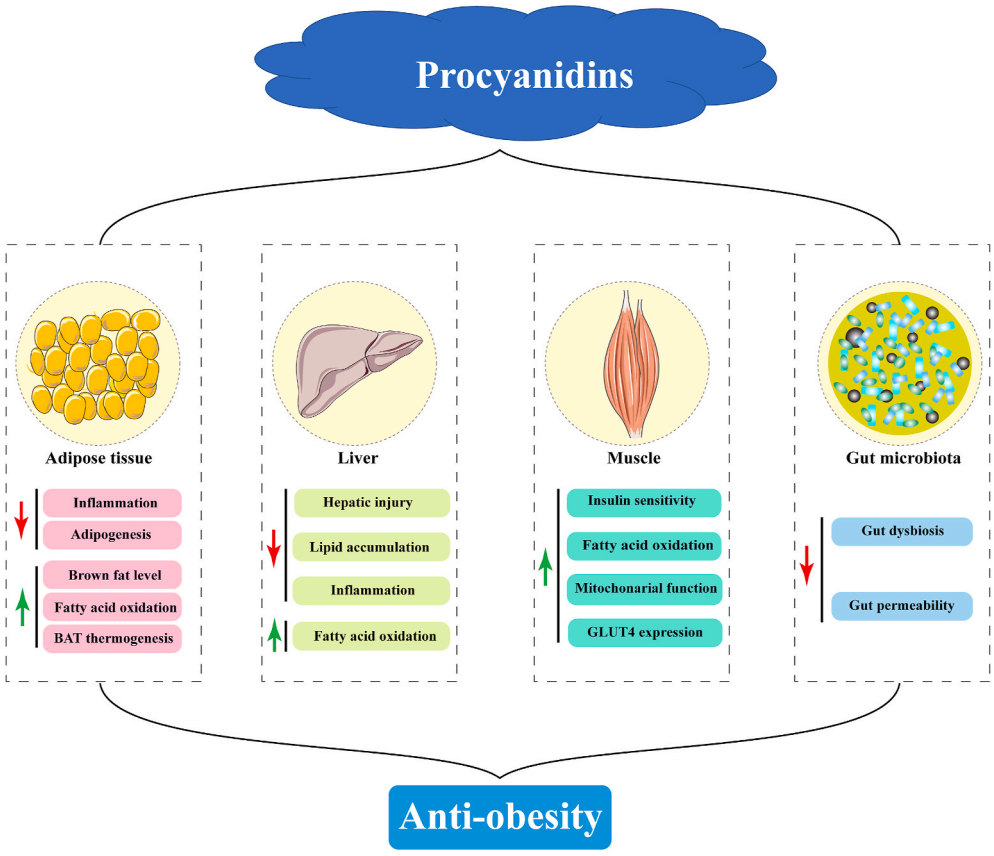

Fig. 6. Proposed anti-obesity mechanisms of procyanidins.

expression of lipid metabolism-related genes and gut microflora in C57BL/6J mice fed with a high fat/high sugar diet (Masumoto et al., 2016). Recently, PB2 was found to modulate gut microbiota by improving the proportions of *Bacteroidetes* at the phylum level and *Akkermansia* at the genus level, which prevented weight gain in a high fat cholesterol fed animal model (Xing et al., 2019).

10. Other bioactivities

Procyanidins are reported as an effective treatment option for Alzheimer's disease (AD). The underlying mechanism is related to the regulation of oxidative stress in brain cells, prevention of lipid peroxidation, and blockage of the production of toxic peptides containing the amyloid precursor protein (APP) processing, amyloid β-protein (Aβ) aggregation, and tau protein aggregation (Ksiezak-Reding et al., 2012; Nehlig, 2013; Santa-Maria et al., 2012; Toda et al., 2011). Procyanidins also ameliorate cognitive function by regulating the CREB-SIRT1 axis, thereby improving AD (Zhao et al., 2019). In previous studies, it was shown that insomnia can be reversed using PB2 of the lotus seedpods, which exert their activity by regulating the NO/ADMA/DDAH pathways (Xiao et al., 2019). The potential antiviral activities of procyanidins have been studied. Our previous study shows that PB2 inhibits the activity of human norovirus by binding directly to the viral capsid protein of the norovirus, thus altering the viral capsid structure and blocking the antigen-binding site (Liu et al., 2018). Larch bark procyanidins strongly inhibit the growth of *Staphylococcus aureus* by damaging the integrity and permeability of the bacterial cell wall and membrane, affecting protein synthesis, and binding to DNA (Li et al., 2017). Recent studies report that the aqueous extracts of *Castanopsis lamontii* are rich in epicatechin and PB2, inhibit the periodontitis pathogen *Porphyromonas gingivalis* and the pharyngitis pathogen β-hemolytic *Streptococcus* (Gao et al., 2019). Grape seed-derived procyanidins significantly reduce pain associated with gout and suppress swelling in the ankle by inhibiting the NLRP3 inflammasome in macrophages (Liu et al., 2017). In addition, PB2 mitigated the neurotoxicity of dorsal root ganglion neurons damage induced by high glucose stimulation via the PI3K/Akt signaling pathway, suggesting the neuroprotective effects of procyanidins (Zhang et al., 2018).

11. Conclusions

Procyanidins are structurally diverse compounds widely found in plants and can be classified as monomeric, oligomeric, or polymeric variants depending on the DP. Since these low molecular weight procyanidins (DP < 3) are completely absorbed in the gastrointestinal tract and relatively easy to be purified, most research is focused on oligomers. All published studies indicate that procyanidins exert various effects that are beneficial to human health depending on several aspects including the source and type of procyanidins and the *in vivo/in vitro* models and biomarkers used in these studies. Importantly, the biological activities of procyanidins vary with their DP. New discoveries shedding light on the relationship between DP and the biological activities of procyanidins are approaches worth considering. The diversity and complexity of these chemical compounds and the difficulties encountered in the isolation of plant procyanidins continue to be major challenges. In addition, the bioavailability of procyanidins is low, especially for macromolecular components (trimers or higher), and thus, methods to improve the bioavailability need to be focused on, in future studies. Moreover, more studies that explore the impact of different DP on the effects of procyanidins are underway, and these may promote the use of phenolic compounds in improving human health.

