



OPEN ACCESS

EDITED BY

Ramith Ramu,
JSS Academy of Higher Education and
Research, India

REVIEWED BY

Jin-Long Tian,
Shenyang Agricultural University, China
Priyanka Choudhury,
Medical College of Wisconsin, United States

*CORRESPONDENCE

Yongfu Fan,
✉ fyf8031@163.com
Huan Huan Liu,
✉ 15638943753@163.com

[†]These authors have contributed equally to
this work

RECEIVED 21 November 2024

ACCEPTED 14 January 2025

PUBLISHED 10 February 2025

CITATION

Zhang Y, Li M, Liu H, Fan Y and Liu HH (2025)
The application of procyanidins in diabetes and
its complications: a review of preclinical studies.
Front. Pharmacol. 16:1532246.
doi: 10.3389/fphar.2025.1532246

COPYRIGHT

© 2025 Zhang, Li, Liu, Fan and Liu. This is an
open-access article distributed under the terms
of the [Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in
other forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in this
journal is cited, in accordance with accepted
academic practice. No use, distribution or
reproduction is permitted which does not
comply with these terms.

The application of procyanidins in diabetes and its complications: a review of preclinical studies

Yongchuang Zhang^{1†}, Mengna Li^{2†}, Haoyuan Liu^{3†}, Yongfu Fan^{4*}
and Huan Huan Liu^{5*}

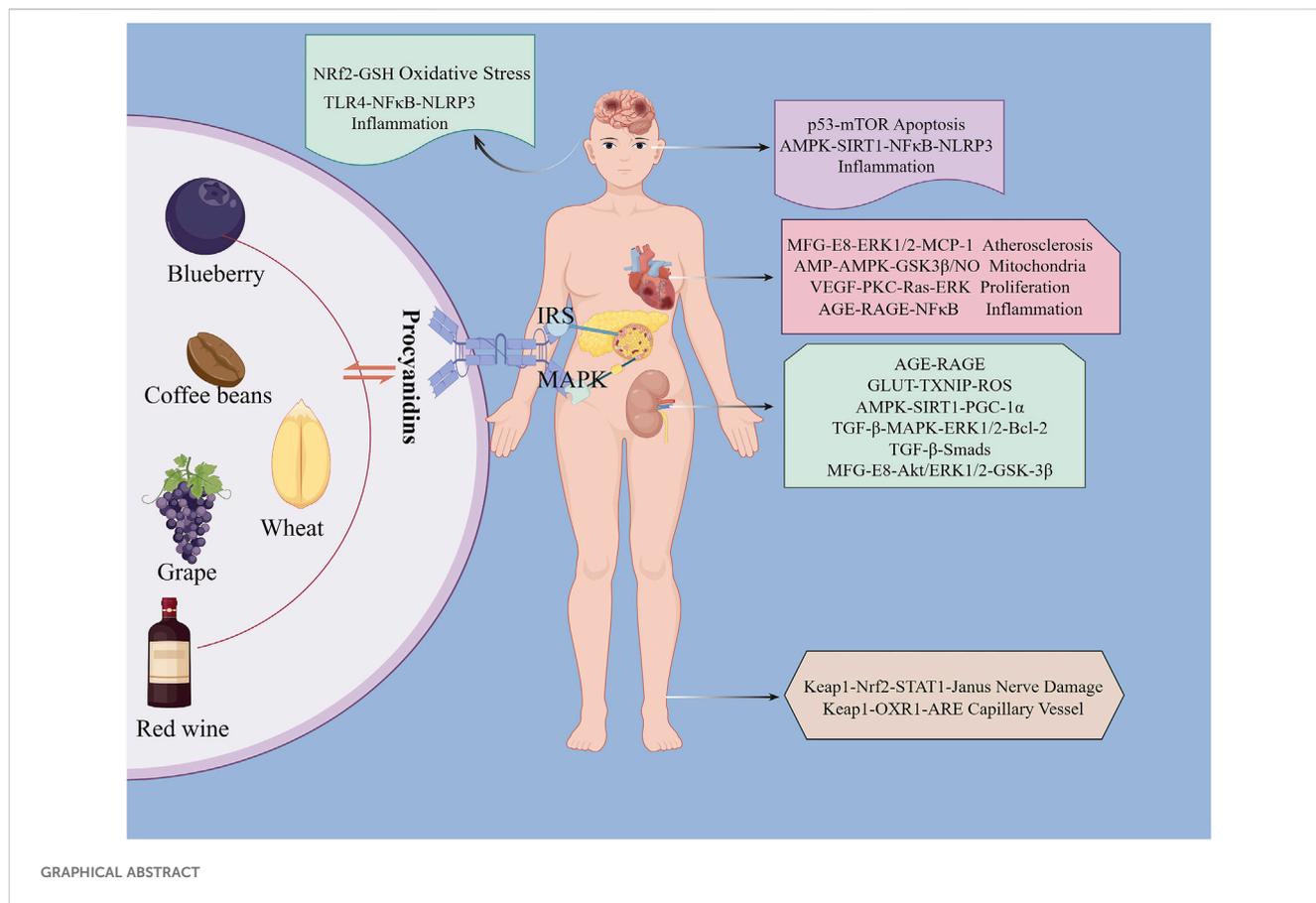
¹Department of Rehabilitation Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, ²Institute of Pain Medicine and Special Environmental Medicine, Nantong University, Nantong, China, ³Rehabilitation Department, Henan Provincial Hospital of Traditional Chinese Medicine, Zhengzhou, China, ⁴School of Rehabilitation Medicine, Henan University of Chinese Medicine, Zhengzhou, China, ⁵International Institute for Traditional Chinese Medicine, Guanzhou University of Chinese Medicine, Guangzhou, China

Diabetes mellitus (DM) and its various complications, including diabetic nephropathy, retinopathy, neuropathy, cardiovascular disease, and ulcers, pose significant challenges to global health. This review investigates the potential of procyanidins (PCs), a natural polyphenolic compound, in preventing and managing diabetes and its complications. PCs, recognized for their strong antioxidant, anti-inflammatory, and anti-hyperglycemic properties, play a crucial role in reducing oxidative stress and enhancing endothelial function, which are essential for managing diabetic complications. This review elucidates the molecular mechanisms by which PCs improve insulin sensitivity and endothelial health, thereby providing protection against the various complications of diabetes. The comprehensive analysis underscores the promising therapeutic role of PCs in diabetes care, indicating the need for further clinical studies to confirm and leverage their potential in comprehensive diabetes management strategies.

