Current Research in Food Science 9 (2024) 100926

Contents lists available at ScienceDirect

Current Research in Food Science

journal homepage: www.sciencedirect.com/journal/current-research-in-food-science

Review Article

Revisiting dietary proanthocyanidins on blood glucose homeostasis from a multi-scale structural perspective

Yi Wang [a], Laiming Zhang [a], Hang Xiao [a,b], Xingqian Ye [a,c], Haibo Pan [a,d,**], Shiguo Chen [a,c,d,*]

[a] College of Biosystems Engineering and Food Science, National-Local Joint Engineering Laboratory of Intelligent Food Technology and Equipment, Zhejiang Key Laboratory for Agro-Food Processing, Zhejiang Engineering Laboratory of Food Technology and Equipment, Zhejiang University, Hangzhou, 310058, PR China
[b] Department of Food Science, University of Massachusetts, Amherst, 01003, USA
[c] Zhejiang University Zhongyuan Institute, Zhengzhou, 450000, PR China
[d] Innovation Center of Yangtze River Delta, Zhejiang University, Jiaxing, 314102, PR China

ARTICLE INFO

Handling Editor: Dr. Quancai Sun

Keywords:
Dietary proanthocyanidins
Blood glucose
Absorption
Structure

ABSTRACT

Multi-dimensional studies have consistently indicated the benefits of dietary proanthocyanidins on blood glucose homeostasis through consumption of them from fruits, cereals and nuts. Proanthocyanidins from various sources possess different structures, but even the minor variations in structures influence their regulation on blood glucose, including the degree of polymerization, galloacylation at C3, number of hydroxyl groups in B ring and linkage type. Therefore, this Review details the role of three types of proanthocyanidins (procyanidins, prodelphinidins and propelargonidins) in blood glucose control and their underlying mechanisms, and various structural features contribute to. Due to the extremely low bioavailability, proanthocyanidins mainly ameliorate high blood glucose by luminal effects: inhibit enzyme activities, improve the structure of gut microbiota, and protect the intestinal barrier function. A few absorbed proanthocyanidins exert insulin-like effects on targeted organs. Prodelphinidin gallates exhibit greater hypoglycemic activities than others, due to their galloacylation at C3 and high amounts of hydroxyl groups in B ring. Because of different action pathways, comprehensive consideration on the degree of polymerization, linkage type and density of hydroxyl groups was required. Further understanding of these relationships can concrete diet therapeutic opportunities for proanthocyanidins.

1. Introduction

The term ‘tannin’ was first coined in 1796 to denote substances derived from plants that convert animal skin into leather, and then identified as polyphenols with molecular weight between 500 and 3000 (Jansman, 1993). Afterwards, given the application value of tannins in multiple fields was gradually emerging, the definition of ‘plant polyphenol’ was raised to describe tannin analogs without molecular weight limitations and classified them into hydrolysable and condensed categories (Mcmanus et al., 1981). Among them, proanthocyanidins, also known as condensed tannins, are secondary metabolites of plants protecting them from ultraviolet radiation, insect pests, and other adverse conditions (Rao et al., 2019). As the second largest dietary polyphenols, proanthocyanidins with health benefits are widely distributed in grape seeds, bayberry leaves, peanut peels, and cranberries.

Diabetes mellitus (DM) is a metabolic disease caused by the deficiency of insulin secretion and/or insulin resistance, causing the death of one person every 5 s worldwide (Chou et al., 2023). Multi-factors drive the occurrence and development of DM, and medical therapy including oral hypoglycemic drugs and insulin injection is the main treatment of diabetes, but related drugs were reported with multiple side effects, unstable pesticide effect and poor patient compliance (Fig. 1) (Lee and Lee, 2022; Tian et al., 2023; Wu et al., 2023). However, dietary proanthocyanidins have been shown in numerous epidemiological and animal studies to have significant associations with the occurrence and mortality of diabetes. For example, a meta-analysis of nine cohorts including 324,141 person-years of follow-up showed that proanthocyanidins-rich tea consumption ≥4 cups per day was associated with reduced risk of type 2 DM (RR 0.8, 95% CI 0.70–0.93) (Jing et al., 2009). A meta-analysis of six prospective cohorts involving 284,806 participants

* Corresponding author. Zhejiang University Zhongyuan Institute, Zhengzhou, 450000, PR China.
** Corresponding author. Innovation Center of Yangtze River Delta, Zhejiang University, Jiaxing, 314102, PR China.
E-mail addresses: apanhaibo@126.com (H. Pan), chenshiguo210@163.com (S. Chen).

https://doi.org/10.1016/j.crfs.2024.100926
Received 1 September 2024; Received in revised form 7 November 2024; Accepted 12 November 2024
Available online 14 November 2024

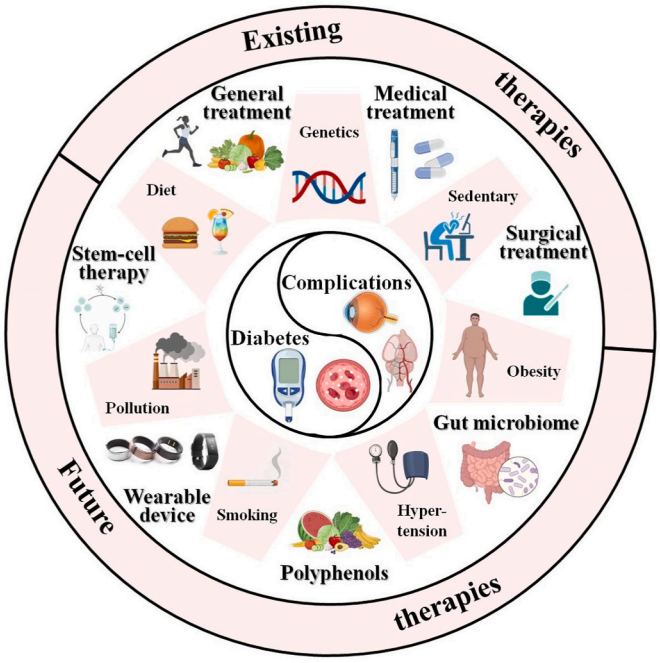

Fig. 1. The risk factors and therapies of diabetes mellitus.

indicated that for each increase in total flavonoids (including catechins and anthocyanidins) intake of 500 mg per day there was a reduced risk in diabetes of 5% (Liu et al., 2014). Both analyses emphasized the importance of the quantity and duration of proanthocyanidins required to regulate blood glucose. Thus, a daily intake of flavan-3-ols for adults of 400–600 g per day was recommended to reduce the risk of diabetes, but the average intake of dietary proanthocyanidins by adults worldwide remains low (Crowe-White et al., 2022).

Dietary proanthocyanidins have the potential to be used as a prevention and therapeutic intervention for diabetes. Due to the extremely low bioavailability, the gastrointestinal tract is the main action site for proanthocyanidins to maintain blood glucose homeostasis, such as the delay in carbohydrate digestion and the improvement of gut microbiota (Baron et al., 2024). A few absorbed proanthocyanidins mimic the actions of insulin in the liver, skeletal muscle and other peripheral tissue (Martín and Ramos, 2021). However, owing to the difficulty in separation and purification, most studies focused on crude extracts of proanthocyanidins, which contain different types of proanthocyanidins and other impurities such as proteins and polysaccharides, hindering the exploration of their structure-activity relationships and the key bioactive proanthocyanidins components (Liu et al., 2024; Monfoulet et al., 2020; Morzel et al., 2022).

Proanthocyanidins from various sources possess different structures, but even the minor variations in structures influence their regulation on blood glucose, including the mean degree of polymerization (mDP), galloacylation at C3, the amount of hydroxyl groups in B ring and linkage types, leading to the challenges in exploring their hypoglycemic activities. Furthermore, the activities of proanthocyanidins are also affected by the dosage, administration time, photoperiod, and model selection. Therefore, this Review aims to detail the role of three types of proanthocyanidins (procyanidins, prodelphinidins and propelargonidins) in blood glucose control and their underlying mechanisms at the molecular, cellular and organismal levels, as well as the contributions of various structural features.

2. Structures and sources of dietary proanthocyanidins

Dietary proanthocyanidins are oligomeric and polymeric flavan-3-ols, widely distributed in seeds, flesh, skin, leaves, and roots of plants. According to the hydroxylation mode of B ring, proanthocyanidins can be divided into procyanidins, prodelphinidins and propelargonidins, corresponding to constituent units of (epi)catechin, (epi)gallocatechin and (epi)afzelechin (Xu et al., 2024). Procyanidins are more common than two others (Table 1). Grape seeds (15.94 g/100 g dry weight) and skin (6.46 g/100 g dry weight) of Ugni blanc variety at harvest are good sources of procyanidins, which varies with the growth period and planting period (Freitas and Glories, 1999). Besides, the C3 position of flavan-3-ol can be esterified by gallic acid, for example, prodelphinidin gallates are rich in oolong tea (Hashimoto et al., 1989). Flavan-3-ols linked by C4–C8 and/or C4–C6 bonds are classified as B-type proanthocyanidins commonly found in plant resources (such as cocoa and grape seeds), while additional C2–O–C7 ether bonds exist in A-type proanthocyanidins rarely distributed in nature (such as peanut skins and persimmon pulp) (Dong et al., 2013; Jing et al., 2022; Qi et al., 2018). The mDP is another important structural feature closely related to functions. Proanthocyanidins with mDP of 2–3, 4–10 and $>$ 10 are defined as oligomers, polymers and high polymers, respectively (Kylli et al., 2011). The mDP of proanthocyanidins changes during the ripening of fruits, but no unanimous conclusion has been reached yet. Kennedy et al. (2001) reported that the mDP of proanthocyanidins in grape (*Vitis vinifera* L. cv. Shiraz) skin and seeds increased with the growth process, while Downey, Harvey and Robinson (2003) proposed that the mDP of proanthocyanidins in grape seeds was stable at around 5 and grape skin polymer length decreased after veraison. Environment stress is the principal factor affecting the growth of plants, for example, cooling and damping significantly decreased mDP of grape berries (*Vitis vinifera* L. cv. Merlot) (Cohen et al., 2008). Notably, there are slight differences in the results of mDP obtained by distinct measurement methods (Kennedy et al., 2000).

Greater intake of dietary proanthocyanidins, mainly from fruits and vegetables, has been associated with physiological homeostasis (Table 1). Following 2915 members of the Framingham Offspring cohort and a follow-up period of 11.9 y, each 2.5-fold increase in flavan-3-ol intake has been shown to lower the incidence of T2DM by 11% (RR 0.89, 95% CI 0.80–1.00) (Zamora-Ros et al., 2014). It was reported that Spaniards had the greatest daily intake of proanthocyanidins (175 mg/day) and pome fruits (28%) are the major contributors, while Dutch consumed the least (96 mg/day) (Di Lorenzo et al., 2021). This is far below the recommended intake of flavan-3-ols for adults of 400–600 g per day to reduce the risk of DM, so additional supplementation of proanthocyanidins is necessary (Crowe-White et al., 2022). Coleman and Shaw (2017) indicated that various proanthocyanidins derived from fruits produced biomarkers for alleviating allergic airway inflammation, but Villegas et al. (2008) thought vegetable but not fruit consumption was associated with a reduced risk of type 2 diabetes (T2DM) in Chinese women. Hence, the structural complexity results in the lack of the intake type, dosage, and other detailed guidance standards for proanthocyanidins.

3. Absorption and metabolism of dietary proanthocyanidins

Proanthocyanidins biosynthesized from simple aromatic amino acids are end-products in a branched pathway of flavonoids, encompassing the shikimate, phenylpropanoid and flavonoid pathways (Fig. 2). The bioactivities of dietary proanthocyanidins vary greatly depending on their absorption and metabolism. Proanthocyanidins are released from the matrix and combine with salivary proteins in the oral cavity through non-covalent interaction, producing the characteristic astringency (Lei et al., 2023). Substrate type and mastication efficiency affect the bioaccessibility and bioavailability of proanthocyanidins. Pineda-Vadillo et al. (2016) proposed that the addition of grape extracts into the egg and dairy food matrices markedly enhanced their digestive stability. A very few proanthocyanidin monomers are absorbed by the oral epithelial cells, while most enter the stomach and are released from the matrix in full form (Hirasawa et al., 2002). Rios et al. (2002) showed that cocoa

Table 1
Composition of proanthocyanidins from diverse sources and their bioactivities.

Source	Extraction method	Concentration	Composition	Bioactivity	Reference
Fruits					
Apple	Successive extraction by hexane, methanol and acetone, which was purified by C18 Sep-PaK and fractionated by normal- or reversed-phase HPLC	Each Avrolles apple contained on average 240 mg at 200 days after full bloom	Main constitutive units were (−)-epicatechin (>98%) linked by B-type linkage. Oligomeric procyanidins with mDP from 2 to 8, while polymeric procyanidins with mDP from 7 to 190.	Antioxidant, anticancer, anti-inflammatory, anti-obesity and antibacterial activity	(Guyot et al., 2001; Renard et al., 2007)
Cranberry	Isolation by Sephadex LC-20 resin with 70% acetone, follow by purification of Develosil 100 Diol-5 column	Varied from 18 to 92 g/kg dried fruit	304 A-type and B-type procyanidins, including 40 trimers, 68 tetramers, 53 pentamers, 54 hexamers, 49 heptamers, 28 octamers, and 12 nonamers	Antidiabetic anti-angiogenic, anti-inflammatory, anticancer, antiviral, antioxidant and anti-aging activity	(Carpenter et al., 2014; Y. Wang et al. (2020b))
Grape seeds	80% methanol extraction with ultrasound	159 mg/g dry weight	Gallic acid ethyl ester, catechin, epicatechin and 43 procyanidin oligomers with DP of up to 7 and degree of galloylation of up to 2	Antidiabetic, cardioprotective, antitumor, hypocholesterolemic, antioxidant, antiulcer, anti-inflammatory, antinociceptive activity	Montero et al. (2013)
Chinese bayberry leaves	70% acetone containing 0.1% acetic acid extraction and purification of hexane and Sephadex LH-20 column	324.19 mg/g dry weight	B-type prodelphinidins containing EGC(G) as subunits with mDP of 6.5	Antidiabetic, anti-obesity, anticancer, antioxidant, antimicrobial, neuroprotective and antiproliferative activity	Zhang et al. (2016)
Kiwifruit leaves	80% acetone extraction and purification of hexane, AB-8 Macroporous resin column and Sephadex LH-20 column	87.52 ± 5.31 mg catechin equivalents/g dry weight	Procyanidins, propelargonidins, and prodelphindins ranging from dimers to hexamers with (E)C as terminal units and (epi)afzelechin or (E)GC as dominant extension units	Antioxidant, antidiabetic, and anti-proliferative	Lv et al. (2022)
Persimmon	70% acetone containing 0.1% ascorbic acid extraction and purification of D101 macroporous resin and Sephadex LH-20 column	0.67 ± 0.02 mg catechin equivalents/g dry weight	A-type and B-type procyanidins (25.21%) and prodelphindins (74.79%) containing EGC, EGCG, EC, ECG as extension units and EGCG as terminal unit with mDP of 10.18	Antidiabetic, antihypertensive antibacterial, antioxidant, anti-aging and anti-inflammatory activity	Ye et al. (2022)
Strawberry	Acetone:water:acetic acid at 70:29.5:0.5 for extraction and Sep-Pack C-18 solid phase extraction cartridge for purification	53.9−163.2 mg/100 g	B-type proanthocyanidins containing (epi)catechin (17.36−29.93%) as terminal unit and (epi)catechin (61.66−75.39%) or (epi)afzelechin (4.50−10.54%) as extension units with the mDP of 4.3	Antioxidant, neuroprotective, antimicrobial, anti-inflammatory activity	Buendia et al. (2010)
Vegetables					
Rheum tanguticum	80% acetone extraction, which was further purified by Sephadex LH-20 and reversed phase gel column	19.14 mg/g of proanthocyanidins and their monomers	Catechin, ECG, procyanidin B-2 3′-gallate and procyanidin B-2 3,3′-di-gallate	Anticancer, antiviral, anti-inflammatory, anti-diabetic and antioxidant activity	Komatsu et al. (2006)
Indian squash	Acetone:water:acetic acid at 70:29.5:0.5 for extraction and Sep-Pack C-18 solid phase extraction cartridge for purification	16.4 ± 1.6 mg/100 g fresh weight (21.34% oligomers, 47.56% polymers and 21.34% high polymers)	B-type procyanidins	Antibacterial, antioxidant, anti-cancer activity	Sulistiyani et al. (2022)
Mini white carrot	30% methanol containing 2% ascorbic acid and 1% acetic acid for extraction with ultrasound	78.92 mg/100 g dry weight of polymeric procyanidins	Procyanidins with the highest DP of 2.06	Anti-diabetic, antioxidant and anti-obesity	Yusuf et al. (2021)
Cereals and pseudocereals					
Wheat bran	70% acetone with 0.1% ascorbic acid	20−40 μg/g fresh weight of proanthocyanidins and their monomers	Oligomeric proanthocyanidins consist of mostly prodelphinidins, some procyanidins and propelargonidins	Antioxidant, antifungal and anti-diabetic activity	McCallum and Walker (1990)
Barley	80% acetone extraction	293.2–652.6 μg/g dry weight	Catechin, EC, procyanidin dimer, prodelphinidin dimer, procyanidin trimer, monogalloylated prodelphinidin trimer, digalloylated prodelphinidin trimer, procyanidin tetramer, digalloylated prodelphinidin tetramer and procyanidin pentamer	Antioxidant, anti- diabetic and hair-growth stimulating activity	Verardo et al. (2015)
Sorghum testa	70% acetone containing 0.1% acetic acid extraction and purification of hexane and Sephadex LH-20 column		A-type and B-type procyanidins with DP from 3 to 11	Antioxidant, anti- diabetic and anti-inflammatory activity	Qian et al. (2022)
Nuts					
Peanut skin	Free phenolics were extracted by 70% acetone and equal volumes of diethyl ether and ethyl acetate, esterified phenolics were released by adding an equal volume of 4 M NaOH to free	The contents (mg catechin equivalents/g dry weight) of free, esterified and insoluble-bound proanthocyanidins	Catechin, EC, GC, proanthocyanidin dimer B, procyanidin dimer A, procyanidin dimer B, prodelphinidin dimer A,	Antioxidant, anti-inflammatory, anti-melanogenic activity	de Camargo et al. (2015)