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References

Abe, Y., Shoji, T., Kawahara, N., Kamakura, H., Kanda, T., Goda, Y., & Ozeki, Y. (2008). Structural characterization of a procyanidin tetramer and pentamer from the apple by low-temperature NMR analysis. *Tetrahedron Letters, 49*(45), 6413–6418. https://doi.org/10.1016/j.tetlet.2008.08.087

Andriambeloson, E., Magnier, C., Haan-Archipoff, G., Lobstein, A., Anton, R., Beretz, A., Stoclet, J. C., & Andriantsitohaina, R. (1998). Natural dietary polyphenolic compounds cause endothelium-dependent vasorelaxation in rat thoracic aorta. *Journal of Nutrition, 128*(12), 2324–2333. https://doi.org/10.1093/jn/128.12.2324

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

Bak, M. J., Truong, V. L., Ko, S. Y., Nguyen, X. N. G., Ingkasupart, P., Jun, M., Shin, J. Y., & Jeong, W. S. (2016). Antioxidant and hepatoprotective effects of procyanidins from wild grape (Vitis amurensis) seeds in ethanol-induced cells and rats. *International Journal of Molecular Sciences, 17*(5), 1–16. https://doi.org/10.3390/ijms17050758

Bansode, R. R., Randolph, P., Ahmedna, M., Hurley, S., Hanner, T., Baxter, S. A. S., Johnston, T. A., Su, M., Holmes, B. M., Yu, J., & Williams, L. L. (2014). Bioavailability of polyphenols from peanut skin extract associated with plasma lipid lowering function. *Food Chemistry, 148*, 24–29. https://doi.org/10.1016/j.foodchem.2013.09.129

Belcaro, G., Ledda, A., Hu, S., Cesarone, M. R., Feragalli, B., & Dugall, M. (2013). Grape seed procyanidins in pre- and mild hypertension: A registry study. *Evidence-based Complementary and Alternative Medicine, 2013*, Article 313142. https://doi.org/10.1155/2013/313142, 2013.

Bettaieb, A., Vazquez Prieto, M. A., Rodriguez Lanzi, C., Miatello, R. M., Haj, F. G., Fraga, C. G., & Oteiza, P. I. (2014). (-)-Epicatechin mitigates high-fructose-associated insulin resistance by modulating redox signaling and endoplasmic reticulum stress. *Free Radical Biology and Medicine, 72*, 247–256. https://doi.org/10.1016/j.freeradbiomed.2014.04.011

Bittner, K., Rzeppa, S., & Humpf, H. U. (2013). Distribution and quantification of flavan-3-ols and procyanidins with low degree of polymerization in nuts, cereals, and legumes. *Journal of Agricultural and Food Chemistry, 61*(38), 9148–9154. https://doi.org/10.1021/jf4024728

Bitzer, Z. T., Glisan, S. L., Dorenkott, M. R., Goodrich, K. M., Ye, L., O'Keefe, S. F., Lambert, J. D., & Neilson, A. P. (2015). Cocoa procyanidins with different degrees of polymerization possess distinct activities in models of colonic inflammation. *Journal of Nutritional Biochemistry, 26*(8), 827–831. https://doi.org/10.1016/j.jnutbio.2015.02.007

Bowser, S. M., Moore, W. T., McMillan, R. P., Dorenkott, M. R., Goodrich, K. M., Ye, L., O'Keefe, S. F., Hulver, M. W., & Neilson, A. P. (2017). High-molecular-weight cocoa procyanidins possess enhanced insulin-enhancing and insulin mimetic activities in human primary skeletal muscle cells compared to smaller procyanidins. *Journal of Nutritional Biochemistry, 39*, 48–58. https://doi.org/10.1016/j.jnutbio.2016.10.001

Bruyne, T. De, Pieters, L., Deelstra, H., & Vlietinck, A. (1999). Condensed vegetable tannins: Biodiversity in structure and biological activities. *Biochemical Systematics and Ecology, 27*(4), 445–459. https://doi.org/10.1016/S0305-1978(98)00101-X

Byun, E. B., Ishikawa, T., Suyama, A., Kono, M., Nakashima, S., Kanda, T., Miyamoto, T., & Matsui, T. (2012). A procyanidin trimer, C1, promotes NO production in rat aortic endothelial cells via both hyperpolarization and PI3K/Akt pathways. *European Journal of Pharmacology, 692*(1–3), 52–60. https://doi.org/10.1016/j.ejphar.2012.07.011

Catalkaya, G., Venema, K., Lucini, L., Rocchetti, G., Delmas, D., Daglia, M., de Filippis, A., Xiao, H., Quiles, J. L., Xiao, J. B., & Capanoglu, E. (2020). Interaction of dietary polyphenols and gut microbiota: Microbial metabolism of polyphenols, influence on the gut microbiota and implications on host health. *Food Frontiers, 1*, 109–133.

Caton, P. W., Pothecary, M. R., Lees, D. M., Khan, N. Q., Wood, E. G., Shoji, T., Kanda, T., Rull, G., & Corder, R. (2010). Regulation of vascular endothelial function by procyanidin-rich foods and beverages. *Journal of Agricultural and Food Chemistry, 58*(7), 4008–4013. https://doi.org/10.1021/jf9031876

Cedó, L., Castell-Auví, A., Pallarès, V., Blay, M., Ardévol, A., & Pinent, M. (2013). Grape seed procyanidin extract improves insulin production but enhances Bax protein expression in cafeteria-treated male rats. *International Journal of Food Science, 2013*, Article 875314. https://doi.org/10.1155/2013/875314

David, I. M. B., de Souza Fernandes, F., dos Santos Silva Ferreira, J. B., Lüdtke, D. D., Martins, D. F., Bobinski, F., da Silva, T. B. G. C., Buffon, L. D., Kopper, M. B. R., da Silva, G. S., Zeferino, R. C., Pedrosa, R. C., & Kviecinski, M. R. (2019). Dietary supplementation with procyanidin-rich Pinus pinaster extract is associated with attenuated Ehrlich tumor development in mice. *Nutrition Research, 62*, 41–50. https://doi.org/10.1016/j.nutres.2018.11.005

Deka, A., & Vita, J. A. (2011). Tea and cardiovascular disease. *Pharmacological Research, 64*(2), 136–145. https://doi.org/10.1016/j.phrs.2011.03.009

Ding, E. L., Hutfless, S. M., Ding, X., & Girotra, S. (2006). Chocolate and prevention of cardiovascular disease: A systematic review. *Nutrition and Metabolism, 3*(Cvd). https://doi.org/10.1186/1743-7075-3-2