KEYWORDS

diabetes mellitus, procyanidins, antioxidant, anti-inflammatory, insulin sensitivity

Abbreviations: PCs, Procyanidins; DM, Diabetes Mellitus; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; DN, Diabetic Nephropathy; DR, Diabetic Retinopathy; DN, Diabetic Neuropathy; CVD, Cardiovascular Disease; DFU, Diabetic Foot Ulcers; AGE, Advanced Glycation End-products; RAGE, Receptor for Advanced Glycation End-products; VEGF, Vascular Endothelial Growth Factor; DCD, Diabetic Cardiomyopathy; GSH-Px, Glutathione Peroxidase; NQO1, NAD(P)H Quinone Dehydrogenase 1; ZO-1, Zonula Occludens-1; TLR4, Toll-like Receptor 4; MCP-1, Monocyte Chemoattractant Protein-1; AMPK, AMP-activated Protein Kinase; GSK-3 β , Glycogen Synthase Kinase 3 Beta; ERK1/2, Extracellular Signal-Regulated Kinases 1/2; ACC, Acetyl-CoA Carboxylase; GLUT4, glucose transporter type 4; ATGL, Adipose Triglyceride Lipase; CPT1A, Carnitine Palmitoyltransferase 1A; SIRT1, Sirtuin 1; NRF1, Nuclear Respiratory Factor 1; PERK, Protein kinase RNA-like ER kinase; IRE1, Inositol-Requiring Enzyme 1; ATF6, Activating Transcription Factor 6; ROS, Reactive Oxygen Species; TGF- β , Transforming Growth Factor Beta; EMT, Epithelial-to-Mesenchymal Transition; MAPK, Mitogen-Activated Protein Kinase; mTOR, Mechanistic Target of Rapamycin; NF- κ B, nuclear factor kappa-B; miR-34a, MicroRNA-34a; Keap1, Kelch-like ECH-associated protein 1; ARE, Antioxidant Response Element; 3-NT, 3-Nitrotyrosine; 4-HNE, 4-Hydroxynonenal; PI3K, Phosphoinositide 3-Kinase; CAT, Catalase; OXR1, Oxidation Resistance 1; NRF2, Nuclear Factor Erythroid 2-Related Factor 2; JAK, Janus Kinases; SOD, Superoxide Dismutase; RNS, Reactive Nitrogen Species; M1/M2, Macrophage phenotypes 1 and 2; IL-6, Interleukin 6; IL-17, Interleukin 17; IL-12, Interleukin 12; IL-1 β , Interleukin 1 Beta; Arg1, Arginase 1; Ym1, Chitinase-Like Protein 3; Fizz1, Found in Inflammatory Zone 1; ABCG1, ATP Binding Cassette Subfamily G Member 1; CD36, Cluster of Differentiation 36.