(*continued on next page*)

Table 1 (*continued*)

Source	Extraction method	Concentration	Composition	Bioactivity	Reference
	phenolic extracts and extracted by equal volumes of diethyl ether and ethyl acetate	were 35.19 ± 0.0, 4.34 ± 0.09 and 1.92 ± 0.1	prodelphinidin dimer B, procyanidin trimer A, procyanidin trimer C2, prodelphinidin trimer A, procyanidin tetramer A and procyanidin pentamer A		
Cocoa	50% acetone extraction and purification of reverse-phase HPLC and Sephadex LH-20 column	25.4 mg EC equivalents/g non-fatty dry weight	Catechin, EC, procyanidin B2, procyanidin C1, procyanidin tetramer A2	Anti-inflammatory, antioxidant, anti-diabetic, anti-obesity, anti-cancer, antiradical, antibacterial activity	Pedan et al. (2016)
Hazelnut skin	80% methanol extraction and purification of n-hexane, chloroform, methanol and Sephadex LH-20 column	25.0 ± 8.8 g catechin equivalents/100 g	Main B-type and some A-type procyanidins and their gallate derivatives with the DP up to 10, as well as some EC subunits	Antioxidant, antiglycation, anti-inflammatory, antimicrobial, neuroprotective activity	Piccinelli et al. (2016)
Nonpareil almond	Acetone:water:acetic acid at 70:29.5:0.5 for extraction with ultrasound	110.6 mg/100 g	The contents (mg/100 g) of catechin, EC, procyanidin B1, B2, B3, trimer, tetramer, pentamer, hexamer, heptamer and other polymers were 0.4 ± 0.1, 4.6 ± 1.2, 3.4 ± 1.4, 8.3 ± 2.9, 8.4 ± 2.2, 14.0 ± 3.3, 15.1 ± 3.5, 10.9 ± 4.1, 7.2 ± 2.3, 6.3 ± 2.1 and 31.9 ± 8.8, respectively	Antioxidant and anti- diabetic activity	Xie et al. (2012)
Pecan	70% acetone extraction	15.316 ± 0.554 mg/100 g fresh weight	The contents (mg/100 g fresh weight) of catechin, procyanidin B1, B2, B3, B6, B7 and C2 were 2.418 ± 0.160, 1.761 ± 0.152, 0.178 ± 0.013, 4.865 ± 0.129, 0.585 ± 0.017, 0.488 ± 0.019 and 5.020 ± 0.064, respectively	Antioxidant, antimicrobial, anti-cancer and antiproliferative activity	Bittner et al. (2013)
Beverage					
Grape wine	Extraction of tC18 Sep-Pak and C18 Sep-Pak		Oligomeric and polymeric proanthocyanidins 4.8 and 22.1, respectively, containing catechin, EC and ECG, such as procyanidin B3, procyanidin B1, procyanidin trimer 2, procyanidin B4, procyanidin B2, procyanidin B2 3-O-gallate, procyanidin B1 3-O-gallate and procyanidin C1	Antioxidant activity	Sun et al. (1998)
Ouvagalia black tea	Water	74 ± 10 mg/g dry weight	The concentrations (μg/g dry weight) of catechin, EC, ECG, EGC, EGCG, procyanidins B1 and B2 were 1671 ± 241, 11,917 ± 1253, 8265 ± 863, 1793 ± 49, 7103 ± 746, 4020 ± 597 and 3023 ± 673, respectively	Antioxidant activity	Luximon-Ramma et al. (2005)
Spices					
Cinnamon	70% acetone extraction and purification of Sephadex LH-20 column	24.2 g/100 g	21% of A-type and 79% of B-type procyanidins with the mDP of 5.2	Anthelmintic, anti-diabetic, anti-tumor and anti-inflammatory activity	Williams et al. (2015)

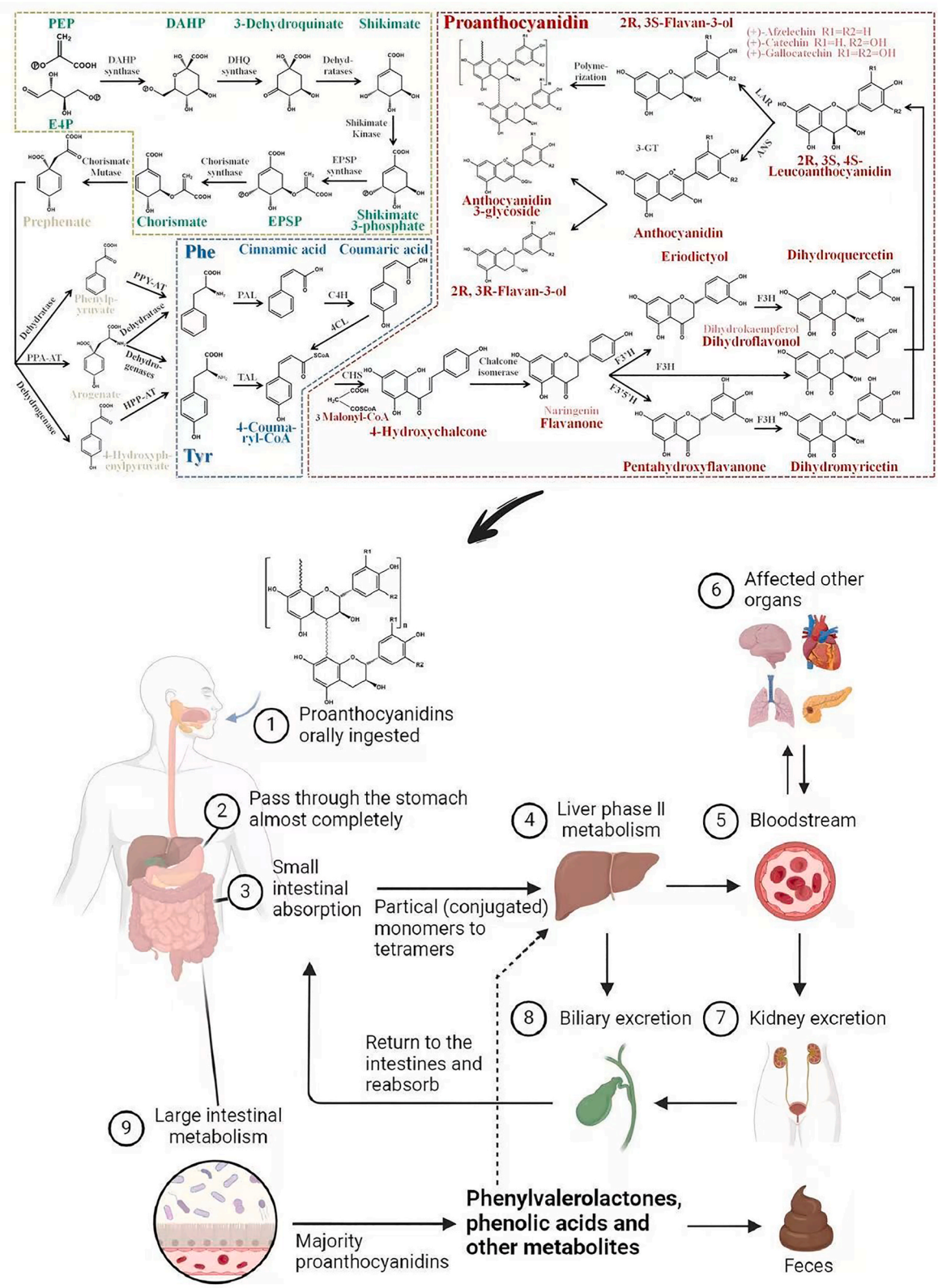

Fig. 2. The biosynthesis and metabolism of proanthocyanidins. PEP, phosphoenolpyruvate; E4P, D-erythrose-4-phosphate; DAHP, 3-deoxy-D-arabinoheptulosonate 7-phosphate; DHQ, 3-dehydroquinate; EPSP, 5-enolpyruvylshikimate-3-phosphate.

procyanidins are significantly stable in the stomach, while Spencer et al. (2000) illustrated that cocoa procyanidins degraded into monomers and dimmers during gastric transit. Their opposite conclusions might be attributed to the different origin of cocoa procyanidins and pre-treatments before determination. Proanthocyanidin monomers and oligomers with DP < 5 can be absorbed in the small intestine through passive diffusion (Steck et al., 2022). Absorbed proanthocyanidins are metabolized by enterocyte or hepatocyte phase-II enzymes, forming corresponding glucuronidated, sulfated and methylated metabolites into other organs via systemic circulation or excreted in urine. A study of 10

humans found that within 24 h after the ingestion of 500 mL green tea, urinary excretion of (epi)catechin and (epi)gallocatechin accounted for 28.5%and 11.4% of intake, respectively (Clifford, van der Hooft, and Crozier, 2013). Proanthocyanidins are metabolized in a dose or matrix-dependent manner, which are associated with the sites of metabolism. Serra et al. (2013) discovered the clear metabolic difference of Wistar rats fed cocoa cream (CC), procyanidin hazelnut skin extract (PE) and PE-riched CC (PECC): the plasmatic metabolites of PECC are the combination of PE and CC; methyl-sulfated procyanidins in the plasma were only detected after feeding PECC; liver is main metabolic organ of PE and other procyanidin-rich simple food matrices, while kidney is closely related with the metabolism of CC, PECC and other procyanidin-rich complex food matrices. Unabsorbed proanthocyanidins (almost two-thirds) reach the colon and convert to phenylvalerolactones, phenolic acids and other metabolites by gut microbiota (Engemann et al., 2012; Liu et al., 2020). Furthermore, the role of gut microbiota in the metabolism of proanthocyanidins has been identified, including C-ring cleavage (*Gordonibacter* spp., *Eggerthella Lenta*, *Adlercreutzia equolifaciens*), dehydroxylation of B-ring (*Eggerthella* sp. SDG-2, *A. equolifaciens* MT4s-5), degradation of A-ring (*Eubacterium ramulus*, *Pseudomonas* sp.) and ring fission (*Flavonifractor plautii*, *Slackiae quolifaciens*, *Lactobacillus splantarum*) (Jin and Hattori, 2012; Kutschera et al., 2011; Schoefer et al., 2002; Sordon et al., 2016; Takagaki et al., 2014). Gut microbial conversion of polyphenols exhibited individual differences, so the stratification of individuals based on their metabolic profiles has been applied for ellagitannins and isoflavones. However, due to the influence of exoteric factors (such as the source, intake dose and intake time), gut microbiota metabotypes of proanthocyanidins remain undefined (Cortes-Martin et al., 2019).

Bioavailability is a key factor responsible for the bioactivity of proanthocyanidins, which is negatively correlated with their mDP. Ou et al. (2012) demonstrated that cranberry A-type procyanidin dimers, trimers, and tetramers crossed Caco-2 cell monolayers with low transport ratio of 0.6%, 0.4%, and 0.2%, respectively. Pan et al. (2021) combined acid-catalytic depolymerization of proanthocyanidins from Chinese bayberry leaves with epigallocatechin gallate (mDP decreased by about 40%) and purification with Amberlite XAD-2, which significantly improved their bioavailability by two folds. Therefore, reducing the mDP to improve the bioavailability of proanthocyanidins is a promising method to broaden their application fields.

4. Regulation of blood glucose by dietary proanthocyanidins

T2DM accounts for 90%–95% of all diabetics, and its common pathogenesis is unhealthy diets that disrupt the balance between insulin secretion and action. Normal pancreatic islet cells can respond to the vibration of blood glucose concentrations by secreting proteohormones and/or changing their quantity, but excessive glucose into cells to flow through alternative pathways (such as sorbitol metabolism and protein kinase C activation) rather than oxidative phosphorylation, leading to the decrease in insulin genes expression and increase in proapoptotic genes expression (Robertson et al., 2003). Besides, the presence of high glucose induces fatty acids from β-oxidation to lipid synthesis, impairing insulin secretion of β cells (Chaurasia et al., 2019). As a result, β cell decompensation eventually turns into β cell failure, and the pathological phenomenon is characterized by the evolution of postprandial hyperglycemia into fasting hyperglycemia (Brereton et al., 2015). Furthermore, decreased sensitivity of peripheral organs to insulin is found in T2DM patients, including the obstruction of glucose uptake in skeletal muscle and the acceleration of hepatic gluconeogenesis and the transformation from lipogenesis to lipolysis in adipose tissue. Systematical mechanisms of insulin resistance are further needed to explore.

Proanthocyanidins have gained popularity in the field of blood glucose regulation, involving carbohydrate metabolism, immunological factors, microbial factors and so on. However, the regulation of proanthocyanidins on blood glucose homeostasis is structure-dependent, and even minor variations in structures influence their regulation on blood glucose. Therefore, the effects and mechanisms of procyanidins, prodelphinidins and propelargonidins on blood glucose homeostasis are considerably different (Table 2). Besides, the selection of research models significantly influences their bioactivities (Wang et al., 2022a).

4.1. Inhibition against carbohydrate hydrolytic enzymes and monosaccharide transporters

Blood glucose homeostasis depends on the balance of carbohydrate absorption rate in the gastrointestinal tract and targeted tissues. Carbohydrates ingested are first hydrolyzed into monosaccharides by hydrolytic enzymes (such as α-amylase and α-glucosidase) and then absorbed into the bloodstream through transporters. So this is the first step in carbohydrate digestion and is a prime target for regulating glucose metabolism.