Ding, H., Li, X., Li, J., Li, Z., Niu, Y., Ren, W., Tan, J., & Yin, S. (2018). Role of NADPH oxidase pathway in renal protection induced by procyanidin B2: In L-NAME induced rat hypertension model. *Journal of Functional Foods, 47*(June), 405–415. https://doi.org/10.1016/j.jff.2018.04.005

Dorenkott, M. R., Griffin, L. E., Goodrich, K. M., Thompson-Witrick, K. A., Fundaro, G., Ye, L., Stevens, J. R., Ali, M., O'Keefe, S. F., Hulver, M. W., & Neilson, A. P. (2014). Oligomeric cocoa procyanidins possess enhanced bioactivity compared to monomeric and polymeric cocoa procyanidins for preventing the development of obesity, insulin resistance, and impaired glucose tolerance during high-fat feeding. *Journal of Agricultural and Food Chemistry, 62*(10), 2216–2227. https://doi.org/10.1021/jf500333y

Downing, L. E., Ferguson, B. S., Rodriguez, K., & Ricketts, M. L. (2017). A grape seed procyanidin extract inhibits HDAC activity leading to increased Pparα phosphorylation and target-gene expression. *Molecular Nutrition & Food Research, 61*(2), 1–7. https://doi.org/10.1002/mnfr.201600347

Draijer, R., de Graaf, Y., Slettenaar, M., de Groot, E., & Wright, C. I. (2015). Consumption of a polyphenol-rich grape-wine extract lowers ambulatory blood pressure in mildly hypertensive subjects. *Nutrients, 7*(5), 3138–3153. https://doi.org/10.3390/nu7053138

Esatbeyoglu, T., Wray, V., & Winterhalter, P. (2015). Isolation of dimeric, trimeric, tetrameric and pentameric procyanidins from unroasted cocoa beans (Theobroma cacao L.) using countercurrent chromatography. *Food Chemistry, 179*, 278–289. https://doi.org/10.1016/j.foodchem.2015.01.130

Feliciano, R. P., Shea, M. P., Shanmuganayagam, D., Krueger, C. G., Howell, A. B., & Reed, J. D. (2012). Comparison of isolated cranberry (Vaccinium macrocarpon Ait.) proanthocyanidins to catechin and procyanidins A2 and B2 for use as standards in the 4-(dimethylamino)cinnamaldehyde assay. *Journal of Agricultural and Food Chemistry, 60*(18), 4578–4585. https://doi.org/10.1021/jf3007213

Gangopadhyay, N., Rai, D. K., Brunton, N. P., Gallagher, E., & Hossain, M. B. (2016). Antioxidant-guided isolation and mass spectrometric identification of the major polyphenols in barley (Hordeum vulgare) grain. *Food Chemistry, 210*, 212–220. https://doi.org/10.1016/j.foodchem.2016.04.098

Gao, Y., Zhang, X., Yin, J., Du, Q., Tu, Y., Shi, J., & Xu, Y. (2019). Castanopsis lamontii water extract shows potential in suppressing pathogens, lipopolysaccharide-induced inflammation and oxidative stress-induced cell injury. *Molecules, 24*(2). https://doi.org/10.3390/molecules24020273

Gardana, C., & Simonetti, P. (2019). Evaluation of the degree of polymerization of the proanthocyanidins in cranberry by molecular sieving and characterization of the low molecular weight fractions by UHPLC-Orbitrap mass spectrometry. *Molecules, 24*(8). https://doi.org/10.3390/molecules24081504

Gómez-Guzmán, M., Jiménez, R., Sánchez, M., Romero, M., O'Valle, F., Lopez-Sepulveda, R., Quintela, A. M., Galindo, P., Zarzuelo, M. J., Bailón, E., Delpón, E., Perez-Vizcaino, F., & Duarte, J. (2011). Chronic (-)-epicatechin improves vascular oxidative and inflammatory status but not hypertension in chronic nitric oxide-deficient rats. *British Journal of Nutrition, 106*(9), 1337–1348. https://doi.org/10.1017/S0007114511004314

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

Gopalakrishnan, S., Ediga, H. H., Reddy, S. S., Reddy, G. B., & Ismail, A. (2018). Procyanidin-B2 enriched fraction of cinnamon acts as a proteasome inhibitor and anti-proliferative agent in human prostate cancer cells. *IUBMB Life*, 445–457. https://doi.org/10.1002/iub.1735. March.

Gossé, F., Guyot, S., Roussi, S., Lobstein, A., Fischer, B., Seiler, N., & Raul, F. (2005). Chemopreventive properties of apple procyanidins on human colon cancer-derived metastatic SW620 cells and in a rat model of colon carcinogenesis. *Carcinogenesis, 26*(7), 1291–1295. https://doi.org/10.1093/carcin/bgi074

Grace, M. H., Warlick, C. W., Neff, S. A., & Lila, M. A. (2014). Efficient preparative isolation and identification of walnut bioactive components using high-speed counter-current chromatography and LC-ESI-IT-TOF-MS. *Food Chemistry, 158*, 229–238. https://doi.org/10.1016/j.foodchem.2014.02.117

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

Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., Gebhardt, S., & Prior, R. L. (2004). Concentrations of proanthocyanidins in common foods and estimations of normal consumption. *Journal of Nutrition, 134*(3), 613–617. https://doi.org/10.1093/jn/134.3.613

Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., & Prior, R. L. (2003). Screening of foods containing proanthocyanidins and their structural characterization using LC-MS/MS and thiolytic degradation. *Journal of Agricultural and Food Chemistry, 51*(25), 7513–7521. https://doi.org/10.1021/jf034815d

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

Hagerman, A. E., Riedl, K. M., Jones, G. A., Sovik, K. N., Ritchard, N. T., Hartzfeld, P. W., & Riechel, T. L. (1998). High molecular weight plant polyphenolics (tannins) as biological antioxidants. *Journal of Agricultural and Food Chemistry, 46*(5), 1887–1892. https://doi.org/10.1021/jf970975b

Hibi, Y., & Yanase, E. (2019). Oxidation of procyanidins with various degrees of condensation: Influence on the color-deepening phenomenon. *Journal of Agricultural and Food Chemistry, 67*(17), 4940–4946. https://doi.org/10.1021/acs.jafc.9b02085