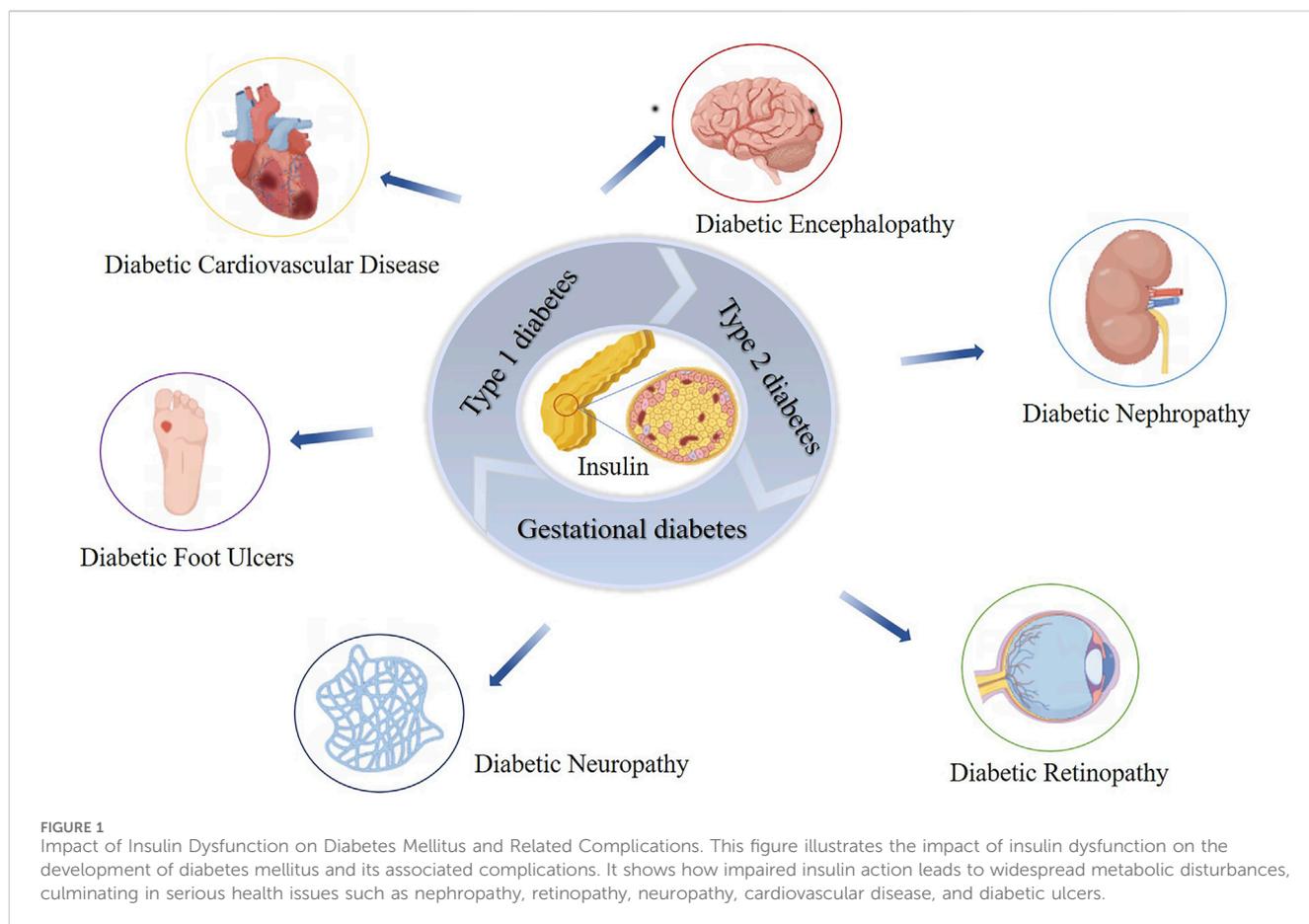
1 Introduction

DM is a major global health issue characterized by persistent hyperglycemia due to insufficient insulin secretion or action (Ill-Min et al., 2020; Constanze et al., 2017; Zhimei et al., 2019). The main symptoms include increased appetite, thirst, urination, and weight loss (Diagnosis and Classification of Diabetes Mellitus, 2013). In 2021, approximately 536.6 million people aged 20–79 were diagnosed with diabetes globally, and this number is projected to reach 783.2 million by 2045 (Hong et al., 2022). Diabetes is triggered by genetic and environmental factors, leading to the autoimmune destruction of pancreatic- β -cells, impairing insulin production, and disrupting metabolic processes, resulting in hyperglycemia (Décio et al., 2020; Aleksey and Peter, 2008; Kathryn et al., 2013). Prolonged hyperglycemia can lead to severe complications such as diabetic nephropathy, neuropathy, retinopathy, and cardiomyopathy (Janika et al., 2022; David et al., 2023) (Figure 1). Cardiovascular diseases are the leading cause of death among diabetic patients, particularly cardiac complications (Justin et al., 2016; Anoop et al., 2015).

Over the past few decades, several pharmacological agents have been developed to regulate blood glucose. Metformin primarily reduces hepatic gluconeogenesis through the activation of AMP-activated protein kinase (AMPK), while sulfonylureas (e.g., glimepiride) enhance insulin secretion by closing pancreatic β -cell ATP-sensitive potassium channels (Reuben et al., 2005; Gaochao et al., 2001; Mary, 2004). Thiazolidinediones (e.g., pioglitazone) improve insulin sensitivity via peroxisome proliferator-activated receptor gamma

(PPAR- γ) modulation (Aya et al., 2020; Zhiwei et al., 2021). More recent approaches include dipeptidyl peptidase-4 (DPP-4) inhibitors, which prolong the half-life of incretin hormones, and glucagon-like peptide-1 (GLP-1) receptor agonists, which stimulate insulin secretion and reduce glucagon levels (Daniel and Michael, 2006). Additionally, sodium-glucose cotransporter 2 (SGLT2) inhibitors lower blood glucose by promoting urinary glucose excretion (André, 2019). Current antidiabetic drugs mainly control blood glucose levels but cannot prevent or reverse complications (Dandan et al., 2020). Therefore, effective therapeutic strategies are urgently needed to halt or mitigate the progression of diabetes and its complications.

PCs, composed of flavan-3-ol and flavan-3, 4-diol units, include catechins, apocynin, and gallicolates (Chunhui, 2014; Liwei et al., 2002; Linards et al., 2022; Liang et al., 2016). Their main sources encompass grains, legumes, fruits, chocolate, and drinks like tea and wine (Abdur et al., 2019; Feng et al., 2016) (Figure 2). PCs exhibit diverse bioactivities such as anti-obesity, anti-diabetic, anti-cancer, anti-inflammatory, antioxidant, and cardiovascular protective effects (Eskandar et al., 2023; Antoni et al., 2012; Qian et al., 2023; Chuntang et al., 2022; Van Long et al., 2014; Liang et al., 2012). Studies suggest that PCs can lower blood glucose, improve insulin resistance, regulate insulin secretion, protect pancreatic β -cells in diabetic patients, and effectively alleviate diabetes complications (Javier et al., 2018; Suzanne et al., 2017; Anna et al., 2012). This review summarizes the molecular mechanisms and protective effects of PCs in diabetes treatment, which are shown in Table 1.



2 Pharmacokinetics of procyanidins

PCs are characterized by their double and single bonds, with catechols or epicatechols as fundamental components (Kaul, 1996). The health benefits of PCs are constrained by their low oral bioavailability due to incomplete intestinal absorption and extensive metabolism and excretion (Brigitte et al., 1989; Yue et al., 2021; Claudine et al., 2005; Ying Yng et al., 2014). It is estimated that over 90% of dietary polyphenols remain in the colon, with only a small fraction being indirectly absorbed in the small intestine through interactions with carbohydrates, fibers, and proteins (Michael, 2004; Gary and Claudine, 2005). Multiple factors influence the hydrolytic absorption of PCs, including gastrointestinal pH, dietary composition, and solubility in gastric and intestinal fluids. The acidic environment of the stomach may facilitate initial PCs release from food matrices but can also degrade certain oligomers, reducing their structural integrity and bioavailability. In the small intestine, dietary fibers and proteins can form complexes with PCs, limiting absorption, whereas lipids may enhance PCs solubility through micelle or emulsion formation. Tannins can further decrease bioavailability by competing for binding sites or forming insoluble complexes. Once in the colon, unabsorbed PCs oligomers and polymers interact with enterocyte membrane proteins, potentially modulating metabolic pathways (Liang et al., 2016). Meanwhile, gut microbiota convert these higher-order PCs into smaller phenolic acids (e.g., hydroxybenzoic, hydroxyphenylacetic, and hydroxycinnamic