Procyanidins are the most common type of proanthocyanidins in the plant kingdom with (epi)catechin as subunits. It was reported that procyanidins from apple, red grape and cinnamon were shown to have inhibitory activity against α-amylase (half maximal inhibitory concentration (IC_{50}) of 38.4, 56.1 and 3.54 μg/mL, respectively), α-glucosidase (IC_{50} of 544, 445 and 1592 μg/mL, respectively) and lipase (IC_{50} of 52.7, 581 and 49.6 μg/mL, respectively), deferring carbohydrate digestibility to control postprandial hyperglycemia (Ercan and El, 2021). Prodelphinidins containing (epi)gallocatechin as subunits possess stronger inhibitory activities against carbohydrate hydrolytic enzymes than procyanidins. Prodelphinidins from Chinese bayberry leaves (BLPs) were a mixed inhibitor of α-amylase ($IC_{50} = 3.075 \pm 0.073$ μg/mL) driven by hydrogen bonding and/or van der Waals force and a noncompetitive-type inhibitor of α-glucosidase ($IC_{50} = 37 \pm 0.001$ μg/mL) through hydrogen bonding and hydrophobic interaction (M. Wang et al., 2020; Wang et al., 2019). Actually, minor alterations in structure may significantly influence their activities. Zhong et al. (2018) observed that procyanidins extracted from grape seeds markedly inhibited α-amylase activity in the small intestine and pancreas of mice, especially high polymers (1.95 and 1.73 times higher than oligomers). Wang et al. (2022) improved the inhibitory activities of BLPs against α-glucosidase via acid-catalytic depolymerization. Propelargonidin-type proanthocyanidins with (epi)afzelechin as subunits are relatively rare in nature, resulting in very limited research on their hypoglycemic effects. Proanthocyanidins with high mDP usually have stronger inhibitory activities against carbohydrate hydrolytic enzymes (Lee et al., 2007; Xiang et al., 2022). Conformation is another factor, and epicatechin showed stronger inhibition on α-glucosidase than catechin (Xiang et al., 2022). Notably, proanthocyanidins varied the physical-chemical and digestive properties of carbohydrates, reducing the glycemic index of food, among which prodelphinidin gallates showed the strongest (Wang et al., 2023).

Inhibition of monosaccharide transporters is another strategy for managing blood glucose disorders. Cinnamon procyanidins (300 μg/mL) reduced glucose absorption in Caco-2 cells by 57.43% through decreasing the expression of sodium/glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2) by 88.07% and 69.30% (Liu et al., 2023). Prodelphinidins also suppressed the absorption of carbohydrates in the intestinal tract by inhibiting glucose transporter (Wang et al., 2024). The 65% reduction of green tea polyphenols (1 mM) on glucose uptake was related to competitive inhibition of SGLT1 in rabbit jejunum (Kobayashi et al., 2000).

Apart from delaying digestion of carbohydrates, anti-oxidation, lipid-lowering, anti-inflammation and anti-amyloidogenesis are effective ways for proanthocyanidins to prevent or treat T2DM and its complications, especially for prodelphinidins (Dai et al., 2024; Nie et al., 2017; Zhu et al., 2024). Obviously, structural properties were also suggested to play a vital role in the free radical scavenging capabilities of proanthocyanidins. BLPs extracted using hot water and purified by Sephadex LH-20 column established stronger antioxidant activities than those extracted using conventional methods (Zhang et al., 2017). Lee

Table 2
Effects of proanthocyanidins on T2DM and its complications in diverse models.

Model	Source or proanthocyanidin type	Biomarker	Reference
Chemical experiments	Lotus seedpod procyanidins	Inhibited α-amylase, α-glucosidase and protein tyrosine phosphatase 1 B with IC_{50} of 5.5, 1.0 and 0.33 μg/mL, respectively	(Xiang et al., 2022)
Chemical experiments	*Quercus gilva* Blume leaf procyanidins	Inhibited α-glucosidase with IC_{50} of 40.05 ± 0.51 μg/mL. Scavenged DPPH radical and hydrogen peroxide with IC_{50} of 7.86 ± 0.41 μg/mL and 34.51 ± 1.34 μg/mL, respectively	(Indrianingsih et al., 2022)
Chemical experiments	Red grape procyanidins	Inhibited α-amylase, α-glucosidase and lipase with IC_{50} of 56.1 ± 3.60, 445 ± 15.67 and 52.7 ± 2.05 μg/mL, respectively	Ercan and El (2021)
Chemical experiments	Persimmon peel proanthocyanidins	The EC_{50} of polymers on DPPH radical scavenging activities was 4.35 μg/mL. They showed α-amylase, α-glucosidase and AGE inhibition of 53.9%, 74.0% and 98.0 at 100 μg/mL, respectively. The EC_{50} of oligomers on DPPH radical scavenging activities was 2.4 μg/mL. They showed α-amylase, α-glucosidase and AGE inhibition of 4.6%, 97.4% and 98.1 at 100 μg/mL, respectively	(Lee et al., 2007)
HepG2 cells	Pigmented rice proanthocyanidins	Up-regulated GLUT2 and GYS2. Down-regulated fructose-1,6-bisphosphatase 1 and phosphoenolpyruvate carboxy kinase 1. Decreased AGE formation and oxidation	Krishnan et al. (2021)
HepG2 cells	Procyanidin B1 and B2	Down-regulated protein tyrosine phosphatase-1B	(Li et al., 2021)
HepG2 cells	Persimmon proanthocyanidins	Down-regulated SREBP-2 and NPC1L1. Up-regulated ABCA1, ABCG1, SR-BI, CYP7A1 and ABCG5/G8	Ge et al. (2016)
HepG2 cells	Grape seed proanthocyanidin oligomers	Regulation on Ca^{2+} concentration and ROS formation in a mitochondrial pathway.	An et al. (2014)
HepG2 cells	Persimmon proanthocyanidins	Inhibited SREBP-2 and NPC1L1. Up-regulated ATP-binding cassette transporterA1, G1, G5, G8 scavenger receptor class B type I, cholesterol-7α-hydroxylase	(Ge et al., 2016)
Caco-2 cells			
L6 myotubes	Cacao liquor procyanidins	Stimulated glucose transporter-4 translocation to cell membrane and phosphorylated AMPK	Yamashita et al. (2012b)
3T3-L1 cells	Procyanidin C1	Improved cell differentiation and activated the AKT-eNOS pathway	Sun et al. (2019)
3T3-L1 cells	Persimmon proanthocyanidins	Down-regulated C/EBPα, PPARγ, SREBP1 and FABP. Up-regulated micro-27a and micro-27 b	Zou et al. (2015)
3T3-L1 cells	A-type ECG and EGCG dimers	Bonded to lipid rafts cholesterol and inhibited mitotic clonal expansion. Down-regulated PPARγ, C/EBPα, SREBP1c and PPARγ. Up-regulated micro-27a and micro-27 b	(Zhu et al., 2017; Zhu et al., 2015)
INS-1E cells	Grape seed procyanidins	Up-regulated CPT1a and AMPK. Down-regulated Fasn and Srebf1	Castell-Auvi et al. (2013)
EA.hy926 cells	Grape seed procyanidins	Increased nitric oxide formation and SIRT3 expression. Decreased p53 and PARP expressions. Regulated mitochondrial function	Cerbaro et al. (2020)
Podocyte cells	Procyanidin B2	Up-regulated nuclear respiratory factor 1 and mitochondrial transcription factor A. Actived AMPK-SIRT1-PPAR coactivator-1α	(Cai et al., 2016)
Human retinal pigment epithelial cells	Procyanidin	Regulated apoptosis via p53-mTOR	(Li et al., 2022)
Human umbilical endothelial cells	Grape seed procyanidin B2	Inhibited caspase-3 and lactadherin expressions. Phosphorylated GSK3β	Li et al. (2011)
HK-2 human renal proximal tubular epithelial cells	Procyanidin B2	Up-regulated E-cadherin. Down-regulated vimentin and α-SMA. Decreased phosphorylation of small mothers against decapentaplegic 2, 3 and P38. Increased phosphorylation of small mothers against decapentaplegic 7	Li et al. (2015)
Murine macrophage RAW264 cells	Prodelphinidin B-4 3′-O-gallate	Down-regulated NFκB. Inhibited phosphorylation and degradation of IκBα, and nuclear translocation of p65. Inhibited phosphorylation of IκB kinase α/β and TAK1	Hou et al. (2007)
KKAy mice	Acacia bark-derived proanthocyanidins	Blood: actived AMPK and inhibited DPP-4. Liver: down-regulated SREBP1c, ACC, fatty acid synthase (FAS), PPARγ and lipoprotein lipase. Skeletal muscle: up-regulated fatty acyl CoA oxidase, CPT1 and UCP3. Adipose tissue: up-regulated PPARγ and down-regulated TNF-α	(Kashiwada et al., 2021)
C57BL/6 J mice	Wild blueberry proanthocyanidins	Increased the number of mucin-secreting goblet cells. Increased the proportion of *Adlercreutzia equolifaciens* and *Akkermansia muciniphila*	(Rodriguez-Daza et al., 2020)
Rats	Cinnamon bark proanthocyanidin oligomers	Up-regulated GLUT4 and insulin receptors. Down-regulated GSK3 and actived PI3K/Akt pathway	El-Ashmawy et al. (2022)
C57BL/6 J mice	Blueberry proanthocyanidins	Increased *Muribaculum intestinale*. Actived oxidative phosphorylation metabolic pathway. Increased SCFAs and decreased branched-chain fatty acids production	Morissette et al. (2020)
Wistar rats	Hawthorn procyanidins	Liver: active AMPK, increased superoxide dismutase and glutathione, decreased SREBP1c, malondialdehyde, alanine aminotransferase and aspartate aminotransferase. Gut microbiota: decreased *Firmicutes*, *Blautia*, increased the *Adlercreutzia equolifaciens*, *Akkermansia muciniphila*, *Bacteroides*. Gut barrier: Inhibited TLR4-NFκB pathway.	(Han et al., 2022)
C57BL/6 J mice	GC-(4 → 8)-GCG	Down-regulated PPARγ, C/EBPα, SREBP1c, FAS and ACC. Inhibited MAPK, NFκB, and janus tyrosine kinase-signal transducer and activator of transcription pathways	Peng et al. (2019)
ICR mice	Lotus seedpod procyanidin oligomers	Inhibited $p66^{Shc}$-mTOR Pathway. Liver: up-regulated GLUT2, GK, PFK, PK, and down-regulated FoxO1a, PEPCK, G6Pase, SREBP1c, ACC1, ATP-citrate lyase, FAS, stearoyl CoA desaturase and S6 kinase 1. Muscle: up-regulated GLUT4, GK, PFK and PK. White adipose tissue: up-regulated GLUT4/1, PFK, PK, hexokinase II, and down-regulated SREBP1c. Brown adipose tissue: up-regulated GLUT4/1 and UCP1	Li et al. (2017)
ob/ob mice	Apple procyanidins	Promoted insulin-stimulated Akt phosphorylation. Decreased TNF-α, IL-6 and c-Jun N-terminal kinase phosphorylation	(Ogura et al., 2016)
C57BL/6 J mice	Peanut skin procyanidins	Decreased LPS, IL-6, myeloperoxidase, and increased IL-10. Increased *Lachnospiraceae_NK4A136_group*, *Alloprevotella*, *Akkermansia*, *Faecalibaculum*, and reduced *Muribaculaceae*. Increased impressions of Zona Occludens 1, claudin 1 and occludin in colon. Decreased LPS-TLR4-JNK and increased IRS1/phosphatidylinositol-3-kinase/PKB	(Liu et al., 2022)
ICR mice	Cinnamtannin A2	Actived GLP-1 and IRS-1 in the soleus muscle	Yamashita et al. (2013)
Wistar rats	Grape seed procyanidins	Decreased LPS content and increased tight junction proteins expressions. Increased the proportion of $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs in gut-associated lymphoid tissue. Decreased *Anaerotruncus*, *Blautia*, *Oscillibacter* and *Ruminococcaceae_UCG-004*	Gao et al. (2020)

(*continued on next page*)

Table 2 (*continued*)

Model	Source or proanthocyanidin type	Biomarker	Reference
Wistar rats	Persimmon proanthocyanidins	Down-regulated FAS, SREBP1 and ACC. Stimulated AMPK phosphorylation and up-regulated carnitine palmitoyltransferase-1. Decreased TNFα, C-reactive protein (CRP) and NFκB	Zou et al. (2014)
C57BL/6 J mice	Cacao liquor procyanidins	Up-regulated GLUT4, UCP-1 and UCP-2. Stimulated AMPKα phosphorylation	Yamashita et al. (2012c)
Japanese adults	Acacia bark proanthocyanidins	Decreased fasting blood glucose and HbA1c levels	Baba et al. (2021)
Humans	Persimmon proanthocyanidins	Decreased postprandial plasma glucose	Takemori et al. (2022)

et al. (2007) showed radical scavenging abilities of oligomeric prodelphinidins from persimmon peel were stronger than that of polymers, while Gu et al. (2008) indicted condensed tannins from persimmon pulp with high molecular weight are the major antioxidant composition rather than low molecular weight tannins. Their opposite results are attributed to the different preparation methods of samples and the selection of antioxidant indicators.

4.2. Improvement of pancreatic function

Procyanidins could directly improve insulin secretion by enhancing antioxidant defense and increasing the number of β-cells in the pancreas (Li et al., 2024; Rajasekhar et al., 2021). BLPs stimulated the insulin signaling pathway of high sugar-induced *Drosophila melanogaster*, involving insulin like-peptide, SREBP and other glycolipid metabolism-related genes (Wang et al., 2022b). However, Yang et al. (2015) showed that the hydrolysis of prodelphinidins from pea seed coats caused a 2.5-fold increase in insulin secretion and a 2-fold decrease in α/β-cell area ratio, suggesting the anti-hyperglycemic effect of prodelphinidins depends on their bioavailability.

4.3. Regulation of glucose metabolism in insulin-targeted tissues

The liver is the central organ for carbohydrate synthesis and metabolism. Procyanidins were reported to dose-dependently inhibit gluconeogenesis cyclic and increase glycogen synthesis in insulin-resistant hepatocytes (Huang et al., 2013; Liu and Li, 2021). Procyanidin B1 and procyanidin B2 were also discovered to be mixed inhibitors against protein tyrosine phosphatase-1B activity in HepG cells with IC_{50} of 0.60 and 4.79 μmol/L respectively, which disrupted insulin signal transduction via dephosphorylation of tyrosine residues in insulin receptors and their substrates (Li et al., 2021). Apart from regulating glycometabolism, procyanidin A1 could relieve inflammation in palmitic acid-treated HepG2 cells, according to the antioxidation mediated by inactivating c-Jun N-terminal kinase (JNK)-p38 mitogen-activated protein kinase pathways (D. Yu et al., 2022). Similar to procyanidins, BLPs improved hepatic glucose metabolism in insulin-resistant HepG2 cells by promoting glycogen synthesis (up-regulation of p-GSK3β and GYS2) and attenuating gluconeogenesis (down-regulation of PEPCK and G6Pase) (M. Wang, H. Mao, J. Chen, Q. Li et al., 2022). On the other side, anti-inflammation and anti-oxidation provide BLPs with additional protection against T2DM, and the antioxidant capacities of BLPs were significantly correlated to bioavailability, revealing that BLPs with lower mDP had a much stronger antioxidation (Pan et al., 2021). A similar phenomenon was found in persimmon peel proanthocyanidins (Lee et al., 2008). Propelargonidins from *Senna alata* leaves (SALPs) restored insulin sensitivity by reducing hepatic gluconeogenesis and increasing glucose uptake and relieved impaired lipid metabolism via up-regulating PPARα and down-regulating SREBP 1c and PPARγ in obese mice (Naowaboot and Piyabhan, 2017; Ramsay and Mueller-Harvey, 2016). However, Ogura et al. (2016) supposed that apple procyanidins relieved hepatic insulin resistance of diabetic ob/ob mice by upregulating Akt phosphorylation and downregulating c-JNK phosphorylation rather than inhibiting fat accumulation in liver, but Yin et al. (2015) thought that grape seed procyanidin B2 decreased lipid synthesis and increased free fatty acids β-oxidation in the liver of db/db mice. This difference may result from the selection of animal models and the source of procyanidins. The dynamic balance between hyperglycemia-induced reactive oxygen species and the antioxidant defense system is critical to body homeostasis. Persimmon tannin with high molecular weight protected bromobenzene-stimulated mice from oxidative damage by improving superoxide dismutase and glutathione peroxidase activities in serum and liver, and reducing liver malondialdehyde (Tian et al., 2023). The regulation of bile acid metabolism is another approach to hypolipidemic effects of persimmon tannin for lipid-lowing, including binding with bile acids and increasing bile acid excretion (Zou et al., 2014).