Hollands, W. J., Tapp, H., Defernez, M., Moral, N. P., Winterbone, M. S., Philo, M., Lucey, A. J., Kiely, M. E., & Kroon, P. A. (2018). Lack of acute or chronic effects of epicatechin-rich and procyanidin-rich apple extracts on blood pressure and cardiometabolic biomarkers in adults with moderately elevated blood pressure: A randomized, placebo-controlled crossover trial. *American Journal of Clinical Nutrition, 108*(5), 1006–1014. https://doi.org/10.1093/ajcn/nqy139

Horowitz, B., Miskulin, D., & Zager, P. (2015). Epidemiology of hypertension in CKD. *Advances in Chronic Kidney Disease, 22*(2), 88–95. https://doi.org/10.1053/j.ackd.2014.09.004

Huang, P. L., Chi, C. W., & Liu, T. Y. (2010). Effects of Areca catechu L. containing procyanidins on cyclooxygenase-2 expression in vitro and in vivo. *Food and Chemical Toxicology, 48*(1), 306–313. https://doi.org/10.1016/j.fct.2009.10.014

Kato, E., Kushibiki, N., Inagaki, Y., Kurokawa, M., & Kawabata, J. (2017). Astilbe thunbergii reduces postprandial hyperglycemia in a type 2 diabetes rat model via pancreatic alpha-amylase inhibition by highly condensed procyanidins. *Bioscience Biotechnology & Biochemistry, 81*(9), 1699–1705. https://doi.org/10.1080/09168451.2017.1353403

Kaur, M., Singh, R. P., Gu, M., Agarwal, R., & Agarwal, C. (2006). Grape seed extract inhibits in vitro and in vivo growth of human colorectal carcinoma cells. *Clinical Cancer Research, 12*(20 PART 1), 6194–6202. https://doi.org/10.1158/1078-0432.CCR-06-1465

Kehrer, J. P., & Klotz, L. O. (2015). Free radicals and related reactive species as mediators of tissue injury and disease: Implications for Health. *Critical Reviews in Toxicology, 45*(9), 765–798. https://doi.org/10.3109/10408444.2015.1074159

Kennedy, J. A., & Jones, G. P. (2001). Analysis of proanthocyanidin cleavage products following acid-catalysis in the presence of excess phloroglucinol. *Journal of Agricultural and Food Chemistry, 49*(4), 1740–1746. https://doi.org/10.1021/jf001030o

Khan, H., Ullah, H., Tundis, R., Belwal, T., Devkota, H. P., Daglia, M., Cetin, Z., Saygili, E. I., Campos, M. da G., Capanoglu, E., Du, M., Dar, P., & Xiao, J. (2020). Dietary flavonoids in the management of huntington's disease: Mechanism and clinical perspective. *EFood, 1*(1), 38. https://doi.org/10.2991/efood.k.200203.001

Kim, K. J., Hwang, E.-S., Kim, M.-J., Park, J.-H., & Kim, D.-O. (2020). Antihypertensive effects of polyphenolic extract from Korean red pine (Pinus densiflora Sieb. et Zucc.) Bark in Spontaneously Hypertensive Rats. *Antioxidants, 9*(4), 333. https://doi.org/10.3390/antiox9040333

Ksiezak-Reding, H., Ho, L., Santa-Maria, I., Diaz-Ruiz, C., Wang, J., & Pasinetti, G. M. (2012). Ultrastructural alterations of Alzheimer's disease paired helical filaments by grape seed-derived polyphenols. *Neurobiology of Aging, 33*(7), 1427–1439. https://doi.org/10.1016/j.neurobiolaging.2010.11.006

Labarbe, B., Cheynier, V., Brossaud, F., Souquet, J. M., & Moutounet, M. (1999). Quantitative fractionation of grape proanthocyanidins according to their degree of polymerization. *Journal of Agricultural and Food Chemistry, 47*(7), 2719–2723. https://doi.org/10.1021/jf990029q

Lamuela-Raventós, R. M., Romero-Pérez, A. I., Andrés-Lacueva, C., & Tornero, A. (2005). Review: Health effects of cocoa flavonoids. *Food Science and Technology International, 11*(3), 159–176. https://doi.org/10.1177/1082013205054498

Lee, K. W., Kang, N. J., Oak, M. H., Hwang, M. K., Kim, J. H., Schini-Kerth, V. B., & Lee, H. J. (2008). Cocoa procyanidins inhibit expression and activation of MMP-2 in vascular smooth muscle cells by direct inhibition of MEK and MT1-MMP activities. *Cardiovascular Research, 79*(1), 34–41. https://doi.org/10.1093/cvr/cvn056

Li, X., He, C., Song, L., Li, T., Cui, S., Zhang, L., & Jia, Y. (2017). Antimicrobial activity and mechanism of Larch bark procyanidins against Staphylococcus aureus. *Acta Biochimica et Biophysica Sinica, 49*(12), 1058–1066. https://doi.org/10.1093/abbs/gmx112

Li, T., Li, Q., Wu, W., Li, Y., Hou, D. X., Xu, H., Zheng, B., Zeng, S., Shan, Y., Lu, X., Deng, F., & Qin, S. (2018). Lotus seed skin proanthocyanidin extract exhibits potent antioxidant property via activation of the Nrf2-ARE pathway. *Acta Biochimica et Biophysica Sinica, 51*(1), 31–40. https://doi.org/10.1093/abbs/gmy148

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

Liu, D., Deng, J., Joshi, S., Liu, P., Zhang, C., Yu, Y., Zhang, R., Fan, D., Yang, H., & D'Souza, D. H. (2018). Monomeric catechin and dimeric procyanidin B2 against human norovirus surrogates and their physicochemical interactions. *Food Microbiology, 76*(May), 346–353. https://doi.org/10.1016/j.fm.2018.06.009

Liu, H., Pan, X., Liu, B., Gui, X., Hu, L., Jiang, C., Han, Y., Fan, Y., Tang, Y., & Liu, W. (2017). Grape seed-derived procyanidins alleviate gout pain via NLRP3 inflammasome suppression. *Journal of Neuroinflammation, 14*(1), 1–10. https://doi.org/10.1186/s12974-017-0849-y

Liu, L. L., Zhang, L., Ren, L. C., & Xie, Y. X. (2020). Advances in structures required of polyphenols for xanthine oxidase inhibition. *Food Frontiers, 1*, 152–167.