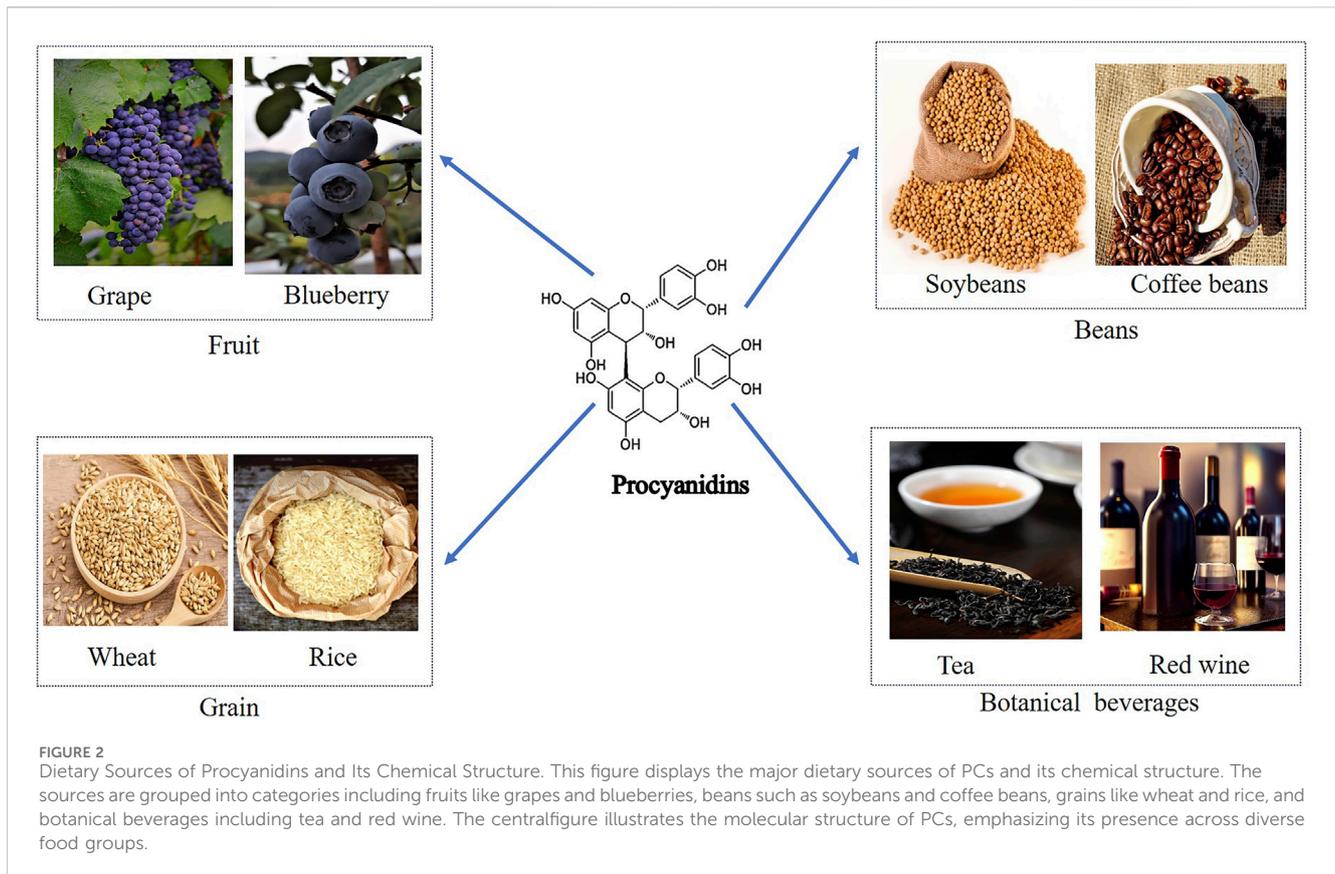
acids) with better solubility and increased absorption (Maaik et al., 2009). Ultimately, these metabolites are excreted in the urine (Figure 3).

Low bioavailability remains a major hurdle for harnessing the therapeutic benefits of PCs, necessitating innovative delivery approaches such as nano-encapsulation, phospholipid complexation, and co-administration with permeability enhancers. These strategies aim to stabilize PCs structure against pH-induced degradation, improve solubility, and promote systemic circulation. Further studies are required to elucidate the optimal conditions, formulations, and dietary adjuncts that maximize PCs efficacy in diabetes management. By advancing our understanding of PCs pharmacokinetics, including absorption, distribution, metabolism, and excretion, and refining targeted formulations, we can better leverage their therapeutic potential in preventing and managing diabetes and its complications.

3 Methods

3.1 Literature search

We conducted a comprehensive search on the PubMed (www.pubmed.com) and Web of Science (www.webofscience.com) databases for articles on procyanidins and diabetes published from 1 January 2000, to 30 December 2024. The research methodology is illustrated in Figure 4.



3.2 Search strategy

Procyanidins OR Procyanidin B2 OR GSPE OR Procyanidin B3 OR Catechin OR flavan-3-ol) AND (Diabetes mellitus OR diabetic nephropathy OR diabetic retinopathy OR diabetic neuropathy OR diabetic foot ulcer OR diabetic encephalopathy OR diabetic cardiovascular disease OR diabetic cardiomyopathy).

3.3 Inclusion criteria

(1): The document type is limited to original research articles or reviews; (2) Relevant to the topic of “procyanidins” and “diabetes”.

3.4 Exclusion criteria

(1) Irrelevant to the objective of this review; (2) Duplicated or outdated literature.

4 Mechanism of the protective effect of PCs on diabetes mellitus

4.1 Improve the insulin resistance

Insulin, an essential hormone secreted by pancreatic β -cells, regulates glucose metabolism and exerts a profound influence on blood glucose levels (Gary and Patricia, 2021). Typically, insulin

binds to receptors on the surfaces of target cells, thereby reducing hepatic glucose output and promoting glucose uptake in skeletal muscle and adipose tissue (Benedetta et al., 2019). When various internal and external factors drive target cells toward insulin resistance, greater amounts of insulin are required to trigger glucose transport and utilization. This phenomenon, referred to as insulin resistance, features elevated glucose and insulin levels in the bloodstream (Roselyn and Solomon, 1960; Christian et al., 2013).

Located in the cell membrane, the insulin receptor exhibits a tetrameric structure with two α -chains and two β -chains, serving as the primary hub for insulin action and orchestrating the insulin signaling cascade. Upon binding to the α -chain, insulin governs glucose transport and adiposity and modulates cell proliferation and differentiation. This interaction enhances gluconeogenesis while suppressing adipose tissue catabolism (Marinko et al., 2021). When insulin engages the β -chain, it triggers the insulin receptor substrate (IRS1/2), thereby boosting glucose metabolism (via the PI3K/PKB/AKT pathway), protein synthesis (via the TSC1/2-mTOR pathway), and cell proliferation and differentiation (via the RAS-MAPK-ERK1/2 pathway) (Rebecca et al., 2017; Barbara Di et al., 2016; Teri et al., 1991). Interruptions throughout the insulin signaling pathway can ultimately lead to insulin resistance. Often, diverse kinases and phosphatases—for instance, phosphorylated tyrosine—amplify serine/threonine phosphorylation, inactivating IRS proteins and worsening insulin resistance (Kyle and Morris, 2012). Additionally, processes involving kappa kinase β (IKK- β), c-Jun N-terminal kinase (JNK-1), protein kinase C (PKC), and mammalian target of rapamycin (mTOR)-driven serine modification of IRS1 also contribute to insulin resistance, further

TABLE 1 Characteristics of the included studies.