Improving dysfunction of insulin-targeted peripheral tissues is an important mechanism of action of proanthocyanidins. Ho et al. (2017) declared that elderberry procyanidins emerged with radical scavenging abilities as inhibitors of 15-lipoxygenase and xanthine oxidase in satellite cells isolated from the obliquus internus abdominis or vastus lateralis while stimulating oleic acid uptake to reduce plasma free fatty acids. The hypoglycemic effect of procyanidins also embodied in stimulating adiponectin secretion, avoiding adipocyte hypertrophy, reducing inflammation, increasing fatty acid oxidation, improving mitochondrial function in adipose tissue of mice and increasing energy expenditure, alleviating oxidative stress and endoplasmic reticulum stress in skeletal muscle of mice (Ding et al., 2013; Gao et al., 2023; Kashiwada et al., 2021). Grape seed procyanidin extract also activated the autophosphorylation of the insulin receptor to improve glucose uptake using 3T3-L1 and CHO-IR cells (Montagut et al., 2010). Procyanidins with a high molecular weight seemed to have stronger glucose utilization (Bowser et al., 2017). It is worth noting that procyanidins regulated blood glucose in a photoperiod-dependent manner and the administration of procyanidins at the rest-phase was more effective (Hironao et al., 2020). It has been confirmed that persimmon tannin suppressed the differentiation of 3T3-L1 preadipocytes through binding with cholesterol in lipid rafts, and this inhibitory effect was highly structure-dependent, in particular, the presence of galloyl moieties and A-type linkage (Peng et al., 2022; Zhu et al., 2015).

4.4. Impact on the colonic microenvironment

Most proanthocyanidins enter the colon in complete form to act on gut microbiota, gut barrier, gut hormones and cytokines levels. According to Liu et al. (2022), peanut skin procyanidins supplementation improved the microbial diversity of mice with streptozotocin (STZ)-T2DM, recovered Firmicutes/Bacteroidetes ratio, and increased SCFAs-producing microbiota (*Lachnospiraceae_NK4A136_group*, *Alloprevotella* and *Faecalibaculum*) (Portincasa et al., 2022). Peanut skin procyanidins also eliminated intestinal inflammation by improving the growth of *Akkermansia* and reducing that of *Muribaculaceae*. Nevertheless, different regulation was found in hawthorn procyanidins, such as the increase in *Akkermansia*, *Bacteroides*, *Adlercreutzia* and the decrease in *Lactobacillus*, *Bifidobacterium*, *Blautia*, *Lachnospiraceae* and

Subdoligranulum (Han et al., 2022). This inconsistency is probably due to the structural difference of procyanidins originating from different sources. BLPs relieved glucose and lipid metabolism disorders in obese mice by sharply decreasing the percentage of endotoxin-producing bacteria (*Desulfovibrionaceae*), and enabling distinct bacteria (such as *Peptococcaceae*, *Clostridiaceae* and *Desulfovibrio*) (Zhang et al., 2022). Notably, the dose of prodelphinidins determines their alterations on gut microbiota, 50 mg/kg BW and 100 mg/kg BW persimmon tannin increased beneficial *Bifidobacterium* and *Lactobacillus*, while 200 mg/kg BW persimmon tannin increased the harmful *Escherichia coli* and *Clostridium* (Zhu et al., 2018b). Oligomeric proanthocyanidins strongly promoted beneficial bacteria, while polymers inhibited harmful bacteria, indicating the mDP impacted their biological activities (Grzelczyk et al., 2024). Except interacting with gut microbiota, proanthocyanidins could increase the expression of tight junction proteins and the number of mucin-secreting goblet cells to reduce intestinal endotoxin transfer and enhance the gut barrier integrality (Rodriguez-Daza et al., 2020). Proanthocyanidins also enhance the release of gut hormones (such as glucagon-like peptide-1, glucose-dependent insulinotropic peptide, peptide YY, cholecystokinin and ghrelin) by promoting L-cell development, which modulates appetite and glucose homeostasis (Casanova-Martí et al., 2017, 2020). In addition, proanthocyanidins also protect the gut from inflammation by inhibiting the NF-κB and MAPK pathway, enhancing the PI3K/Akt pathway, and stimulating antioxidant defensive mechanisms (Koudoufio et al., 2021). Moreover, proanthocyanidins increased the production of short-chain fatty acids, which maintain intestinal homeostasis (Redondo-Castillejo et al., 2023).

Prolonged exposure of other organs to high glucose conditions may also cause pathological changes and proanthocyanidins intervention can effectively prevent and treat complications of T2DM. This generally contributes to oxidative stress attenuation, cell anti-apoptosis, mitochondrial function regulation and inflammation mitigation, such as in endothelial progenitor cells, retinal pigment epithelial cells and podocytes (Cai et al., 2016; Fan et al., 2021; Li et al., 2022). A cross-over PRECISE intervention study in 14 participants with an increased risk of T2DM found that those with bilberry and grape seed extract had greater decreases in systolic and diastolic ambulatory blood pressure (-4.8 ± 15.5 mmHg and -2.6 ± 12.1 mmHg, respectively) than those with 550 mg of a control extract for 12 weeks, suggesting that individuals at risk of T2DM following a habitual bilberry and grape seed extract intake are more likely to improve cardio metabolism, and individual responsiveness is related with the metabolic capability of certain gut bacterial strains (Grohmann et al., 2023).

As mentioned above, proanthocyanidins are beneficial in preventing and treating T2DM and its complications through multiple channels, although the results of different types of proanthocyanidins are inconsistent with variation in major targets (Fig. 3). Briefly, proanthocyanidins first interact with carbohydrates to diminish their glycemic index and delay the absorption of carbohydrates by inhibiting digestive enzymes and glucose-related transporters in the small intestine. Then, absorbed proanthocyanidins act as signaling molecules to regulate glucose metabolism in insulin-targeted tissues (that is, liver, skeletal muscle and adipose tissue). Unabsorbed proanthocyanidins play a key role in the large intestine, including gut microbiota regulation, intestinal barrier enhancement and intestinal hormone secretion promotion. Meanwhile, insulin synthesis of islets can be directly improved by proanthocyanidins. The mechanisms underpinning the alleviation of T2DM-related complications by proanthocyanidins include antioxidation, anti-inflammatory and so on. However, due to the difficulty in separation and purification, most studies focused on crude extracts of proanthocyanidins, which contain different types of proanthocyanidins, impeding the exploration of their structure-activity relationships. The active sites of different proanthocyanidin components are various, so *in vitro* experiments with a single factor are difficult to evaluate their real activities. Due to the high density of hydroxyl and galloacylation, prodelphinidins exhibited stronger activities to regulate glucose and lipid metabolism. Additionally, bioavailability is another major determinant, contributing to the hypoglycemic effects of prodelphinidins.

5. Influence of structural features on hypoglycemic proanthocyanidins

As mentioned above, procyanidins, prodelphinidins and propelargonidins possessed varying degrees of hypoglycemic effects due to differences in structural features, mainly including the mDP, galloacylation at C3, hydroxyl number in B ring and linkage types (Fig. 4). In terms of the mDP, most studies showed that the inhibition of proanthocyanidins on carbohydrate digestive enzymes was positively

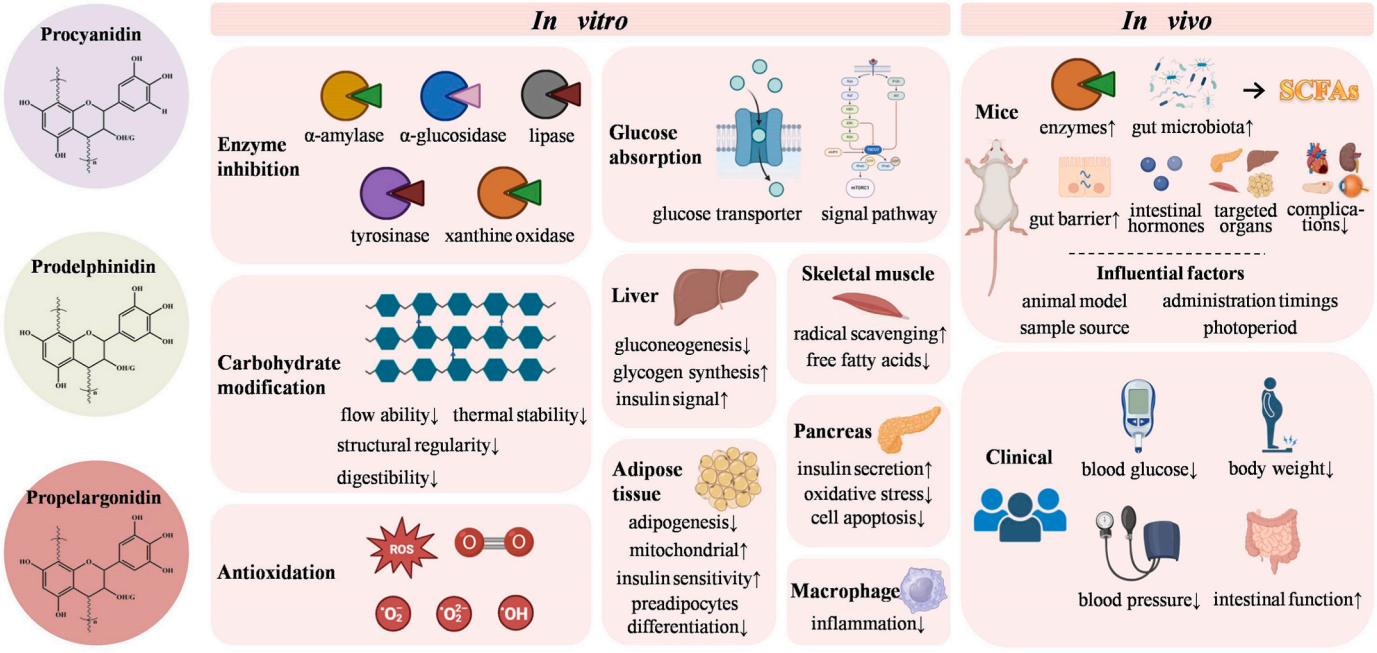

Fig. 3. The role of three different types of proanthocyanidins in blood glucose at the molecular, cellular and organismal levels.

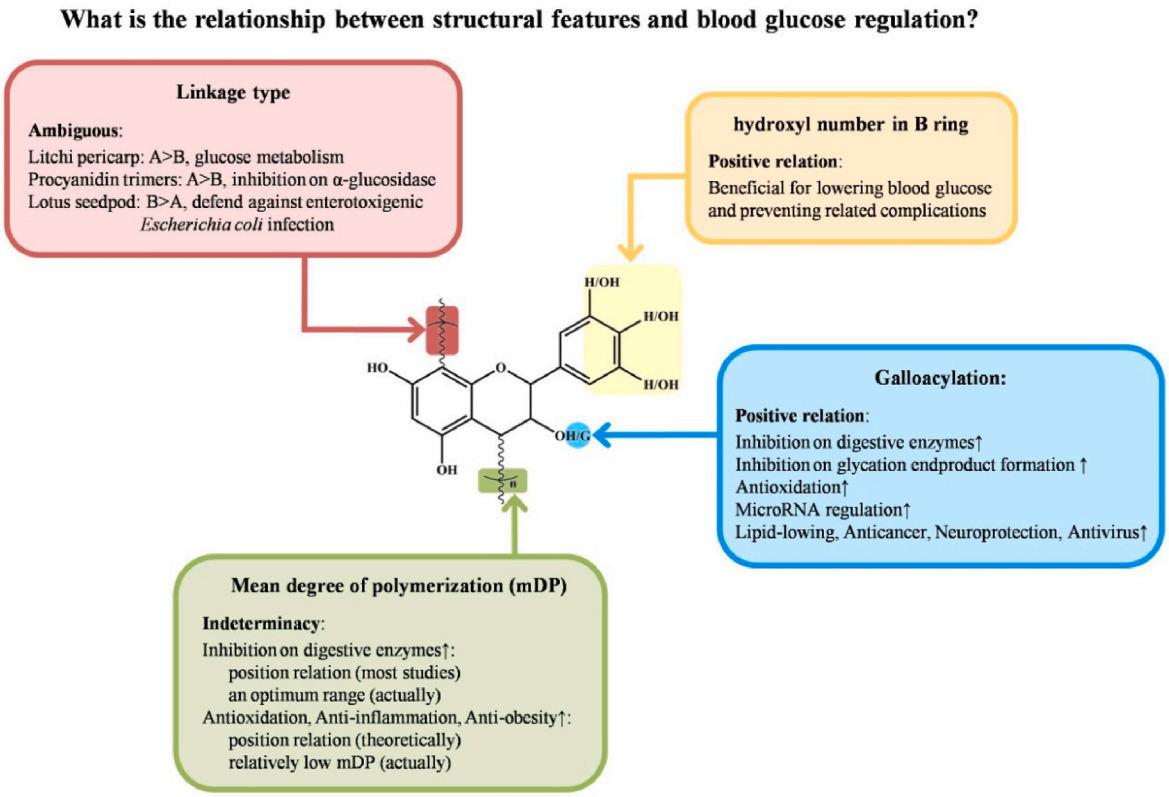

Fig. 4. Effects of structural features on hypoglycemic proanthocyanidins.

correlated to their mDP because more active sites were able to bind with enzymes (Xiang et al., 2022; Zhang et al., 2020). Nevertheless, Lee et al. observed that PPPs with the mDP <3 exhibited stronger inhibitory activities against α-glucosidase than PPPs with the mDP >4. Oligomeric proanthocyanidins could enter the specific cavities and then bind the enzymes, while polymers interacted with the surface of enzymes but were distant from the active sites of enzymes (Vazquez-Flores et al., 2018). Besides, proanthocyanidins are not broad-spectrum inhibitors of digestive enzymes, and the influence of mDP cannot be generalized (Quintero-Soto et al., 2021). Whereas the mDP was closely related to specific bioactivities, proanthocyanidins with an optimum range of mDP had the best inhibitory activities against certain carbohydrate digestive enzymes. Theoretically, polymeric proanthocyanidins possess stronger antioxidant capacity than oligomers, because more hydroxyl groups can provide protons to neutralize free radicals. Actually, the antioxidation of oligomeric proanthocyanidins is stronger than polymers *in vivo*. The possible reasons for this difference are bioavailability and simplification of models *in vitro* (Bowser et al., 2017). Therefore, a growing number of researchers focused on seeking methods to improve the bioavailability of proanthocyanidins, and it turned out that oligomers were stronger antioxidants. Moreover, the bioavailability of proanthocyanidin-derived metabolites was improved by hydrolysis, which was crucial to the improvements in β-cell function in glucose-intolerant rats according to Yang et al. (2015). The mDP appears to affect the anti-inflammation of proanthocyanidins in the same manner. Andersen-Civil et al. (2021) indicated that proanthocyanidins with medium mDP (9.1) enhanced inflammatory cytokine responses in murine macrophages, but proanthocyanidins with either low (2.6) or high (12.3) mDP were not. Conversely, polymeric persimmon proanthocyanidins demonstrated stronger anti-obesity potency than oligomers, probably attributed to their disturbance of the gut microbiota (Y. Yu et al., 2022). Besides, the hypoglycemic activity of proanthocyanidins is the result of multiple factors, and the contribution of mDP to each mechanism varies, so the influence of mDP should be comprehensively considered from multiple levels.

Galloacylation related to the effects of proanthocyanidins has been observed. Broadly, the presence of galloyl groups is beneficial to the hypoglycemic effects of proanthocyanidins. Xiang et al. (2022) found that the inhibitory effects of procyanidins from lotus seedpods on α-amylase, α-glucosidase and protein tyrosine phosphatase 1 B increased with the existence of galloyl groups. Proanthocyanidins containing galloyl groups possessed stronger inhibitory effects against AGE formation and scavenging activity on free radicals (Park et al., 2012). According to Serrano et al. (2016), the galloyl groups of grape seed proanthocyanidins are responsible for food intake inhibition, suggesting that proanthocyanidins without galloyl moieties were not as effective as grape-seed-derived forms. It was reported that the presence of galloyl groups in proanthocyanidins was helpful to their regulation of microRNA, which was closely related to glucose metabolism (Wang et al., 2022a). Apart from regulating blood glucose, galloyl groups of proanthocyanidins also played an important role in lipid-lowing, anticancer, neuroprotection and antivirus (Actis-Goretta et al., 2008; Isaacs et al., 2011; Nie et al., 2017; Zhu et al., 2017). Concerning hydroxyl number in the B ring, prodelphinidins containing pyrogallol in B ring had higher antioxidant capacity than that of procyanidins and propelargonidins, which attributed to their high density of active hydroxyl groups (Elessawy et al., 2021). Therefore, proanthocyanidins with high density of active phenolic hydroxyl groups exhibited the strongest anti-hyperglycemic effect.