Li, Q., Wang, X., Chen, J., Liu, C., Li, T., McClements, D. J., Dai, T., & Liu, J. (2016). Antioxidant activity of proanthocyanidins-rich fractions from Choerospondias axillaris peels using a combination of chemical-based methods and cellular-based assay. *Food Chemistry, 208*, 309–317. https://doi.org/10.1016/j.foodchem.2016.04.012

Li, S., Xiao, J., Chen, L., Hu, C., Chen, P., Xie, B., & Sun, Z. (2012). Identification of A-series oligomeric procyanidins from pericarp of Litchi chinensis by FT-ICR-MS and LC-MS. *Food Chemistry, 135*(1), 31–38. https://doi.org/10.1016/j.foodchem.2012.04.039

Lizarraga, D., Lozano, C., Briedé, J. J., Van Delft, J. H., Touriño, S., Centelles, J. J., Torres, J. L., & Cascante, M. (2007). The importance of polymerization and galloylation for the antiproliferative properties of procyanidin-rich natural extracts. *FEBS Journal, 274*(18), 4802–4811. https://doi.org/10.1111/j.1742-4658.2007.06010.x

Longo, E., Rossetti, F., Jouin, A., Teissedre, P. L., Jourdes, M., & Boselli, E. (2019). Distribution of crown hexameric procyanidin and its tetrameric and pentameric congeners in red and white wines. *Food Chemistry, 299*(July), 125125. https://doi.org/10.1016/j.foodchem.2019.125125

Lotito, S. B., Actis-Goretta, L., Renart, M. L., Caligiuri, M., Rein, D., Schmitz, H. H., Steinberg, F. M., Keen, C. L., & Fraga, C. G. (2000). Influence of oligomer chain length on the antioxidant activity of procyanidins. *Biochemical and Biophysical Research Communications, 276*(3), 945–951. https://doi.org/10.1006/bbrc.2000.3571

Lu, Z., Jia, Q., Wang, R., Wu, X., Wu, Y., Huang, C., & Li, Y. (2011). Hypoglycemic activities of A- and B-type procyanidin oligomer-rich extracts from different Cinnamon barks. *Phytomedicine, 18*(4), 298–302. https://doi.org/10.1016/j.phymed.2010.08.008

Luo, X., Chen, M., Duan, Y., Duan, W., Zhang, H., He, Y., Yin, C., Sun, G., & Sun, X. (2016). Chemoprotective action of lotus seedpod procyanidins on oxidative stress in mice induced by extremely low-frequency electromagnetic field exposure. *Biomedicine & Pharmacotherapy, 82*, 640–648. https://doi.org/10.1016/j.biopha.2016.06.005

Luo, L., Cui, Y., Cheng, J., Fang, B., Wei, Z., & Sun, B. (2018). An approach for degradation of grape seed and skin proanthocyanidin polymers into oligomers by sulphurous acid. *Food Chemistry, 256*, 203–211. https://doi.org/10.1016/j.foodchem.2018.02.097. October 2017.

Määttä-Riihinen, K. R., Kähkönen, M. P., Törrönen, A. R., & Heinonen, I. M. (2005). Catechins and procyanidins in berries of Vaccinium species and their antioxidant activity. *Journal of Agricultural and Food Chemistry, 53*(22), 8485–8491. https://doi.org/10.1021/jf050408l

Mackenzie, G. G., Adamo, A. M., Decker, N. P., & Oteiza, P. I. (2008). Dimeric procyanidin B2 inhibits constitutively active NF-κB in Hodgkin's lymphoma cells independently of the presence of IκB mutations. *Biochemical Pharmacology, 75*(7), 1461–1471. https://doi.org/10.1016/j.bcp.2007.12.013

Madigan, D., McMurrough, I., & Smyth, M. R. (1994). Determination of proanthocyanidins and catechins in beer and barley by high-performance liquid chromatography with dual-electrode electrochemical detection. *The Analyst, 119*(5), 863–868. https://doi.org/10.1039/AN9941900863

Mannozzi, C., Tylewicz, U., Chinnici, F., Siroli, L., Rocculi, P., Dalla Rosa, M., & Romani, S. (2018). Effects of chitosan based coatings enriched with procyanidin by-product on quality of fresh blueberries during storage. *Food Chemistry, 251*(December 2017), 18–24. https://doi.org/10.1016/j.foodchem.2018.01.015

Mao, J. T., Lu, Q. Y., Xue, B., Neis, P., Zamora, F. D., Lundmark, L., Qualls, C., & Massie, L. (2019). A pilot study of a grape seed procyanidin extract for lung cancer chemoprevention. *Cancer Prevention Research, 12*(8), 557–565. https://doi.org/10.1158/1940-6207.CAPR-19-0053

Masumoto, S., Terao, A., Yamamoto, Y., Mukai, T., Miura, T., & Shoji, T. (2016). Non-absorbable apple procyanidins prevent obesity associated with gut microbial and metabolomic changes. *Scientific Reports, 6*(July), 1–10. https://doi.org/10.1038/srep31208

Ma, L., Sun, Z., Zeng, Y., Luo, M., & Yang, J. (2018). Molecular mechanism and health role of functional ingredients in blueberry for chronic disease in human beings. *International Journal of Molecular Sciences, 19*(9). https://doi.org/10.3390/ijms19092785

Meeran, S. M., & Katiyar, S. K. (2008). Proanthocyanidins inhibit mitogenic and survival-signaling in vitro and tumor growth in vivo. *Frontiers in Bioscience : Journal of Visual Literacy, 13*, 887—897. https://doi.org/10.2741/2729

Monagas, M., Gómez-Cordovés, C., Bartolomé, B., Laureano, O., & Ricardo Da Silva, J. M. (2003). Monomeric, oligomeric, and polymeric flavan-3-ol composition of wines and grapes from vitis vinifera L. Cv. graciano, tempranillo, and cabernet sauvignon. *Journal of Agricultural and Food Chemistry, 51*(22), 6475–6481. https://doi.org/10.1021/jf030325+

Mukamal, K. J., Maclure, M., Muller, J. E., Sherwood, J. B., & Mittleman, M. A. (2002). Tea consumption and mortality after acute myocardial infarction. *Circulation, 105*(21), 2476–2481. https://doi.org/10.1161/01.CIR.0000017201.88994.F7

Na, W., Ma, B., Shi, S., Chen, Y., Zhang, H., Zhan, Y., & An, H. (2020). Procyanidin B1, a novel and specific inhibitor of Kv10.1 channel, suppresses the evolution of hepatoma. *Biochemical Pharmacology, 178*(February), 114089. https://doi.org/10.1016/j.bcp.2020.114089