Study	Animal/cell model	Groups	Dosage of PC	Administration method of PC	Intervention time	Beneficial effects and involved mechanisms
Castell-Auvi et al. (2013)	Wistar rats	A. Group A Female (150–175) B. Group B male (130–150) C. Group C (225–250) D. Group D (175–200)	0/2.5/5/10/25/ 50 mg/kg/ 1,000 mg/kg	GSPE was gavaged for 36/ 21/45 days/1 h.	0–36 0–21 0–45 0–1 h	Low doses of procyanidins increased the plasma insulin levels and inhibited insulin gene expression, which led to reduced Pdx1 mRNA levels in the pancreas and reduced hepatic Ide gene expression
Caimari et al.	Wistar rats	A. VEH group: low-fat condensed milk B. GSPE group: 100 mg kg ⁻¹ .day ⁻¹ of GSPE dissolved in low-fat condensed milk	100 mg kg ⁻¹ .day ⁻¹ GSPE.	PC was orally daily for 21 days after modelin	1–21 d	GSPE decreased levels of the downstream post-receptor target of adiponectin, p-AMPK, in the soleus muscle
Castell-Auvi et al. (2013)	Wistar lean rats Zucker obese rat	Zucker rats: A. control group (Lean) B. Zucker obese group C. Zucker obese + GSPE group Wistar rats: A. control group B. GSPE group (25 mg GSPE/kg bw)	Zucker rats: 35 mg GSPE/kg/day Wistar rats: 25 mg GSPE/kg/day	Zucker rats: PC was orally daily for 60 and 45 days after modelin	Zucker rats: 0–60d Wistar rats: 0–45d	GSPE targets 11b-HSD1 gene expression that dantidiabetic effects
Najim et al. (2004)	Sprague-Dawley rats	A. control group B. fructose-enriched diet group C. anthocyan-treated fructose-fed group D. procyanidin and galloylated procyanidins-treated fructose-fed group E. vitafavan-treated fructose-fed	21.42 mg/kg of total polyphenols, 10 mL/Kg	Polyphenols was gavaged for 6 weeks	0–6 weeks	Polyphenolic treatments prevented the increased expression of the p91phox NADPH oxidase subunit
Tsai et al.	Sprague-Dawley rats	A. control group (standard Purina chow) B. group F (60% HF Diet) C. group L (HF + PC 125 mg/kg) D. group H (HF + PC 250 mg/kg)	Low-dose group: PC (125 mg dissolved in 0.1 g PC/mL H ₂ O)/kg High-dose group: PC (250 mg dissolved in 0.2 g PC/mL H ₂ O)/kg	PC was gavaged for 14 weeks	0–14 weeks	PC are associated with amelioration of defective insulin action on specific postreceptor insulin signaling related to IRS-1 and GLUT 4 proteins expression
Khanal et al.	Sprague-Dawley rats	A. Control group B. HF group C. HF group + LPC D. HF group + MPC E. HF group + HPC	Low-dose group: 3.3 g/kg; Medium dose group: 6.6 g/kg High-dose group: 33 g/kg	PC was orally daily for 7 weeks	2–7 weeks	PC in the medium level at 6.6 g/kg diet was the most effective in improving factors associated with metabolic syndrome in the high fructose fed growing rats sed in the current study
Liu et al.	C57BL/6 mice	A. Model group B. positive control group C. Low-dose PC D. Medium-dose PC E. High-dose PC	Low-dose PC: 75 mg/kg; Medium-dose PC: 150 mg/kg High-dose PC: 300 mg/kg	PC was orally daily for 4 weeks	0–4 weeks	PC ameliorated insulin resistance by decreasing LPS/TLR4/JNK inflammatory response, and enhancing IRS1/PI3K/AKT insulin signaling pathways in the liver
Cordero-Herrera et al.	Human HepG2 cells	A. EC group B. CPC group	10 μM or 1 μg/mL	HepG2 incubated were incubated with 10 μM or 1 μg/mL PC for 24 h	0–24 h	EC and CPE pre-treatment also prevented the inactivation of the PI3K/AKT pathway and AMPK, as well as the diminution of GLUT-2 levels induced by high glucose

(Continued on following page)

TABLE 1 (Continued) Characteristics of the included studies.

Study	Animal/ cell model	Groups	Dosage of PC	Administration method of PC	Intervention time	Beneficial effects and involved mechanisms
Rui et al. (2020)	HepG/HT22	A. Normal group B. Model group C. Positive group D. Treatment group	3.75 µg/mL LSF	HepG2/HT22 were incubated with 3.75 µg/mL LSF for 24 h	0–24 h	Catechin, procyanidin A1, and procyanidin A2 are the main components in LSF that inhibit Tau hyperphosphorylation through improving IR via the IRS-1/PI3K/Akt/GSK-3β pathway
Gemma et al. (2010a)	Wistar female rats	A. Control group B. Cafeteria group C. Cafeteria+25 mg/kg D. Cafeteria+50 mg/kg	Low-dose:25 mg/kg/d GSPE High-dose:50 mg/kg/d GSPE	GSPE was orally daily for 10 days (short treatment)/30 days (long treatment)	0–10d 0–30d	GSPE is dependent on Irs1 when stimulating glucose uptake but also suggests that GSPE has a direct effect on Glut4 transporter activity
Xinyi et al. (2020)	ApoE KO mice	A. control group B. ApoE KO group C. ApoE KO + PC	100 mg/kg/d	PC was orally daily for 24 weeks	0–24 weeks	PC could ameliorate atherosclerosis in ApoE-KO mice by improving NO bioavailability and reducing oxidative stress through NADPH oxidase dependent mechanisms
Wang et al.	C57BKS db/db	A. vehicle (saline) B. CD-1 (20 mg/kg) C. CD-1 (20 mg/kg)+CQ (20 mg/kg)	20 mg/kg	CD-1 were daily administrated (intraperitoneal injection) with 20 mg/kg for 5weeks	0–5 weeks	CD-1 on activation of Keap1/Nrf2 antioxidant signaling pathway and the amelioration of inflammation, endoplasmic reticulum stress, and apoptosis were through autophagy
Yuta et al. (2013)	KK-A ^y mice	A. Control B. BE diet	22.0 g of BE/kg	PC was orally daily for 1 week	0–1 week	PC via the activation of AMP-activated protein kinase (AMPK) reduced blood glucose levels and enhanced insulin sensitivity
Rodríguez-Carrizalez et al. (2014)	Wistar rats	A. Control group B. GSPE group	25 mg/kg bw/d	GSPE was gavaged for 45 days	0–45d	Procyanidin inhibition of intestinal DPP4 activity, either directly and/or via gene expression downregulation, could be responsible for some of their effects in glucose homeostasis.
Bak et al.	RAW 264.7 cells	A. Control B. 5 µg/mL C. 10 µg/mL D. 25 µg/mL E. 30 µg/mL F. 50 µg/mL	5 µg/mL/10 µg/mL/25 µg/mL/30 µg/mL, 50 µg/mL	Cells were treated with the indicated concentration of WGP for 24 h	0–24 h	WGP exerts potent anti-inflammatory activity through the inhibition of iNOS and COX-2 by regulating NFκB and p38 MAPK pathway
Liu and Wu. (2021)	C57BL/6 mice	A. Chow group B. HFHS group C. HFHS + PC group D. Abs group	27.8 mg/kg bw	PC was gavaged for 4 weeks	0–4 weeks	PA improved IR via NF-κB/NLRP3 pathway in GDM and <i>postpartum</i> mice, which partly through its metabolites by gut microbiome
Tian et al.	Sprague Dawley rats	A. DMSO B. PC	PCB2 (0.1–10 µM)	PCB2 (0.1–10 µM) for 24 h	24 h	PCB2 regulated macrophage M2 polarization via the activation of PPARγ

(Continued on following page)

TABLE 1 (Continued) Characteristics of the included studies.