Linkage type is another influencing factor of proanthocyanidin activities. Li et al. (2016) showed that A-type procyanidins from litchi pericarp regulated hepatic and muscle glucose metabolism via the activation of AMPK in diabetic mice more effectively than B-type procyanidins. A-type procyanidin trimers were reported to have better inhibitory activity against α-glucosidase than B-type procyanidin trimers (Zhao et al., 2020). Generally, the biological activities of A-type proanthocyanidins was better than B-type, because spatially stretched A-type proanthocyanidins exert stronger affinity with deep oxygen

atoms via hydrogen bonds, thus their membrane-interaction potency was better than B-type proanthocyanidins (Zhu et al., 2018a). Nevertheless, B-type procyanidin oligomers from lotus seedpod were more effective in defending against enterotoxigenic *Escherichia coli* infection than A-type procyanidin oligomers (Tang et al., 2017). The impacts of linkage type on the hypoglycemic effects of proanthocyanidins need to be further explored.

6. Mechanism of dietary proanthocyanidins on blood glucose homeostasis

Impaired glucose tolerance accelerates atherogenesis, carrying devastating macrovascular and microvascular complications. Proanthocyanidins, catechin-based secondary metabolites of plants, regulate blood glucose homeostasis in various approaches. Clarifying their molecular mechanisms is crucial to conceptualize their control on glycemia and future clinical applications. Ingested proanthocyanidins generally possess two fates: (1) partial proanthocyanidins are absorbed through intestinal epithelial cells, and reach various tissues via systemic circulation to function. (2) the rest of proanthocyanidins in a complete form enter the large intestine and are metabolized by gut microbiota, and metabolites are absorbed or excreted through feces. The mechanism of proanthocyanidins on blood glucose homeostasis involves absorption-dependent and non-absorption-dependent factors, yet their relative contributions remain obscure (Fig. 5).

In regard to unabsorbed proanthocyanidins, they avoid blood glucose disorder via coelenteron effects. Proanthocyanidins serve as inhibitors of digestive enzymes to retard the hydrolysis of carbohydrates to absorbable monosaccharides. Notably, proanthocyanidins have specific selectivity on enzymes (Yamashita et al., 2012a). Another mechanism of proanthocyanidins in inhibiting digestion and absorption of hypoglycemic nutrients is to decrease the impression of glucose transporters in intestinal epithelial cells. Absorbed proanthocyanidins exert insulin-like effects on target organs. The liver is a central organ of glucose metabolism, but insulin resistance, oxidative stress and inflammation can lead to disorders of glucose and lipid metabolism. Proanthocyanidins promote glucose uptake by up-regulating the impression of glucose transporters, such as GLUT2 in the liver. They also increased the glycolytic gene expressions of phosphofructokinase (PFK) and pyruvate kinase (PK), and glycogenic gene expressions of p-GSK3β and GYS2, while gluconeogenic gene expression of PEPCK, G6Pase and some microRNA were decreased in liver. Furthermore, proanthocyanidins regulate impaired insulin (IRS-1-PI3K-Akt), antioxidation (PPARα and Nrf2) and anti-inflammation (LPS-TLR4-JNK) signaling pathway and improve mitochondrial metabolism to avoid lipid accumulation in the liver. Skeletal muscle is the key organ for non-oxidative glucose metabolism mediated by insulin, and proanthocyanidins can improve mitochondrial bioenergetics, enhance fatty acid oxidation, increase uncoupling protein 2 (UCP2) and energy expenditure-related genes, and ameliorate oxidative stress and endoplasmic reticulum stress. The main effects of proanthocyanidins on adipose tissue are the inhibition of secreting free fatty acids and inflammatory cytokines, involving the increase in adiponectin and the decrease in NF-κB and inhibitor of κB kinase. Proanthocyanidins can repair damaged pancreatic islets by promoting glucose metabolism, scavenging reactive oxygen radicals, reducing lipotoxicity and degrading islet amyloid. Moreover, microbial metabolites of proanthocyanidins can be absorbed into the bloodstream and act on targeted organs to maintain blood glucose homeostasis. Finally, proanthocyanidins can directly stimulate insulin secretion via normalization of β cellular structure and increase in the number and volume of β cells.

Most proanthocyanidins then enter the colon to enhance the intestinal barrier by increasing the impression of tight junction proteins and the amounts of goblet cells, thereby preventing inflammation induced by circulating endotoxin. Importantly, proanthocyanidins also improve the diversity of gut microbiota, increase beneficial bacteria (such as

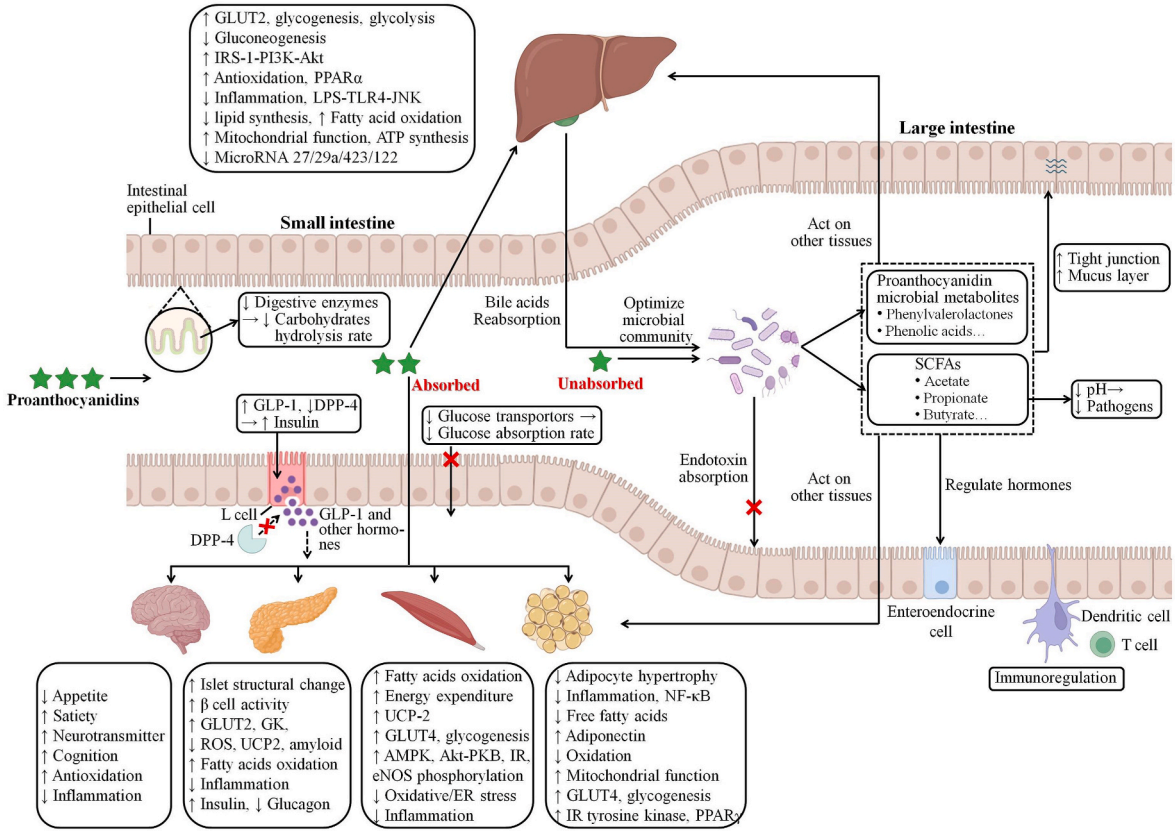

Fig. 5. Mechanism of dietary proanthocyanidins on blood glucose homeostasis.

short-chain fatty acid (SCFAs)-producing bacteria and phenolic-metabolizingbacteria) and reduce pathogens. Proanthocyanidins can stimulate gut L-cells to secrete glucagon-like peptide-1 (GLP-1) which increases insulin levels in response to carbohydrates and suppresses the degradation of GLP-1 via dipeptidyl peptidase-IV (DPP-4) (M. Liu et al., 2023). Additionally, proanthocyanidins maintain intestinal homeostasis by reducing cytokine levels and stimulating antioxidant defensive mechanisms. In a word, unabsorbed proanthocyanidins avoid blood glucose disorder via coelenteron effects, mainly including suppression of carbohydrate digestion and absorption, stimulation of intestinal hormone secretion, inhibition of endotoxin absorption and improvement of gut microbiota. Absorbed proanthocyanidins serve as insulin mimetics, acting on insulin-targeted liver, skeletal muscle and adipose tissue to alleviate insulin resistance. Besides, absorbed proanthocyanidins can directly improve β-cell dysfunction to increase insulin secretion.

Hence, unabsorbed proanthocyanidins mainly play roles in the intestinal lumen, making them more effective in regulating acute postprandial blood glucose rather than fasting blood glucose and preventing the occurrence of T2DM, but absorbed proanthocyanidins are more stable for long-term treatment of T2DM and its complications. Besides, most research indicated that the administration of proanthocyanidins in a daily bolus was more effective than when given with food in treating high-fat diet-induced T2DM.

7. Conclusion and future prospectives

Increasing proanthocyanidins consumption is a promising diet therapy in the regulation of blood glucose homeostasis. Most proanthocyanidins possess extremely low bioavailability and ameliorate high blood glucose by luminal effects: (1) inhibit digestive enzyme activities to reduce the absorption of carbohydrates; (2) improve the diversity of gut microbiota, increase beneficial bacteria (such as short-chain fatty acid (SCFAs)-producing bacteria and phenolic-metabolizing bacteria) and reduce pathogens; (3) reduce circulating endotoxin levels to protect the intestinal barrier function and inhibit inflammation caused by leaky gut. A few absorbed proanthocyanidins exert insulin-like effects in the liver, skeletal muscle and other peripheral tissue. Proanthocyanidins from various sources possess different structures, but even minor variations in structures influence their regulation of blood glucose. Prodelphinidin gallates exhibited the strongest anti-hyperglycemic effect than others, due to their galloacylation at C3 and a large number of hydroxyl groups in the B ring. The mDP and linkage type should be comprehensively considered from multiple levels. Besides, the source, intake dose, intake time and selection of research models should be considered. Here are some prospects.

(1) Owing to the difficulty in separation and purification, most studies focused on the mixtures of proanthocyanidins, hindering the exploration of their structure-activity relationships. So future studies should emphasize the purification of pure proanthocyanidins from extracts for further research.
(2) The contributions of diverse proanthocyanidins on different action sites are different. Although *in vivo* experiments can effectively evaluate the bioactivities of proanthocyanidins, *in vitro* experiments with a single factor are difficult to achieve, and a reliable *in vitro* evaluation system is needed in the future.
(3) Given the various mechanisms of proanthocyanidins, the utility of co-administration of different proanthocyanidins with differing structural features, or proanthocyanidins with diverse mechanisms has yet to be explored and holds promise as a therapeutic strategy across several blood glucose disorders.
(4) The regulation of proanthocyanidins on blood glucose homeostasis remarkably differs based on dietary structure and individual physique, so a personalized guide for the proanthocyanidins intake should be considered in the future.

CRediT authorship contribution statement

Yi Wang: Conceptualization, Investigation, Data curation, Writing – original draft. **Laiming Zhang:** Conceptualization, Resources, Writing – review & editing. **Hang Xiao:** Conceptualization, Writing – review & editing, Supervision, Resources. **Xingqian Ye:** Conceptualization, Supervision, Validation, Project administration, Funding acquisition, Writing – review & editing. **Haibo Pan:** Conceptualization, Supervision, Validation, Project administration, Funding acquisition, Writing – review & editing. **Shiguo Chen:** Conceptualization, Supervision, Validation, Project administration, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was financially supported by National Natural Science Foundation of China, China (Grant No. 31972088 and 32001715) and National Key Research and Development Program of China, China (Grant No. 2022YFF1100204).

Data availability

Data will be made available on request.

References

Actis-Goretta, L., Romanczyk, L.J., Rodriguez, C.A., Kwik-Uribe, C., Keen, C.L., 2008. Cytotoxic effects of digalloyl dimer procyanidins in human cancer cell lines. J. Nutr. Biochem. 19 (12), 797–808. https://doi.org/10.1016/j.jnutbio.2007.10.004.

An, J., Chen, C., Wang, X., Zhong, Y., Zhang, X., Yu, Y., Yu, Z., 2014. Oligomeric proanthocyanidins alleviate hexabromocyclododecane-induced cytotoxicity in HepG2 cells through regulation on ROS formation and mitochondrial pathway. Toxicol. In Vitro 28 (2), 319–326. https://doi.org/10.1016/j.tiv.2013.11.009.

Andersen-Civil, A.I.S., Leppa, M.M., Thamsborg, S.M., Salminen, J.P., Williams, A.R., 2021. Structure-function analysis of purified proanthocyanidins reveals a role for polymer size in suppressing inflammatory responses. Commun. Biol. 4 (1), 896. https://doi.org/10.1038/s42003-021-02408-3.

Baba, A., Hoshino, T., Ogawa, S., Takara, T., 2021. Improvement of glucose metabolism and safety of acacia bark-derived proanthocyanidins in healthy Japanese adults: a randomized, double-blind, placebo-controlled, parallel-group trial. Funct. Food Health Dis 11 (9), 431–455. https://doi.org/10.31989/ffhd.v11i9.822.

Baron, G., Altomare, A., Della Vedova, L., Gado, F., Quagliano, O., Casati, S., Aldini, G., 2024. Unraveling the parahormetic mechanism underlying the health-protecting effects of grapeseed procyanidins. Redox Biol. 69. https://doi.org/10.1016/j.redox.2023.102981.

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. J. Agric. Food Chem. 61 (38), 9148–9154. https://doi.org/10.1021/jf4024728.

Bowser, S.M., Moore, W.T., McMillan, R.P., Dorenkott, M.R., Goodrich, K.M., Ye, L., 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. J. Nutr. Biochem. 39, 48–58. https://doi.org/10.1016/j.jnutbio.2016.10.001.

Brereton, M.F., Vergari, E., Zhang, Q., Clark, A., 2015. Alpha-, delta- and PP-cells: are they the architectural cornerstones of islet structure and co-ordination? J. Histochem. Cytochem. 63 (8), 575–591. https://doi.org/10.1369/0022155415583535.

Buendia, B., Gil, M.I., Tudela, J.A., Gady, A.L., Medina, J.J., Soria, C., Tomas-Barberan, F.A., 2010. HPLC-MS analysis of proanthocyanidin oligomers and other phenolics in 15 strawberry cultivars. J. Agric. Food Chem. 58 (7), 3916–3926. https://doi.org/10.1021/jf9030597.

Cai, X., Bao, L., Ren, J., Li, Y., Zhang, Z., 2016. Grape seed procyanidin B2 protects podocytes from high glucose-induced mitochondrial dysfunction and apoptosis via the AMPK-SIRT1-PGC-1α axis *in vitro*. Food Funct. 7 (2), 805–815. https://doi.org/10.1039/c5fo01062d.

Carpenter, J.L., Caruso, F.L., Tata, A., Vorsa, N., Neto, C.C., 2014. Variation in proanthocyanidin content and composition among commonly grown North American cranberry cultivars (*Vaccinium macrocarpon*). J. Sci. Food Agric. 94 (13), 2738–2745. https://doi.org/10.1002/jsfa.6618.

Casanova-Martí, À., Gonzalez-Abuín, N., Serrano, J., Blay, M.T., Terra, X., Frost, G., Ardévol, A., 2020. Long term exposure to a grape seed proanthocyanidin extract enhances L-cell differentiation in intestinal organoids. Mol. Nutr. Food Res. 64 (16), 2000303. https://doi.org/10.1002/mnfr.202000303.

Casanova-Martí, À., Serrano, J., Blay, M.T., Terra, X., Ardévol, A., Pinent, M., 2017. Acute selective bioactivity of grape seed proanthocyanidins on enteroendocrine secretions in the gastrointestinal tract. Food Nutr. Res. 61 (1), 1321347. https://doi.org/10.1080/16546628.2017.1321347.

Castell-Auvi, A., Cedo, L., Pallares, V., Blay, M., Pinent, M., Ardevol, A., 2013. Grape seed procyanidins improve β-cell functionality under lipotoxic conditions due to their lipid-lowering effect. J. Nutr. Biochem. 24 (6), 948–953. https://doi.org/10.1016/j.jnutbio.2012.06.015.