Nehlig, A. (2013). The neuroprotective effects of cocoa flavanol and its influence on cognitive performance. *British Journal of Clinical Pharmacology, 75*(3), 716–727. https://doi.org/10.1111/j.1365-2125.2012.04378.x

Nemes, A., Szollosi, E., Stündl, L., Biró, A., Homoki, J. R., Szarvas, M. M., Balogh, P., Cziáky, Z., & Remenyik, J. (2018). Determination of flavonoid and proanthocyanidin profile of Hungarian sour cherry. *Molecules, 23*(12). https://doi.org/10.3390/molecules23123278

Ojeda-Amador, R. M., Salvador, M. D., Fregapane, G., & Gómez-Alonso, S. (2019). Comprehensive study of the phenolic compound profile and antioxidant activity of Eight pistachio cultivars and their residual cakes and virgin oils. *Journal of Agricultural and Food Chemistry, 67*(13), 3583–3594. https://doi.org/10.1021/acs.jafc.8b06509

Oteiza, P. I., Fraga, C. G., Mills, D. A., & Taft, D. H. (2018). Flavonoids and the gastrointestinal tract: Local and systemic effects. *Molecular Aspects of Medicine, 61*, 41–49. https://doi.org/10.1016/j.mam.2018.01.001

Ou, K., & Gu, L. (2014). Absorption and metabolism of proanthocyanidins. *Journal of Functional Foods, 7*(1), 43–53. https://doi.org/10.1016/j.jff.2013.08.004

Pierini, R., Kroon, P. A., Guyot, S., Ivory, K., Johnson, I. T., & Belshaw, N. J. (2008). Procyanidin effects on oesophageal adenocarcinoma cells strongly depend on flavan-3-ol degree of polymerization. *Molecular Nutrition & Food Research, 52*(12), 1399–1407. https://doi.org/10.1002/mnfr.200700513

Quideau, S., Deffieux, D., Douat-Casassus, C., & Pouységu, L. (2011). Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angewandte Chemie International Edition, 50*(3), 586–621. https://doi.org/10.1002/anie.201000044

Quiñones, M., Guerrero, L., Fernández-Vallinas, S., Pons, Z., Arola, L., Aleixandre, A., & Muguerza, B. (2014). Involvement of nitric oxide and prostacyclin in the antihypertensive effect of low-molecular-weight procyanidin rich grape seed extract in male spontaneously hypertensive rats. *Journal of Functional Foods, 6*(1), 419–427. https://doi.org/10.1016/j.jff.2013.11.008

Quiñones, M., Guerrero, L., Suarez, M., Pons, Z., Aleixandre, A., Arola, L., & Muguerza, B. (2013). Low-molecular procyanidin rich grape seed extract exerts antihypertensive effect in males spontaneously hypertensive rats. *Food Research International, 51*(2), 587–595. https://doi.org/10.1016/j.foodres.2013.01.023

Ramirez-Coronel, M. A., Marnet, N., Kolli, V. S. K., Roussos, S., Guyot, S., & Augur, C. (2004). Characterization and estimation of proanthocyanidins and other phenolics in coffee pulp (coffea, arabica) by thiolysis-high-performance liquid chromatography. *Journal of Agricultural and Food Chemistry, 52*(5), 1344–1349. https://doi.org/10.1021/jf035208t

Ramirez, J. E., Zambrano, R., Sepúlveda, B., & Simirgiotis, M. J. (2014). Antioxidant properties and hyphenated HPLC-PDA-MS profiling of chilean pica mango fruits (Mangifera indica L. Cv. piqueño). *Molecules, 19*(1), 438–458. https://doi.org/10.3390/molecules19010438

Rong, S., Hu, X., Zhao, S., Zhao, Y., Xiao, X., Bao, W., & Liu, L. (2017). Procyanidins extracted from the litchi pericarp ameliorate atherosclerosis in ApoE knockout mice: Their effects on nitric oxide bioavailability and oxidative stress. *Food and Function, 8*(11), 4210–4216. https://doi.org/10.1039/c7fo00747g

Rossi, M., Edefonti, V., Parpinel, M., Lagiou, P., Franchi, M., Ferraroni, M., Decarli, A., Zucchetto, A., Serraino, D., Dal Maso, L., Negri, E., & La Vecchia, C. (2013). Proanthocyanidins and other flavonoids in relation to endometrial cancer risk: A case-control study in Italy. *British Journal of Cancer, 109*(7), 1914–1920. https://doi.org/10.1038/bjc.2013.447

Rowley, T. J., Bitner, B. F., Ray, J. D., Lathen, D. R., Smithson, A. T., Dallon, B. W., Plowman, C. J., Bikman, B. T., Hansen, J. M., Dorenkott, M. R., Goodrich, K. M., Ye, L., O'Keefe, S. F., Neilson, A. P., & Tessem, J. S. (2017). Monomeric cocoa catechins enhance β-cell function by increasing mitochondrial respiration. *Journal of Nutritional Biochemistry, 49*, 30–41. https://doi.org/10.1016/j.jnutbio.2017.07.015

Rue, E. A., Rush, M. D., & van Breemen, R. B. (2018). Procyanidins: A comprehensive review encompassing structure elucidation via mass spectrometry. *Phytochemistry Reviews, 17*(1), 1–16. https://doi.org/10.1007/s11101-017-9507-3

Ruiz, D., Egea, J., Gil, M. I., & Tomás-Barberán, F. A. (2005). Characterization and quantitation of phenolic compounds in new apricot (Prunus armeniaca L.) varieties. *Journal of Agricultural and Food Chemistry, 53*(24), 9544–9552. https://doi.org/10.1021/jf051539p

Saito, A., Mizushina, Y., Tanaka, A., & Nakajima, N. (2009). Versatile synthesis of epicatechin series procyanidin oligomers, and their antioxidant and DNA polymerase inhibitory activity. *Tetrahedron, 65*(36), 7422–7428. https://doi.org/10.1016/j.tet.2009.07.018

Sano, A., Uchida, R., Saito, M., Shioya, N., Komori, Y., Tho, Y., & Hashizume, N. (2007). Beneficial effects of grape seed extract on malondialdehyde-modified LDL. *Journal of Nutritional Science & Vitaminology, 53*(2), 174–182. https://doi.org/10.3177/jnsv.53.174

Santa-Maria, I., Diaz-Ruiz, C., Ksiezak-Reding, H., Chen, A., Ho, L., Wang, J., & Pasinetti, G. M. (2012). GSPE interferes with tau aggregation in vivo: Implication for treating tauopathy. *Neurobiology of Aging, 33*(9), 2072–2081. https://doi.org/10.1016/j.neurobiolaging.2011.09.027