Study	Animal/cell model	Groups	Dosage of PC	Administration method of PC	Intervention time	Beneficial effects and involved mechanisms
Farid et al.	MSCs cell	A. gp I: healthy control B. untreated induced type I diabetic group C. gp III: GSE-treated diabetic group D. gp IV: MSCs-treated diabetic group E. gp V: GSE- and MSCs-treated diabetic group	300 mg/kg	PCB1/PC1 was orally daily for 30 days	0–30 days	PCB1/CI/MSCs therapy in type I-induced diabetic rats has dramatically managed homeostasis of glucose and insulin secretion; together with, improvement in levels of inflammatory markers and oxidative stress
Tie et al.	ICR male	A. normal control group B. model group C. Fen group D. PC-H group E. PC-L group	200 mg/kg/50 mg/kg	PC was orally daily for 16 weeks	0–16 weeks	Proanthocyanidins ameliorated lipid metabolism and attenuated hepatic steatosis in mice with HFD/STZ-induced T2DM, for which activation of AMPK/ACC/CPT1A signaling might be an underlying mechanism
Nie et al. (2020)	HUVECs cell	A. Vehicle B. HG C. HG + PCB2	10 μ M	HUVECs were incubated with 10 μ M PCB2 for 24 h	24 h	PCB2 on ER stress and endothelial dysfunction required the interdependent actions of PPAR δ and AMPK.
Muthenna et al. (2014)	Wistar rats	A. control B. Diabetic(D) C. D + cinnamon D. D + PCB2	0.002% PCB2	Type 2 diabetes 3% cinnamon or 0.002% PCB2 fed in diet for 12 weeks	0–12 weeks	PCB2 suppressed renal AGE-RAGE stimulated MCP-1 and PKC- α expression, thereby modulated slit diaphragm proteins nephrin and podocin expression
Zhang et al. (2013)	C57BLKS/J db/db	A. control (db/m) B. Vehicle (C57BLKS/J db/db, saline) C. Diabetic group (GSPB2 (30 mg/kg/day))	30 mg/kg/day	GSPB2 was orally daily for 10 weeks	0–10 weeks	GSPB2 treatment significantly decreased protein levels of MFG-E8, phospho-ERK1/2, phospho-Akt, and phospho-GSK-3 β in the kidneys of db/db mice
Li et al. (2015)	HK-2 cell	A. Normal group B. High glucose C. Normal group + PC D. High glucose + PC	10 μ M PCB2	HK-2 cell was incubated with 10 μ M PCB2 for 24 h	0–24 h	PCB2 inhibited of the expression of TGF- β , p-Smad2 and 3, by modulating P38/MAPK signaling pathway inhibited HG-induced EMT.
Cai et al. (2016)	Mouse podocyte clonal cells (MPC5)	A. Normal group B. High glucose C. High glucose + PCB2(0, 0.625, 1.25, 2.5, 5, 10, 20, 40 μ g mL ⁻¹)	0/0.625/1.25/2.5/5/10/20/40 μ g mL ⁻¹	MPC5 cell was incubated with of GSPB2 (0/0.625/1.25/2.5/5/10/20/40 μ g mL ⁻¹) in 30 mM glucose for 48 h	48 h	GSPB2 activated of AMPK-SIRT1-PGC-1 α signalling, protected podocytes from high glucose-induced mitochondrial dysfunction, oxidative stress and apoptosis
Wei-Jian et al. (2015)	C57BLKS/J db/db	A. db/m B. db/m + GSPE C. db/db D. db/db + GSPE	30 mg/kg	GSPE was given 30 mg/kg/day, gavage for 12 weeks	12 weeks	GSPE enhanced p38MAPK-ERK1/2 signaling pathway oxidase activity, suppressed renal cell apoptosis and expression of TXNIP in renal cell apoptosis