Cerbaro, A.F., Rodrigues, V.S.B., Rigotti, M., Branco, C.S., Rech, G., de Oliveira, D.L., Salvador, M., 2020. Grape seed proanthocyanidins improves mitochondrial function and reduces oxidative stress through an increase in sirtuin 3 expression in EA. hy926 cells in high glucose condition. Mol. Biol. Rep. 47, 3319–3330.

Chaurasia, B., Tippetts, T.S., Mayoral Monibas, R., Liu, J., Li, Y., Wang, L., Summers, S. A., 2019. Targeting a ceramide double bond improves insulin resistance and hepatic steatosis. Science 365 (6451), 386–392. https://doi.org/10.1126/science.aav3722.

Chou, C.Y., Hsu, D.Y., Chou, C.H., 2023. Predicting the onset of diabetes with machine learning methods. J. Personalized Med. 13 (3). https://doi.org/10.3390/jpm13030406.

Clifford, M.N., van der Hooft, J.J., Crozier, A., 2013. Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols. Am. J. Clin. Nutr. 98 (6), 1619S–1630S. https://doi.org/10.3945/ajcn.113.058958.

Cohen, S.D., Tarara, J.M., Kennedy, J.A., 2008. Assessing the impact of temperature on grape phenolic metabolism. Anal. Chim. Acta 621 (1), 57–67. https://doi.org/10.1016/j.aca.2007.11.029.

Coleman, S.L., Shaw, O.M., 2017. Progress in the understanding of the pathology of allergic asthma and the potential of fruit proanthocyanidins as modulators of airway inflammation. Food Funct. 8 (12), 4315–4324. https://doi.org/10.1039/c7fo00789b.

Cortes-Martin, A., Selma, M.V., Espin, J.C., Garcia-Villalba, R., 2019. The human metabolism of nuts proanthocyanidins does not reveal urinary metabolites consistent with distinctive gut microbiota metabotypes. Mol. Nutr. Food Res. 63 (2), e1800819. https://doi.org/10.1002/mnfr.201800819.

Crowe-White, K.M., Evans, L.W., Kuhnle, G.G.C., Milenkovic, D., Stote, K., Wallace, T., Senkus, K.E., 2022. Flavan-3-ols and cardiometabolic health: first ever dietary bioactive guideline. Adv. Nutr. 13 (6), 2070–2083. https://doi.org/10.1093/advances/nmac105.

Dai, J., Liu, Z., Ma, L., Yang, C., Bai, L., Han, D., Wang, Z., 2024. Identification of procyanidins as α-glucosidase inhibitors, pancreatic lipase inhibitors, and antioxidants from the bark of *Cinnamomum cassia* by multi-bioactivity-labeled molecular networking. Food Res. Int. 192 (114833). https://doi.org/10.1016/j.foodres.2024.114833.

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

Di Lorenzo, C., Colombo, F., Biella, S., Stockley, C., Restani, P., 2021. Polyphenols and human health: the role of bioavailability. Nutrients 13(1) 273. https://doi.org/10.3390/nu13010273.

Ding, Y., Dai, X., Jiang, Y., Zhang, Z., Bao, L., Li, Y., Li, Y., 2013. Grape seed proanthocyanidin extracts alleviate oxidative stress and ER stress in skeletal muscle of low-dose streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats. Mol. Nutr. Food Res. 57 (2), 365–369. https://doi.org/10.1002/mnfr.201200463.

Dong, X.Q., Zou, B., Zhang, Y., Ge, Z.Z., Du, J., Li, C.M., 2013. Preparation of A-type proanthocyanidin dimers from peanut skins and persimmon pulp and comparison of the antioxidant activity of A-type and B-type dimers. Fitoterapia 91, 128–139. https://doi.org/10.1016/j.fitote.2013.08.019.

Downey, M.O., Harvey, J.S., Robinson, S.P., 2003. Analysis of tannins in seeds and skins of Shiraz grapes throughout berry development. Aust. J. Grape Wine R. 9 (1), 15–27. https://doi.org/10.1111/j.1755-0238.2003.tb00228.x.

El-Ashmawy, N.E., Khedr, E.G., Alfeky, N.H., Ibrahim, A.O., 2022. Upregulation of GLUT4 and PI3K, and downregulation of GSK3 mediate the anti-hyperglycemic effects of proanthocyanidins. Med. Int. 2 (3), 14. https://doi.org/10.3892/mi.2022.39.

Elessawy, F.M., Vandenberg, A., El-Aneed, A., Purves, R.W., 2021. An untargeted metabolomics approach for correlating pulse crop seed coat polyphenol profiles with antioxidant capacity and iron chelation ability. Molecules 26(13). https://doi.org/10.3390/molecules26133833.

Engemann, A., Hubner, F., Rzeppa, S., Humpf, H.U., 2012. Intestinal metabolism of two A-type procyanidins using the pig cecum model: detailed structure elucidation of unknown catabolites with Fourier transform mass spectrometry (FTMS). J. Agric. Food Chem. 60 (3), 749–757. https://doi.org/10.1021/jf203927g.

Ercan, P., El, S.N., 2021. Inhibitory effects of bioaccessible anthocyanins and procyanidins from apple, red grape, cinnamon on α-amylase, α-glucosidase and lipase. Int. J. Vitam. Nutr. Res. 91 (1–2), 16–24. https://doi.org/10.1024/0300-9831/a000652.

Fan, J., Liu, H., Wang, J., Zeng, J., Tan, Y., Wang, Y., Dai, X., 2021. Procyanidin B2 improves endothelial progenitor cell function and promotes wound healing in diabetic mice *via* activating Nrf2. J. Cell Mol. Med. 25 (2), 652–665. https://doi.org/10.1111/jcmm.16111.

Freitas, V.A.P.D., Glories, Y., 1999. Concentration and compositional changes of procyanidins in grape seeds and skin of white *Vitis vinifera* varieties. J. Sci. Food Agric. 79 (12), 1601. https://doi.org/10.1002/(SICI)1097-0010(199909)79, 1606: 12<1601::AID-JSFA407>3.0.CO;2–1.

Gao, P., Fang, L., Pan, Y., Jiang, L., 2023. Effect of grape seed proanthocyanidins on fat metabolism and adipocytokines in obese rats. Metabolites 13(4). https://doi.org/10.3390/metabo13040568.

Gao, Z., Wu, H., Zhang, K., Hossen, I., Wang, J., Wang, C., Cao, Y., 2020. Protective effects of grape seed procyanidin extract on intestinal barrier dysfunction induced by a long-term high-fat diet. J. Funct.Foods 64 (103663). https://doi.org/10.1016/j.jff.2019.103663.

Ge, Z., Zhu, W., Peng, J., Deng, X., Li, C., 2016. Persimmon tannin regulates the expression of genes critical for cholesterol absorption and cholesterol efflux by LXRα independent pathway. J. Funct.Foods 23, 283–293. https://doi.org/10.1016/j.jff.2016.02.033.

Grohmann, T., Walker, A.W., Russell, W.R., Hoggard, N., Zhang, X., Horgan, G., de Roos, B., 2023. A grape seed and bilberry extract reduces blood pressure in individuals at risk of developing type 2 diabetes: the PRECISE study, a double-blind placebo-controlled cross-over intervention study. Front. Nutrition 10 (1139880). https://doi.org/10.3389/fnut.2023.1139880.

Grzelczyk, J., Budryn, G., Szwajgier, D., Baranowska-Wójcik, E., Zaklos-Szyda, M., 2024. Evaluation of the effect of roasting and digestion on biological activity of compounds of coffee extracts - *in vitro* assessment of the bioavailability, cytoprotective properties and modulation of inflammatory response. Food Chem. 460 (140648). https://doi.org/10.1016/j.foodchem.2024.140648.

Gu, H.F., Li, C.M., Xu, Y.J., Hu, W.F., Chen, M.H., Wan, Q.H., 2008. Structural features and antioxidant activity of tannin from persimmon pulp. Food Res. Int. 41 (2), 208–217. https://doi.org/10.1016/j.foodres.2007.11.011.

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

Han, X., Zhao, W., Zhou, Q., Chen, H., Yuan, J., Xiaofu, Z., Zhang, Z., 2022. Procyanidins from hawthorn (*Crataegus pinnatifida*) alleviate lipid metabolism disorder via inhibiting insulin resistance and oxidative stress, normalizing the gut microbiota structure and intestinal barrier, and further suppressing hepatic inflammation and lipid accumulation. Food Funct. 13 (14), 7901–7917. https://doi.org/10.1039/d2fo00836j.

Hashimoto, F., Nonaka, G.I., Nishioka, I., 1989. Tannins and related compounds. XC.: 8-C-ascorbyl (-)-epigallocatechin 3-O-gallate and novel dimeric flavan-3-ols, oolonghomobisflavans A and B, from oolong tea. (3). Chem. Pharm. Bull. 37 (12), 3255–3263. https://doi.org/10.1248/cpb.37.3255.

Hirasawa, M., Takada, K., Makimura, M., Otake, S., 2002. Improvement of periodontal status by green tea catechin using a local delivery system: a clinical pilot study. J. Periodontal. Res. 37 (6), 433–438. https://doi.org/10.1034/j.1600-0765.2002.01640.x.

Hironao, K.Y., Ashida, H., Yamashita, Y., 2020. The cacao procyanidin extract-caused anti-hyperglycemic effect was changed by the administration timings. J Clin. Biochem. Nutrition 67 (1), 61–66. https://doi.org/10.3164/jcbn.20-45.

Ho, G.T., Kase, E.T., Wangensteen, H., Barsett, H., 2017. Phenolic elderberry extracts, anthocyanins, procyanidins, and metabolites influence glucose and fatty acid uptake in human skeletal muscle cells. J. Agric. Food Chem. 65 (13), 2677–2685. https://doi.org/10.1021/acs.jafc.6b05582.

Hou, D.X., Luo, D., Tanigawa, S., Hashimoto, F., Uto, T., Masuzaki, S., Sakata, Y., 2007. Prodelphinidin B-4 3'-O-gallate, a tea polyphenol, is involved in the inhibition of COX-2 and iNOS via the downregulation of TAK1-NF-kappaB pathway. Biochem. Pharmacol. 74 (5), 742–751. https://doi.org/10.1016/j.bcp.2007.06.006.

Huang, P.L., Chi, C.W., Liu, T.Y., 2013. Areca nut procyanidins ameliorate streptozocin-induced hyperglycemia by regulating gluconeogenesis. Food Chem. Toxicol. 55, 137–143. https://doi.org/10.1016/j.fct.2012.12.057.

Isaacs, C.E., Xu, W., Merz, G., Hillier, S., Rohan, L., Wen, G.Y., 2011. Digallate dimers of (-)-epigallocatechin gallate inactivate herpes simplex virus. Antimicrob. Agents Chemother. 55 (12), 5646–5653. https://doi.org/10.1128/AAC.05531-11.

Jansman, A.J., 1993. Tannins in feedstuffs for simple-stomached animals. Nutr. Res. Rev. 6 (1), 209–236. https://doi.org/10.1079/NRR19930013.

Jin, J.S., Hattori, M., 2012. Isolation and characterization of a human intestinal bacterium Eggerthella sp. CAT-1 capable of cleaving the C-ring of (+)-catechin and (-)-epicatechin, followed by p-dehydroxylation of the B-ring. Biol. Pharm. Bull. 35 (12), 2252–2256. https://doi.org/10.1248/bpb.b12-00726.

Jing, S.X., Reis, M., Alania, Y., McAlpine, J.B., Chen, S.N., Bedran-Russo, A.K., Pauli, G. F., 2022. B-type proanthocyanidins with dentin biomodification activity from cocoa (*Theobroma cacao*). J. Agric. Food Chem. 70 (39), 12456–12468. https://doi.org/10.1021/acs.jafc.2c04288.

Jing, Y.L., Han, G.J., Hu, Y., Bi, Y., Li, L.R., Zhu, D.L., 2009. Tea consumption and risk of type 2 diabetes: a meta-analysis of cohort studies. J. Gen. Intern. Med. 24 (5), 557–562. https://doi.org/10.1007/s11606-009-0929-5.

Kashiwada, M., Nakaishi, S., Usuda, A., Miyahara, Y., Katsumoto, K., Katsura, K., Ochiai, W., 2021. Analysis of anti-obesity and anti-diabetic effects of acacia bark-derived proanthocyanidins in type 2 diabetes model KKAy mice. J. Nat. Med. 75 (4), 893–906. https://doi.org/10.1007/s11418-021-01537-7.

Kennedy, J.A., Hayasaka, Y., Vidal, S., Waters, E.J., Jones, G.P., 2001. Composition of grape skin proanthocyanidins at different stages of berry development. J. Agric. Food Chem. 49 (11), 5348–5355. https://doi.org/10.1021/jf010758h.

Kennedy, J.A., Matthews, M.A., Waterhouse, A.L., 2000. Changes in grape seed polyphenols during fruit ripening. Phytochemistry 55 (1), 77–85. https://doi.org/10.1016/s0031-9422(00)00196-5.

Kobayashi, Y., Suzuki, M., Satsu, H., Arai, S., Hara, Y., Suzuki, K., Shimizu, M., 2000. Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal

epithelial cells by a competitive mechanism. J. Agric. Food Chem. 48 (11), 5618–5623. https://doi.org/10.1021/jf0006832.
Komatsu, K., Nagayama, Y., Tanaka, K., Ling, Y., Basnet, P., Meselhy, M.R., 2006. Development of a high performance liquid chromatographic method for systematic quantitative analysis of chemical constituents in rhubarb. Chem. Pharm. Bull. 54 (7), 941–947. https://doi.org/10.1248/cpb.54.941.
Koudoufio, M., Feldman, F., Ahmarani, L., Delvin, E., Spahis, S., Desjardins, Y., Levy, E., 2021. Intestinal protection by proanthocyanidins involves anti-oxidative and anti-inflammatory actions in association with an improvement of insulin sensitivity, lipid and glucose homeostasis. Sci. Rep. 11 (1). https://doi.org/10.1038/s41598-020-80587-5.
Krishnan, V., Rani, R., Awana, M., Pitale, D., Kulshreshta, A., Sharma, S., Praveen, S., 2021. Role of nutraceutical starch and proanthocyanidins of pigmented rice in regulating hyperglycemia: enzyme inhibition, enhanced glucose uptake and hepatic glucose homeostasis using *in vitro* model. Food Chem. 335 (127505). https://doi.org/10.1016/j.foodchem.2020.127505.
Kutschera, M., Engst, W., Blaut, M., Braune, A., 2011. Isolation of catechin-converting human intestinal bacteria. J. Appl. Microbiol. 111 (1), 165–175. https://doi.org/10.1111/j.1365-2672.2011.05025.x.
Kylli, P., Nohynek, L., Puupponen-Pimia, R., Westerlund-Wikstrom, B., Leppanen, T., Welling, J., Heinonen, M., 2011. Lingonberry (*Vaccinium vitis-idaea*) and European cranberry (*Vaccinium microcarpon*) proanthocyanidins: isolation, identification, and bioactivities. J. Agric. Food Chem. 59 (7), 3373–3384. https://doi.org/10.1021/jf104621e.
Lee, D.S.U., Lee, H., 2022. Adherence and persistence rates of major antidiabetic medications: a review. Diabetol. Metab. Syndrome. 14 (1). https://doi.org/10.1186/s13098-022-00785-1.
Lee, Y.A., Cho, E.J., Tanaka, T., Yokozawa, T., 2007. Inhibitory activities of proanthocyanidins from persimmon against oxidative stress and digestive enzymes related to diabetes. J. Nutr. Sci. Vitaminol. 53 (3), 287–292. https://doi.org/10.3177/jnsv.53.287.
Lee, Y.A., Cho, E.J., Yokozawa, T., 2008. Protective effect of persimmon (*Diospyros kaki*) peel proanthocyanidin against oxidative damage under H_2O_2-induced cellular senescence. Biol. Pharm. Bull. 31 (6), 1265–1269. https://doi.org/10.1248/bpb.31.1265.
Lei, X., Wang, S., Zhao, P., Wang, X., 2023. Mannoproteins, arabinogalactan protein, rhamnogalacturonan II and their pairwise combinations regulating wine astringency induced by the interaction of proanthocyanidins and proteins. Int. J. Biol. Macromol. 224, 950–957. https://doi.org/10.1016/j.ijbiomac.2022.10.180.
Li, B., Fu, R., Tan, H., Zhang, Y., Teng, W., Li, Z., Tian, J., 2021. Characteristics of the interaction mechanisms of procyanidin B1 and procyanidin B2 with protein tyrosine phosphatase-1B: analysis by kinetics, spectroscopy methods and molecular docking. Spectrochim. Acta 259 (119910). https://doi.org/10.1016/j.saa.2021.119910.
Li, B.Y., Li, X.L., Gao, H.Q., Zhang, J.H., Cai, Q., Cheng, M., Lu, M., 2011. Grape seed procyanidin B2 inhibits advanced glycation end product-induced endothelial cell apoptosis through regulating GSK3β phosphorylation. Cell Biol. Int. 35 (7), 663–669. https://doi.org/10.1042/CBI20100656.
Li, D., Zhao, T., Meng, J., Jing, Y., Jia, F., He, P., 2015. Procyanidin B2 inhibits high glucose-induced epithelial-mesenchymal transition in HK-2 human renal proximal tubular epithelial cells. Mol. Med. Rep. 12 (6), 8148–8154. https://doi.org/10.3892/mmr.2015.4445.
Li, H., Zhang, H., Wang, T., Zhang, L., Wang, H., Lu, H., Ding, Y., 2024. Grape seed proanthocyanidins protect pancreatic β cells against ferroptosis via the Nrf2 pathway in type 2 diabetes. Biol. Trace Elem. Res. 202, 5531–5544.
Li, R., Li, H., Zhang, Q., 2022. Procyanidin protects human retinal pigment epithelial cells from high glucose by inhibiting autophagy. Environ. Toxicol. 37 (2), 201–211. https://doi.org/10.1002/tox.23389.
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. J. Funct.Foods 27, 711–722. https://doi.org/10.1016/j.jff.2016.08.010.
Li, X., Sui, Y., Wu, Q., Xie, B., Sun, Z., 2017. Attenuated mTOR signaling and enhanced glucose homeostasis by dietary supplementation with lotus seedpod oligomeric procyanidins in streptozotocin (STZ)-induced diabetic mice. J. Agric. Food Chem. 65 (19), 3801–3810. https://doi.org/10.1021/acs.jafc.7b00233.
Liu, M., Huang, B., Wang, L., Lu, Q., Liu, R., 2022. Peanut skin procyanidins ameliorate insulin resistance via modulation of gut microbiota and gut barrier in type 2 diabetic mice. J. Sci. Food Agric. 102 (13), 5935–5947. https://doi.org/10.1002/jsfa.11945.
Liu, M., Shen, J., Zhu, X., Ju, T., Willing, B.P.W., Wu, X., Liu, R., 2023. Peanut skin procyanidins reduce intestinal glucose transport protein expression, regulate serum metabolites and ameliorate hyperglycemia in diabetic mice. Food Res. Int. 173 (113471). https://doi.org/10.1016/j.foodres.2023.113471.
Liu, X.Y., Zang, L.L., Yu, J.B., Yu, J.J., Wang, S.Q., Zhou, L.L., Li, W.F., 2024. Anti-inflammatory effect of proanthocyanidins from blueberry through NF-κB/NLRP3 signaling pathway *in vivo* and *in vitro*. Immunopharmacol. Immunotoxicol. 46 (4), 425–435. https://doi.org/10.1080/08923973.2024.2358770.
Liu, Y., Pang, D., Xing, D., Wang, W., Li, Q., Liao, S., Zou, Y., 2023. Cinnamon free phenolic extract regulates glucose absorption in intestinal cells by inhibiting glucose transporters. Food Biosci. 52 (102405). https://doi.org/10.1016/j.fbio.2023.102405.
Liu, Y.J., Zhan, J., Liu, X.L., Wang, Y., Ji, J., He, Q.Q., 2014. Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Clin. Nutr. 33 (1), 59–63. https://doi.org/10.1016/j.clnu.2013.03.011.
Liu, Z., de Bruijn, W.J., Bruins, M.E., Vincken, J.P., 2020. Reciprocal interactions between epigallocatechin-3-gallate (EGCG) and human gut microbiota *in vitro*. J. Agric. Food Chem. 68 (36), 9804–9815. https://doi.org/10.1021/acs.jafc.0c03587.
Liu, Z.H., Li, B., 2021. Procyanidin B1 and p-coumaric acid from highland barley grain showed synergistic effect on modulating glucose metabolism via IRS-1/PI3K/Akt Pathway. Mol. Nutr. Food Res. 65 (18), e2100454. https://doi.org/10.1002/mnfr.202100454.
Luximon-Ramma, A., Bahorun, T., Crozier, A., Zbarsky, V., Datla, K.P., Dexter, D.T., Aruoma, O.I., 2005. Characterization of the antioxidant functions of flavonoids and proanthocyanidins in Mauritian black teas. Food Res. Int. 38 (4), 357–367. https://doi.org/10.1016/j.foodres.2004.10.005.
Lv, J.M., Gouda, M., Bekhit, A.E.D., He, Y.K., Ye, X.Q., Chen, J.C., 2022. Identification of novel bioactive proanthocyanidins with potent antioxidant and anti-proliferative activities from kiwifruit leaves. Food Biosci. 46 (101554). https://doi.org/10.1016/j.fbio.2022.101554.
Martín, M.A., Ramos, S., 2021. Dietary flavonoids and insulin signaling in diabetes and obesity. Cells-Basel. 10 (6). https://doi.org/10.3390/cells10061474.
McCallum, J.A., Walker, J.R.L., 1990. Proanthocyanidins in wheat bran. Cereal Chem. 67 (3), 282–285.
Mcmanus, J.P., Davis, K.G., Lilley, T.H., Haslam, E., 1981. The association of proteins with polyphenols. J. Chem. Soc., Chem. Commun. 309–311. https://doi.org/10.1039/C3981000309B.
Monfoulet, L.E., Buffiere, C., Istas, G., Dufour, C., Le Bourvellec, C., Mercier, S., Morand, C., 2020. Effects of the apple matrix on the postprandial bioavailability of flavan-3-ols and nutrigenomic response of apple polyphenols in minipigs challenged with a high fat meal. Food Funct. 11 (6), 5077–5090. https://doi.org/10.1039/d0fo00346h.
Montagut, G., Onnockx, S., Vaque, M., Blade, C., Blay, M., Fernandez-Larrea, J., Pinent, M., 2010. Oligomers of grape-seed procyanidin extract activate the insulin receptor and key targets of the insulin signaling pathway differently from insulin. J. Nutr. Biochem. 21 (6), 476–481. https://doi.org/10.1016/j.jnutbio.2009.02.003.
Montero, L., Herrero, M., Prodanov, M., Ibanez, E., Cifuentes, A., 2013. Characterization of grape seed procyanidins by comprehensive two-dimensional hydrophilic interaction x reversed phase liquid chromatography coupled to diode array detection and tandem mass spectrometry. Anal. Bioanal. Chem. 405 (13), 4627–4638. https://doi.org/10.1007/s00216-012-6567-5.
Morissette, A., Kropp, C., Songpadith, J.P., Junges Moreira, R., Costa, J., Marine-Casado, R., Marette, A., 2020. Blueberry proanthocyanidins and anthocyanins improve metabolic health through a gut microbiota-dependent mechanism in diet-induced obese mice. Am. J. Physiol.-Endoc. M. 318 (6), E965–E980. https://doi.org/10.1152/ajpendo.00560.2019.
Morzel, M., Canon, F., Guyot, S., 2022. Interactions between salivary proteins and dietary polyphenols: potential consequences on gastrointestinal digestive events. J. Agric. Food Chem. 70 (21), 6317–6327. https://doi.org/10.1021/acs.jafc.2c01183.
Naowaboot, J., Piyabhan, P., 2017. Senna alata leaf extract restores insulin sensitivity in high-fat diet-induced obese mice. Clin. Phytosci. 2 (1), 1–7. https://doi.org/10.1186/s40816-016-0032-5.
Nie, R.Z., Zhu, W., Peng, J.M., Ge, Z.Z., Li, C.M., 2017. Comparison of disaggregative effect of A-type EGCG dimer and EGCG monomer on the preformed bovine insulin amyloid fibrils. Biophys. Chem. 230, 1–9. https://doi.org/10.1016/j.bpc.2017.07.009.
Ogura, K., Ogura, M., Shoji, T., Sato, Y., Tahara, Y., Yamano, G., Nagashima, K., 2016. Oral administration of apple procyanidins ameliorates insulin resistance via suppression of pro-inflammatory cytokine expression in liver of diabetic ob/ob mice. J. Agric. Food Chem. 64 (46), 8857–8865. https://doi.org/10.1021/acs.jafc.6b03424.
Ou, K., Percival, S.S., Zou, T., Khoo, C., Gu, L., 2012. Transport of cranberry A-type procyanidin dimers, trimers, and tetramers across monolayers of human intestinal epithelial Caco-2 cells. J. Agric. Food Chem. 60 (6), 1390–1396. https://doi.org/10.1021/jf2040912.
Pan, H., Wang, Y., Xu, X., Qian, Z., Cheng, H., Ye, X., Chen, S., 2021. Simultaneous extraction and depolymerization of condensed tannins from Chinese bayberry leaves for improved bioavailability and antioxidant activity. J. Agric. Food Chem. 69 (38), 11292–11302. https://doi.org/10.1021/acs.jafc.1c03962.
Park, C.H., Tanaka, T., Kim, H.Y., Park, J.C., Yokozawa, T., 2012. Protective Effects of corni fructus against advanced glycation endproducts and radical scavenging. Evid.-Based Compl. Alt. 2012 (418953). https://doi.org/10.1155/2012/418953.
Pedan, V., Fischer, N., Rohn, S., 2016. Extraction of cocoa proanthocyanidins and their fractionation by sequential centrifugal partition chromatography and gel permeation chromatography. Anal. Bioanal. Chem. 408 (21), 5905–5914. https://doi.org/10.1007/s00216-016-9705-7.
Peng, J., Jia, Y., Hu, T., Du, J., Wang, Y., Cheng, B., Li, K., 2019. GC-(4–>8)-GCG, a proanthocyanidin dimer from *Camellia ptilophylla*, modulates obesity and adipose tissue inflammation in high-fat diet induced obese mice. Mol. Nutr. Food Res. 63 (11), e1900082. https://doi.org/10.1002/mnfr.201900082.
Peng, J., Wen, W., Wang, R., Li, K., Xiao, G., Li, C., 2022. The galloyl moiety enhances inhibitory activity of polyphenols against adipogenic differentiation in 3T3-L1 preadipocytes. Food Funct. 13 (9), 5275–5286. https://doi.org/10.1039/d1fo04179g.
Piccinelli, A.L., Pagano, I., Esposito, T., Mencherini, T., Porta, A., Petrone, A.M., Aquino, R.P., 2016. HRMS profile of a hazelnut skin proanthocyanidin-rich fraction with antioxidant and anti-candida albicans activities. J. Agric. Food Chem. 64 (3), 585–595. https://doi.org/10.1021/acs.jafc.5b05404.
Pineda-Vadillo, C., Nau, F., Dubiard, C.G., Cheynier, V., Meudec, E., Sanz-Buenhombre, M., Dupont, D., 2016. *In vitro* digestion of dairy and egg products enriched with grape extracts: effect of the food matrix on polyphenol bioaccessibility