Santhakumar, A. B., Battino, M., & Alvarez-Suarez, J. M. (2018). Dietary polyphenols: Structures, bioavailability and protective effects against atherosclerosis. *Food and Chemical Toxicology, 113*, 49–65. https://doi.org/10.1016/j.fct.2018.01.022. . (Accessed December 2017)

Schmitzer, V., Slatnar, A., Veberic, R., Stampar, F., & Solar, A. (2011). Roasting affects phenolic composition and antioxidative activity of hazelnuts (Corylus avellana L.). *Journal of Food Science, 76*(1). https://doi.org/10.1111/j.1750-3841.2010.01898.x

Serra, A., MacI, A., Romero, M. P., Valls, J., Bladé, C., Arola, L., & Motilva, M. J. (2010). Bioavailability of procyanidin dimers and trimers and matrix food effects in in vitro and in vivo models. *British Journal of Nutrition, 103*(7), 944–952. https://doi.org/10.1017/S0007114509992741

Shoji, T., Masumoto, S., Moriichi, N., Akiyama, H., Kanda, T., Ohtake, Y., & Goda, Y. (2006). Apple procyanidin oligomers absorption in rats after oral administration: Analysis of procyanidins in plasma using the porter method and high-performance liquid chromatography/tandem mass spectrometry. *Journal of Agricultural and Food Chemistry, 54*(3), 884–892. https://doi.org/10.1021/jf052260b

Shoji, T., Masumoto, S., Moriichi, N., Kobori, M., Kanda, T., Shinmoto, H., & Tsushida, T. (2005). Procyanidin trimers to pentamers fractionated from apple inhibit melanogenesis in B16 mouse melanoma cells. *Journal of Agricultural and Food Chemistry, 53*(15), 6105–6111. https://doi.org/10.1021/jf050418m

Simonetti, P., Ciappellano, S., Gardana, C., Bramati, L., & Pietta, P. (2002). Procyanidins from Vitis vinifera seeds: In vivo effects on oxidative stress. *Journal of Agricultural and Food Chemistry, 50*(21), 6217–6221. https://doi.org/10.1021/jf011412+

Souquet, J. M., Cheynier, V., Brossaud, F., & Moutounet, M. (1996). Polymeric proanthocyanidins from grape skins. *Phytochemistry, 43*(2), 509–512. https://doi.org/10.1016/0031-9422(96)00301-9

Steffen, Y., Gruber, C., Schewe, T., & Sies, H. (2008). Mono-O-methylated flavanols and other flavonoids as inhibitors of endothelial NADPH oxidase. *Archives of Biochemistry and Biophysics, 469*(2), 209–219. https://doi.org/10.1016/j.abb.2007.10.012

Sugiyama, H., Akazome, Y., Shoji, T., Yamaguchi, A., Yasue, M., Kanda, T., & Ohtake, Y. (2007). Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *Journal of Agricultural and Food Chemistry, 55*(11), 4604–4609. https://doi.org/10.1021/jf070569k

Su, H., Li, Y., Hu, D., Xie, L., Ke, H., Zheng, X., & Chen, W. (2018). Procyanidin B2 ameliorates free fatty acids-induced hepatic steatosis through regulating TFEB-mediated lysosomal pathway and redox state. *Free Radical Biology and Medicine, 126*(866), 269–286. https://doi.org/10.1016/j.freeradbiomed.2018.08.024

Sun, B., Leandro, C., Ricardo Da Silva, J. M., & Spranger, I. (1998). Separation of grape and wine proanthocyanidins according to their degree of polymerization. *Journal of Agricultural and Food Chemistry, 46*(4), 1390–1396. https://doi.org/10.1021/jf970753d

Sun, B. S., Pinto, T., Leandro, M. C., Ricardo-Da-Silva, J. M., & Spranger, M. I. (1999). Transfer of catechins and proanthocyanidins from solid parts of the grape cluster into wine. *American Journal of Enology and Viticulture, 50*(2), 179–184.

Sun, C. D., Zhao, C., Guven, E. C., Paoli, P., Simal-Gandara, J., Ramkumar, K. M., Wang, S. P., Buleu, F., Vladiana, A. P., Damian, T. G., Dragan, S., Tomas, M., Khan, W., Wang, M. F., Delmas, D., Portillo, M. P., Dar, P., Chen, L., Sutcliffe, T. C., … Linseman, D. A. (2017). Procyanidin B2 protects neurons from oxidative, nitrosative, and excitotoxic stress. *Antioxidants, 6*(4), 77. https://doi.org/10.3390/antiox6040077

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

Theodoratou, E., Kyle, J., Cetnarskyj, R., Farrington, S. M., Tenesa, A., Barnetson, R., Porteous, M., Dunlop, M., & Campbell, H. (2007). Dietary flavonoids and the risk of colorectal cancer. *Cancer Epidemiology Biomarkers and Prevention, 16*(4), 684–693. https://doi.org/10.1158/1055-9965.EPI-06-0785

Toda, T., Sunagawa, T., Kanda, T., Tagashira, M., Shirasawa, T., & Shimizu, T. (2011). Apple procyanidins suppress amyloid β-protein aggregation. *Biochemistry Research International*, 784698. https://doi.org/10.1155/2011/784698, 2011.

Tsao, R. (2010). Chemistry and biochemistry of dietary polyphenols. *Nutrients, 2*(12), 1231–1246. https://doi.org/10.3390/nu2121231

Tsujita, T., Shintani, T., & Sato, H. (2013). α-Amylase inhibitory activity from nut seed skin polyphenols. 1. purification and characterization of almond seed skin polyphenols. *Journal of Agricultural and Food Chemistry, 61*(19), 4570–4576. https://doi.org/10.1021/jf400691q

Wang, L., Fumoto, T., Masumoto, S., Shoji, T., Miura, T., Naraoka, M., Matsuda, N., Imaizumi, T., & Ohkuma, H. (2017). Regression of atherosclerosis with apple procyanidins by activating the ATP-binding cassette subfamily A member 1 in a rabbit model. *Atherosclerosis, 258*, 56–64. https://doi.org/10.1016/j.atherosclerosis.2017.01.032

Wang, L., Yamashita, Y., Komeda, S., Saito, A., & Ashida, H. (2018). Absorption, metabolism, distribution and faecal excretion of B-type procyanidin oligomers in mice after a single oral administration of black soybean seed coat extract. *Food and Function, 9*(10), 5362–5370. https://doi.org/10.1039/c8fo00852c

Wu, X., Li, M. X., Xiao, Z. G., Daglia, M., Dragan, S., Delmas, D., Vong, C. T., Wang, Y. T., Zhao, Y. S., Shen, J., Nabavi, S. M., Sureda, A., Cao, H., Simal-Gandara, J., Wang, M. F., Sun, C. D., Wang, S. P., & Xiao, J. B. (2020). Dietary polyphenols for managing cancers. What have we ignored? *Trends in Food Science & Technology, 101*, 150–164.