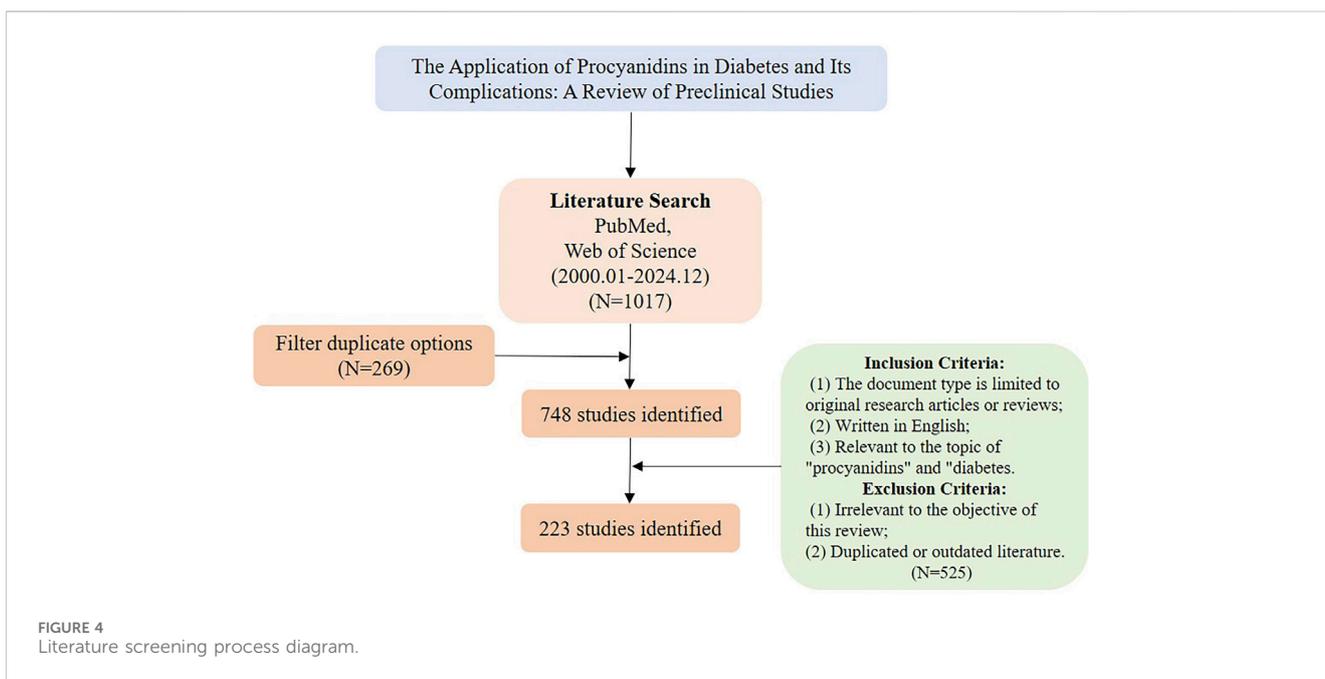
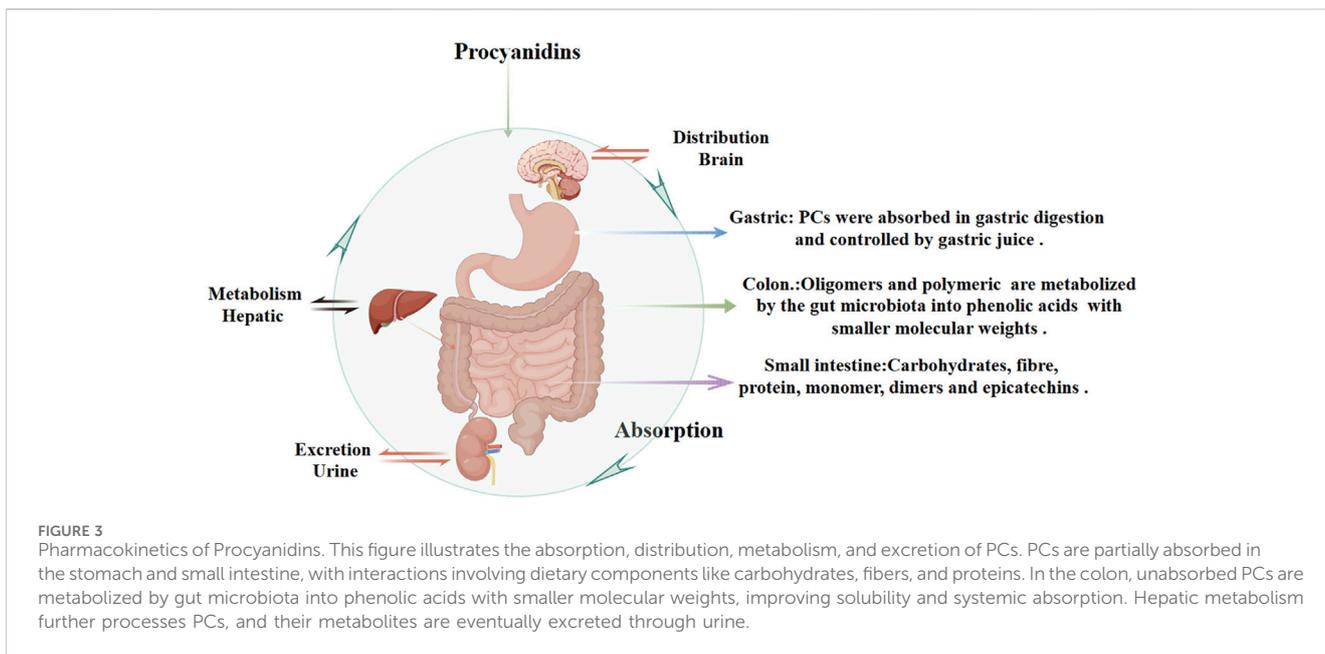
(Continued on following page)

TABLE 1 (Continued) Characteristics of the included studies.

Study	Animal/cell model	Groups	Dosage of PC	Administration method of PC	Intervention time	Beneficial effects and involved mechanisms
Zhou et al. (2016)	C57BLKS/J db/db	A. Vehicle B. GSPB2	30 mg/kg	GSPB2 was given 30 mg/kg/day, gavage for 10 weeks	10 weeks	GSPB2 by suppressing expression of nuclear factor- κ B (NF- κ B) p65 in nuclear extracts and restoring expression of Mincan protein has beneficial effects on oxidative stress and renal fibrosis in the diabetic kidney
Li et al. (2022)	Retinal pigment epithelial cells (RPE)	A. Normal control group B. High glucose group C. High glucose with PC groups	PC (0.05/0.1/0.5/1/5/10/50/and 100 μ M)	RPE cells were incubated with of GSPB2 (0.05/0.1/0.5/1/5/10/50/and 100 μ M) in 30 mM glucose for 48 h	48 h	PC throughs the p53/mTOR autophagy pathway to protect RPE cells from high glucose-induced injury
Zou et al. (2023)	Rat retinal capillary endothelial cells (TR-iBRB2)	A. High glucose B. High glucose + PCB2	PCB2 (0/5/10 and 25 μ M)	TR-iBRB2 cells were pre-treated with various concentrations of PCB2(0, 5, 10 and 25 μ M) for 24	24 h	PCB2 Protects TR-iBRB2 Cells Against Hyperglycemia Stress by Attenuating Oxidative Stress and Inflammasome Activation via Regulation of Redoxosomes/NF- κ B Signaling
Fan et al. (2021)	Endothelial progenitor cells (EPCs)	A. Mannitol B. HG C. HG + PCB2(0.1 μ mol/L, 0.5 μ mol/L, 2.5 μ mol/L)	PCB2 (0.1 μ mol/L, 0.5 μ mol/L, 2.5 μ mol/L)	EPCs were pre-treated with various concentrations of PCB2(0.1 μ mol/L/0.5 μ mol/L/2.5 μ mol/L) for for 24 h	24 h	PCB2 treatment accelerates wound healing and increases angiogenesis in diabetic mice, which may be mediated by activating of Nrf2 improving the mobilization and function of EPCs
Li et al. (2013)	HUVEC	A. gly-LDL B. gly-LDL + GSPB2-L (2.5 μ mol/L) C. gly-LDL + GSPB2-M(5.0 μ mol/L) D. gly-LDL + GSPB2-H (10.0 μ mol/L)	GSPB2(2.5 μ mol/L/5.0 μ mol/L/10.0 μ mol/L)	HUVEC were pre-treated with various concentrations of GSPB2 (2.5, 5.0, 10.0 μ mol/L) for 48 h	48 h	Procyanidin B2 (GSPB2) protect against gly-LDL induced VEC apoptosis through PIMT regulation
Yu et al. (2012)	C57BLKS/J db/db db/m mice	A. Control db/m group B. DMT:untreated db/db group C. DMT + GSPB2 group	GSPB2 (30 mg/kg/day)	GSPB2 was given diluted in normal saline solution by intragastric administration for 10 weeks	10 weeks	GSPB2 inhibits aortic expression and serum level of MFG-E8 and reduces atherogenesis in db/db mice
Luan et al. (2014)	C57BLKS/J db/db db/m mice	A. Control db/m group B. DMT:untreated db/db group C. DMT + GSPB2 group	GSPB2 (30 mg/kg/day)	GSPB2 was given diluted in normal saline solution by intragastric administration for 10weeks	10 weeks	GSPB2 activates S100A11/RAGE/PPAR γ signaling pathway to alleviate cardiac fibrosis in advanced glycation end-induced rats in type 2 diabetic rats