and antioxidant activity. Food Res. Int. 88, 284–292. https://doi.org/10.1016/j.foodres.2016.01.029.
Portincasa, P., Bonfrate, L., Vacca, M., De Angelis, M., Farella, I., Lanza, E., Di Ciaula, A., 2022. Gut microbiota and short chain fatty acids: implications in glucose homeostasis. Int. J. Mol. Sci. 23 (3). https://doi.org/10.3390/ijms23031105.
Qi, Y.J., Zhang, H., Wu, G.C., Zhang, H., Wang, L., Qian, H.F., Qi, X.G., 2018. Reduction of 5-hydroxymethylfurfural formation by flavan-3-ols in Maillard reaction models and fried potato chips. J. Sci. Food Agric. 98 (14), 5294–5301. https://doi.org/10.1002/jsfa.9068.
Qian, Z., Wang, Y., Shen, S., Tao, W., Zhang, Y., Ye, X., Pan, H., 2022. Analysis of proanthocyanidins in plant materials using hydrophilic interaction HPLC-QTOF-MS. Molecules 27(9). https://doi.org/10.3390/molecules27092684.
Quintero-Soto, M.F., Chavez-Ontiveros, J., Garzon-Tiznado, J.A., Salazar-Salas, N.Y., Pineda-Hidalgo, K.V., Delgado-Vargas, F., Lopez-Valenzuela, J.A., 2021. Characterization of peptides with antioxidant activity and antidiabetic potential obtained from chickpea (*Cicer arietinum* L.) protein hydrolyzates. J. Food Sci. (N. Y.) 86 (7), 2962–2977. https://doi.org/10.1111/1750-3841.15778.
Rajasekhar, S., Subramanyam, M.V.V., Asha Devi, S., 2021. Grape seed proanthocyanidin extract suppresses oxidative stress in the rat pancreas of type-1 diabetes. Arch. Physiol. Biochem. 1–13. https://doi.org/10.1080/13813455.2021.1894452.
Ramsay, A., Mueller-Harvey, I., 2016. Senna alata leaves are a good source of propelargonidins. Nat. Prod. Res. 30 (13), 1548–1551. https://doi.org/10.1080/14786419.2015.1108976.
Rao, M.J., Xu, Y.T., Huang, Y., Tang, X.M., Deng, X.X., Xu, Q., 2019. Ectopic expression of citrus UDP-GLUCOSYL TRANSFERASE gene enhances anthocyanin and proanthocyanidins contents and confers high light tolerance in Arabidopsis. BMC Plant Biol. 19 (1). https://doi.org/10.1186/s12870-019-2212-1.
Redondo-Castillejo, R., Garcimartín, A., Hernández-Martín, M., López-Oliva, M.E., Bocanegra, A., Macho-González, A., Sánchez-Muniz, F.J., 2023. Proanthocyanidins: impact on gut microbiota and intestinal action mechanisms in the prevention and treatment of metabolic syndrome. Int. J. Mol. Sci. 24 (6). https://doi.org/10.3390/ijms24065369.
Renard, C.M., Dupont, N., Guillermin, P., 2007. Concentrations and characteristics of procyanidins and other phenolics in apples during fruit growth. Phytochemistry 68 (8), 1128–1138. https://doi.org/10.1016/j.phytochem.2007.02.012.
Rios, L.Y., Bennett, R.N., Lazarus, S.A., Rémésy, C., Scalbert, A., Williamson, G., 2002. Cocoa procyanidins are stable during gastric transit in humans. Am. J. Clin. Nutr. 76 (5), 1106–1110. https://doi.org/10.1093/ajcn/76.5.1106.
Robertson, R.P., Harmon, J., Tran, P.O., Tanaka, Y., Takahashi, H., 2003. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. Diabetes 52 (3), 581–587. https://doi.org/10.2337/diabetes.52.3.581.
Rodriguez-Daza, M.C., Daoust, L., Boutkrabt, L., Pilon, G., Varin, T., Dudonne, S., Desjardins, Y., 2020. Wild blueberry proanthocyanidins shape distinct gut microbiota profile and influence glucose homeostasis and intestinal phenotypes in high-fat high-sucrose fed mice. Sci. Rep. 10 (1). https://doi.org/10.1038/s41598-020-58863-1, 2217.
Schoefer, L., Mohan, R., Braune, A., Birringer, M., Blaut, M., 2002. Anaerobic C-ring cleavage of genistein and daidzein by *Eubacterium ramulus*. FEMS Microbiol. Lett. 208 (2), 197–202. https://doi.org/10.1111/j.1574-6968.2002.tb11081.x.
Serra, A., Macia, A., Rubió, L., Angles, N., Ortega, N., Morelló, J.R., Motilva, M.J., 2013. Distribution of procyanidins and their metabolites in rat plasma and tissues in relation to ingestion of procyanidin-enriched or procyanidin-rich cocoa creams. Eur. J. Nutr. 2013 (52), 1029–1038. https://doi.org/10.1007/s00394-012-0409-2.
Serrano, J., Casanova-Marti, A., Gil-Cardoso, K., Blay, M.T., Terra, X., Pinent, M., Ardevol, A., 2016. Acutely administered grape-seed proanthocyanidin extract acts as a satiating agent. Food Funct. 7 (1), 483–490. https://doi.org/10.1039/c5fo00892a.
Sordon, S., Madej, A., Poplonski, J., Bartmanska, A., Tronina, T., Brzezowska, E., Huszcza, E., 2016. Regioselective ortho-hydroxylations of flavonoids by yeast. J. Agric. Food Chem. 64 (27), 5525–5530. https://doi.org/10.1021/acs.jafc.6b02210.
Spencer, J.P.E., Chaudry, F., Pannala, A.S., Srai, S.K., Debnam, E., Rice-Evans, C., 2000. Decomposition of cocoa procyanidins in the gastric milieu. Biochem. Bioph. Res. Co 272 (1), 236–241. https://doi.org/10.1006/bbrc.2000.2749.
Steck, J., Junker, F., Eichhofer, H., Bunzel, M., 2022. Chemically different but often mistaken phenolic polymers of food plants: proanthocyanidins and lignin in seeds. J. Agric. Food Chem. 70 (37), 11704–11714. https://doi.org/10.1021/acs.jafc.2c03782.
Sulistiyani, N.I., Ainurrofiq, A., Suryanti, V., 2022. Antibacterial activity of chayote (*Sechium edule* Swartz) squash extracts and their phytochemical constituents. J. Biomed. Biotechnol. 2 (1), 26–32. https://doi.org/10.20961/jbb.v2i1.61330.
Sun, B., Leandro, C., Ricardo da Silva, J.M., Spranger, I., 1998. Separation of grape and wine proanthocyanidins according to their degree of polymerization. J. Agric. Food Chem. 46 (4), 1390–1396. https://doi.org/10.1021/jf970753d.
Sun, P., Li, K., Wang, T., Ji, J., Wang, Y., Chen, K.X., Wang, H.Y., 2019. Procyanidin C1, a component of cinnamon extracts, is a potential insulin sensitizer that targets adipocytes. J. Agric. Food Chem. 67 (32), 8839–8846. https://doi.org/10.1021/acs.jafc.9b02932.
Takagaki, A., Kato, Y., Nanjo, F., 2014. Isolation and characterization of rat intestinal bacteria involved in biotransformation of (-)-epigallocatechin. Arch. Microbiol. 196 (10), 681–695. https://doi.org/10.1007/s00203-014-1006-y.
Takemori, K., Akaho, K., Iwase, M., Okano, M., Kometani, T., 2022. Effects of persimmon fruit polyphenols on postprandial plasma glucose elevation in rats and humans. J. Nutr. Sci. Vitaminol. 68 (4), 331–341. https://doi.org/10.3177/jnsv.68.331.
Tang, C., Xie, B., Sun, Z., 2017. Antibacterial activity and mechanism of B-type oligomeric procyanidins from lotus seedpod on enterotoxigenic *Escherichia coli*. J. Funct.Foods 38, 454–463. https://doi.org/10.1016/j.jff.2017.09.046.
Tian, J.Z., Li, C., Dong, Z.X., Yang, Y.P., Xing, J., Yu, P.J., Jiang, W.H., 2023. Inactivation of the antidiabetic drug acarbose by human intestinal microbial-mediated degradation. Nat. Metab. https://doi.org/10.1038/s42255-023-00796-w.
Vazquez-Flores, A.A., Martinez-Gonzalez, A.I., Alvarez-Parrilla, E., Diaz-Sanchez, A.G., de la Rosa, L.A., Gonzalez-Aguilar, G.A., Aguilar, C.N., 2018. Proanthocyanidins with a low degree of polymerization are good inhibitors of digestive enzymes because of their ability to form specific inter.: A hypothesis. J. Food Sci. 83 (12), 2895–2902. https://doi.org/10.1111/1750-3841.14386.
Verardo, V., Cevoli, C., Pasini, F., Gomez-Caravaca, A.M., Marconi, E., Fabbri, A., Caboni, M.F., 2015. Analysis of oligomer proanthocyanidins in different barley genotypes using high-performance liquid chromatography-fluorescence detection-mass spectrometry and near-infrared methodologies. J. Agric. Food Chem. 63 (16), 4130–4137. https://doi.org/10.1021/acs.jafc.5b01425.
Villegas, R., Shu, X.O., Gao, Y.T., Yang, G., Elasy, T., Li, H., Zheng, W., 2008. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. J. Nutr. 138 (3), 574–580. https://doi.org/10.1093/jn/138.3.574.
Wang, M., Chen, J., Ye, X., Liu, D., 2020. In vitro inhibitory effects of Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves proanthocyanidins on pancreatic α-amylase and their interaction. Bioorg. Chem. 101 (104029). https://doi.org/10.1016/j.bioorg.2020.104029.
Wang, M., Jiang, J., Tian, J., Chen, S., Ye, X., Hu, Y., Chen, J., 2019. Inhibitory mechanism of novel allosteric inhibitor, Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves proanthocyanidins against α-glucosidase. J. Funct.Foods 56, 286–294. https://doi.org/10.1016/j.jff.2019.03.026.
Wang, M., Mao, H., Chen, J., Li, Q., Ma, W., Zhu, N., Wang, J., 2022a. Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves proanthocyanidins alleviate insulin-resistance via activating PI3K/AKT pathway in HepG2 cells. J. Funct.Foods 99 (105297). https://doi.org/10.1016/j.jff.2022.105297.
Wang, M., Mao, H., Chen, J., Qi, L., Wang, J., 2022b. Ameliorative effect of bayberry leaves proanthocyanidins on high sugar diet induced Drosophila melanogaster. Front. Pharmacol. 13 (1008580). https://doi.org/10.3389/fphar.2022.1008580.
Wang, M., Mao, H., Ke, Z., Chen, J., Qi, L., Wang, J., 2024. Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves proanthocyanidins inhibit intestinal glucose transport in human Caco-2 cells. Front. Pharmacol. 15 (1284268). https://doi.org/10.3389/fphar.2024.1284268.
Wang, M., Mao, H., Ke, Z., Huang, R., Chen, J., Qi, L., Wang, J., 2023. Effect of proanthocyanidins from different sources on the digestibility, physicochemical properties and structure of gelatinized maize starch. Int. J. Biol. Macromol. 248 (125935). https://doi.org/10.1016/j.ijbiomac.2023.125935.
Wang, Y., de, B.H.P., Chang, T., Wu, X., Chen, P., 2020b. Analysis of cranberry proanthocyanidins using UPLC-ion mobility-high-resolution mass spectrometry. Anal. Bioanal. Chem. 412 (15), 3653–3662. https://doi.org/10.1007/s00216-020-02601-z.
Wang, Y., Xu, X., Chen, J., Ye, X., Pan, H., Chen, S., 2022. Improving regulation of polymeric proanthocyanidins and tea polyphenols against postprandial hyperglycemia via acid-catalyzed transformation. J. Agric. Food Chem. 70 (16), 5218–5227. https://doi.org/10.1021/acs.jafc.2c01128.
Williams, A.R., Ramsay, A., Hansen, T.V., Ropiak, H.M., Mejer, H., Nejsum, P., Thamsborg, S.M., 2015. Anthelmintic activity of trans-cinnamaldehyde and A- and B-type proanthocyanidins derived from cinnamon (*Cinnamomum verum*). Sci. Rep. 5 (14791). https://doi.org/10.1038/srep14791.
Wu, H., Lu, Z.S., Chen, R.Y., Cai, Q.F., Wang, M.M., Zhang, L.T., Zhu, Z.M., 2023. Factors associated with gastrointestinal side effects after liraglutide treatment for type 2 diabetes. Front. Endocrinol. 14. https://doi.org/10.3389/fendo.2023.1098032.
Xiang, J., Raka, R.N., Zhang, L., Xiao, J., Wu, H., Ding, Z., 2022. Inhibition of three diabetes-related enzymes by procyanidins from lotus (*Nelumbo nucifera* Gaertn.) seedpods. Plant Food Hum. Nutrition 77 (3), 390–398. https://doi.org/10.1007/s11130-022-00987-y.
Xie, L., Roto, A.V., Bolling, B.W., 2012. Characterization of ellagitannins, gallotannins, and bound proanthocyanidins from California almond (*Prunus dulcis*) varieties. J. Agric. Food Chem. 60 (49), 12151–12156. https://doi.org/10.1021/jf303673r.
Xu, S.J., Cui, J., Dai, C.Y., Wei, X., Tian, X.Q., Fang, D., Ma, L., 2024. From waste to eco-friendly biofilms: harnessing cottonseed hull proanthocyanidins for sustainable solutions. Environ. Technol. Innov. 33. https://doi.org/10.1016/j.eti.2023.103448.
Yamashita, Y., Okabe, M., Natsume, M., Ashida, H., 2012a. Cacao liquor procyanidin extract improves glucose tolerance by enhancing GLUT4 translocation and glucose uptake in skeletal muscle. J. Nutr. 1, e2. https://doi.org/10.1017/jns.2012.2.
Yamashita, Y., Okabe, M., Natsume, M., Ashida, H., 2012b. Comparison of anti-hyperglycemic activities between low-and high-degree of polymerization procyanidin fractions from cacao liquor extract. J. Food Drug Anal. 20 (1), 39. https://doi.org/10.38212/2224-6614.2105.
Yamashita, Y., Okabe, M., Natsume, M., Ashida, H., 2012c. Prevention mechanisms of glucose intolerance and obesity by cacao liquor procyanidin extract in high-fat diet-fed C57BL/6 mice. Arch. Biochem. Biophys. 527 (2), 95–104. https://doi.org/10.1016/j.abb.2012.03.018.
Yamashita, Y., Okabe, M., Natsume, M., Ashida, H., 2013. Cinnamtannin A2, a tetrameric procyanidin, increases GLP-1 and insulin secretion in mice. Biosci., Biotechnol., Biochem. 77 (4), 888–891. https://doi.org/10.1271/bbb.130095.
Yang, K., Hashemi, Z., Han, W., Jin, A., Yang, H., Ozga, J., Chan, C.B., 2015. Hydrolysis enhances bioavailability of proanthocyanidin-derived metabolites and improves β-cell function in glucose intolerant rats. J. Nutr. Biochem. 26 (8), 850–859. https://doi.org/10.1016/j.jnutbio.2015.03.002.
Ye, H., Luo, L., Wang, J., Jiang, K., Yue, T., Yang, H., 2022. Highly galloylated and A-type prodelphinidins and procyanidins in persimmon (*Diospyros kaki* L.) peel. Food Chem. 378 (131972). https://doi.org/10.1016/j.foodchem.2021.131972.

Yin, W., Li, B., Li, X., Yu, F., Cai, Q., Zhang, Z., Gao, H., 2015. Anti-inflammatory effects of grape seed procyanidin B2 on a diabetic pancreas. Food Funct. 6 (9), 3065–3071. https://doi.org/10.1039/c5fo00496a.

Yu, D., Xu, J., Chen, Y., Shi, B., 2022. Procyanidin A1 inhibits insulin resistance and oxidative stress in palmitic acid treated HepG2 cells. Curr. Top. Nutraceutical Res. 20 (3), 561–566. https://doi.org/10.37290/ctnr2641-452X.20, 561-566.

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

Yusuf, E., Wojdylo, A., Oszmianski, J., Nowicka, P., 2021. Nutritional, phytochemical characteristics and in vitro effect on α-Amylase, α-glucosidase, lipase, and cholinesterase activities of 12 coloured carrot varieties. Foods 10(4). https://doi.org/10.3390/foods10040808.

Zamora-Ros, R., Forouhi, N.G., Sharp, S.J., Gonzalez, C.A., Buijsse, B., Guevara, M., Wareham, N.J., 2014. Dietary intakes of individual flavanols and flavonols are inversely associated with incident type 2 diabetes in European populations. J. Nutr. 144 (3), 335–343. https://doi.org/10.3945/jn.113.184945.

Zhang, Y., Pan, H., Ye, X., Chen, S., 2022. Proanthocyanidins from Chinese bayberry leaves reduce obesity and associated metabolic disorders in high-fat diet-induced obese mice through a combination of AMPK activation and an alteration in gut microbiota. Food Funct. 13 (4), 2295–2305. https://doi.org/10.1039/d1fo04147a.

Zhang, Y., Santosa, R.W., Zhang, M., Huo, J., Huang, D.J., 2020. Characterization and bioactivity of proanthocyanidins during Malay cherry (*Lepisanthes alata*) fruit ripening. Food Biosci. 36 (100617). https://doi.org/10.1016/j.fbio.2020.100617.

Zhang, Y., Ye, X., Xu, Z., Duan, J., Wei, C., Xu, G., Chen, S., 2017. Inhibitory effect of proanthocyanidins from Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves on the lipid oxidation in an emulsion system. LWT–Food Sci. Technol. 80, 517–522. https://doi.org/10.1016/j.lwt.2017.03.007.

Zhang, Y., Zhou, X., Tao, W., Li, L., Wei, C., Duan, J., Ye, X., 2016. Antioxidant and antiproliferative activities of proanthocyanidins from Chinese bayberry (*Myrica rubra* Sieb. et Zucc.) leaves. J. Funct.Foods 27, 645–654. https://doi.org/10.1016/j.jff.2016.10.004.

Zhao, L., Wen, L., Lu, Q., Liu, R., 2020. Interaction mechanism between α-glucosidase and A-type trimer procyanidin revealed by integrated spectroscopic analysis techniques. Int. J. Biol. Macromol. 143, 173–180. https://doi.org/10.1016/j.ijbiomac.2019.12.021.

Zhong, H., Xue, Y., Lu, X., Shao, Q., Cao, Y., Wu, Z., Chen, G., 2018. The effects of different degrees of procyanidin polymerization on the nutrient absorption and digestive enzyme activity in mice. Molecules 23(11). https://doi.org/10.3390/molecules23112916.

Zhu, W., Deng, X., Peng, J., Zou, B., Li, C., 2017. A-type ECG and EGCG dimers inhibit 3T3-L1 differentiation by binding to cholesterol in lipid rafts. J. Nutr. Biochem. 48, 62–73. https://doi.org/10.1016/j.jnutbio.2017.06.012.

Zhu, W., Khalifa, I., Peng, J., Li, C., 2018a. Position and orientation of gallated proanthocyanidins in lipid bilayer membranes: influence of polymerization degree and linkage type. J. Biomol. Struct. Dyn. 36 (11), 2862–2875. https://doi.org/10.1080/07391102.2017.1369163.

Zhu, W., Lin, K., Li, K., Deng, X., Li, C., 2018b. Reshaped fecal gut microbiota composition by the intake of high molecular weight persimmon tannin in normal and high-cholesterol diet-fed rats. Food Funct. 9 (1), 541–551. https://doi.org/10.1039/c7fo00995j.

Zhu, W., Xiong, L., Oteiza, P.I., 2024. Structure-dependent capacity of procyanidin dimers to inhibit inflammation-induced barrier dysfunction in a cell model of intestinal epithelium. Redox Biol. 75 (103275). https://doi.org/10.1016/j.redox.2024.103275.

Zhu, W., Zou, B., Nie, R., Zhang, Y., Li, C.M., 2015. A-type ECG and EGCG dimers disturb the structure of 3T3-L1 cell membrane and strongly inhibit its differentiation by targeting peroxisome proliferator-activated receptor gamma with miR-27 involved mechanism. J. Nutr. Biochem. 26 (11), 1124–1135. https://doi.org/10.1016/j.jnutbio.2015.05.006.

Zou, B., Ge, Z., Zhu, W., Xu, Z., Li, C., 2015. Persimmon tannin represses 3T3-L1 preadipocyte differentiation via up-regulating expression of miR-27 and down-regulating expression of peroxisome proliferator-activated receptor-gamma in the early phase of adipogenesis. Eur. J. Nutr. 54 (8), 1333–1343. https://doi.org/10.1007/s00394-014-0814-9.

Zou, B., Ge, Z.Z., Zhang, Y., Du, J., Xu, Z., Li, C.M., 2014. Persimmon tannin accounts for hypolipidemic effects of persimmon through activating of AMPK and suppressing NF-kappaB activation and inflammatory responses in high-fat diet rats. Food Funct. 5 (7), 1536–1546. https://doi.org/10.1039/c3fo60635j.