Xiao, J. B. (2020). Dietary polyphenols as antidiabetic agents: Advances and opportunities. *Food Frontiers, 1*, 18–44.

Xiao, H. B., Wang, Y. S., Liang, L., Lu, X. Y., & Sun, Z. L. (2019). Procyanidin B2 from lotus seedpod regulate NO/ADMA/DDAH pathway to treat insomnia in rats. *Fundamental & Clinical Pharmacology, 33*(5), 549–557. https://doi.org/10.1111/fcp.12462

Xing, Y.-W., Lei, G.-T., Wu, Q.-H., Jiang, Y., & Huang, M.-X. (2019). Procyanidin B2 protects against diet-induced obesity and non-alcoholic fatty liver disease via the modulation of the gut microbiota in rabbits. *World Journal of Gastroenterology, 25*(8), 955–966.

Xue, B., Lu, Q. Y., Massie, L., Qualls, C., & Mao, J. T. (2018). Grape seed procyanidin extract against lung cancer: The role of microrna-106b, bioavailability, and bioactivity. *Oncotarget, 9*(21), 15579–15590. https://doi.org/10.18632/oncotarget.24528

Yamashita, Y., Okabe, M., Natsume, M., & Ashida, H. (2012). Prevention mechanisms of glucose intolerance and obesity by cacao liquor procyanidin extract in high-fat diet-fed C57BL/6 mice. *Archives of Biochemistry and Biophysics, 527*(2), 95–104. https://doi.org/10.1016/j.abb.2012.03.018

Yamashita, Y., Wang, L., Nanba, F., Ito, C., Toda, T., & Ashida, H. (2016). Procyanidin promotes translocation of glucose transporter 4 in muscle of mice through activation of insulin and AMPK signaling pathways. *PloS One, 11*(9), 1–19. https://doi.org/10.1371/journal.pone.0161704

Yang, H., Xiao, L., Yuan, Y., Luo, X., Jiang, M., Ni, J., & Wang, N. (2014). Procyanidin B2 inhibits NLRP3 inflammasome activation in human vascular endothelial cells. *Biochemical Pharmacology, 92*(4), 599–606. https://doi.org/10.1016/j.bcp.2014.10.001

Zhang, J., Liang, R., Wang, L., Yan, R., Hou, R., Gao, S., & Yang, B. (2013). Effects of an aqueous extract of Crataegus pinnatifida Bge. var. major N.E.Br. fruit on experimental atherosclerosis in rats. *Journal of Ethnopharmacology, 148*(2), 563–569. https://doi.org/10.1016/j.jep.2013.04.053

Zhang, Y. P., Liu, S. Y., Sun, Q. Y., Ren, J., Liu, H. X., & Li, H. (2018). Proanthocyanidin B2 attenuates high-glucose-induced neurotoxicity of dorsal root ganglion neurons through the PI3K/Akt signaling pathway. *Neural Regeneration Research, 13*(9), 1628–1636. https://doi.org/10.4103/1673-5374.237174

Zhang, L., Wang, S., Liu, Z., Zhang, L., Wang, S., & Wang, B. (2017). Procyanidin, a kind of biological flavonoid, induces protective anti-tumor immunity and protects mice from lethal B16F10 challenge. *International Immunopharmacology, 47*, 251–258. https://doi.org/10.1016/j.intimp.2017.04.007

Zhao, L., Wang, F., Lu, Q., Liu, R., Tian, J., & Huang, Y. (2018). Study on interaction between human salivary α-amylase and sorghum procyanidin tetramer: Binding characteristics and structural analysis. *International Journal of Biological Macromolecules, 118*, 1136–1141. https://doi.org/10.1016/j.ijbiomac.2018.06.189

Zhao, C., Wan, X., Zhou, S., & Cao, H. (2020). Natural polyphenols: A potential therapeutic approach to hypoglycemia. *EFood, 1*, 107–118. https://doi.org/10.2991/efood.k.200302.001

Zhao, S., Zhang, L., Yang, C., Li, Z., & Rong, S. (2019). Procyanidins and Alzheimer's disease. *Molecular Neurobiology, 56*(8), 5556–5567. https://doi.org/10.1007/s12035-019-1469-6

Zhou, Q., Cheng, K. W., Xiao, J. B., & Wang, M. F. (2020). The multifunctional roles of flavonoids against the formation of advanced glycation end products (AGEs) and AGEs-induced harmful effects. *Trends in Food Science & Technology, 103*, 333–347.

Zhou, X., Chen, S., & Ye, X. (2017). The anti-obesity properties of the proanthocyanidin extract from the leaves of Chinese bayberry (Myrica rubra Sieb.et Zucc.). *Food and Function, 8*(9), 3259–3270. https://doi.org/10.1039/c7fo00816c

Zhou, Q., Han, X., Li, R., Zhao, W., Bai, B., Yan, C., & Dong, X. (2018). Anti-atherosclerosis of oligomeric proanthocyanidins from Rhodiola rosea on rat model via hypolipemic, antioxidant, anti-inflammatory activities together with regulation of endothelial function. *Phytomedicine, 51*, 171–180. https://doi.org/10.1016/j.phymed.2018.10.002

Zhou, H., Lin, Y. M., Wei, S. D., & Tam, N. F. Y. (2011). Structural diversity and antioxidant activity of condensed tannins fractionated from mangosteen pericarp. *Food Chemistry, 129*(4), 1710–1720. https://doi.org/10.1016/j.foodchem.2011.06.036

Zhu, M. T., Huang, Y. S., Wang, Y. L., Shi, T., Zhang, L. L., Chen, Y., & Xie, M. Y. (2019). Comparison of (poly)phenolic compounds and antioxidant properties of pomace extracts from kiwi and grape juice. *Food Chemistry, 271*, 425–432. https://doi.org/10.1016/j.foodchem.2018.07.151