intensified by free fatty acids, lipotoxicity, oxidative stress, and inflammation (Stergios et al., 2009). PCs are frequently cited for their ability to improve insulin sensitivity in experimentally induced diabetic rats (Antoni et al., 2017; Anna et al., 2013). Previous studies underscore the marked antihyperglycemic effects of PCs in rats maintained on a high-fructose diet (Najim et al., 2004; Takako et al., 2008; Hsiang-Jung et al., 2008). Ramesh CK and colleagues found that PCs extracts from cranberries and blueberries, administered prophylactically, significantly mitigated insulin resistance, boosted glucose sensitivity, and lowered blood glucose in diabetic rats fed a

high-fructose diet, reinforcing the therapeutic value of PCs (Ramesh et al., 2010; Ramesh et al., 2012). M Liu et al. provided PCs to T2D mice (75, 150, and 300 mg/kg) via continuous gavage for 4 weeks, documenting improvements in intestinal barrier integrity by restoring morphology and raising the expression of tight junction proteins, including Zonula occludens-1 (ZO-1), Claudin-1, and occludin. This approach substantially reduced insulin resistance, promoted glucose uptake, and lowered blood glucose levels by activating the IRS1/PI3K/AKT signaling pathway (Min et al., 2022). Further *in vitro* research corroborated these results. I



Cordero-Herrera et al. cultured insulin-sensitive human HepG2 cells under high-glucose conditions and administered cocoa-derived polyphenols and epicatechin, which blocked tyrosine phosphorylation and lowered total IR, IRS-1, and IRS-2 levels through PI3K/AKT and AMPK pathway inhibition, thereby mitigating high-glucose-induced insulin signaling impairment that alters gluconeogenesis (Isabel et al., 2014). The activation and subsequent engagement of the insulin receptor (IR) and its downstream mediators, IRS-1 and IRS-2, remain critical for regulating insulin signaling (Mary et al., 2002). In hepatic insulin resistance, normal tyrosine phosphorylation of IR and IRS is compromised, diminishing PI3K activity associated with IRS.

Conversely, the oligomeric form of grape seed procyanidin (GSPE) extract induces tyrosine phosphorylation, thereby activating the IR and decreasing AKT and GSK-3 β phosphorylation via PI3K/AKT pathway stimulation. This process augments GS phosphorylation, thereby improving hepatic insulin sensitivity (Aurèle et al., 2019; Rui et al., 2020; Gemma et al., 2010a) (Figure 5). Meanwhile, a glucose-lowering formulation containing hawthorn polyphenols, D-chiro-inositol, and epigallocatechin gallate exhibited synergistic hypoglycemic activity, markedly improving insulin resistance in mice, decreasing fasting blood glucose and hepatic gluconeogenesis, and enhancing hepatic glycogen synthesis and storage (Chao

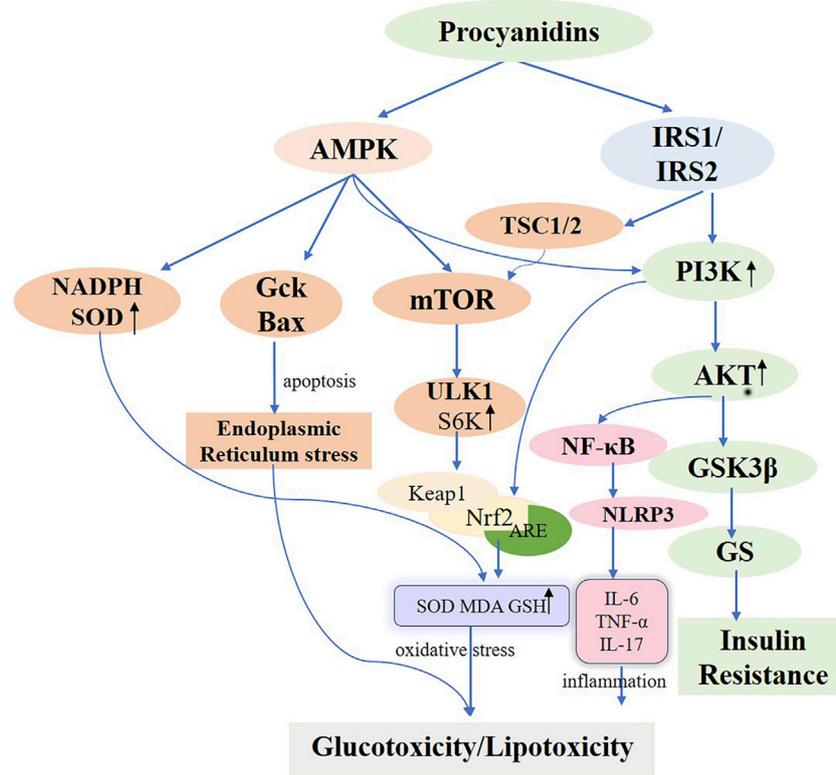


FIGURE 5

Molecular Mechanisms of Procyanidins in Modulating Diabetes Mellitus. This figure delineates the comprehensive molecular pathways impacted by PCs in the management of DM. PCs enhance insulin sensitivity by activating PI3K/AKT signaling via IRS1/IRS2 and reduce insulin resistance through GSK3 β inhibition. PCs also alleviate oxidative stress by activating AMPK and Nrf2 pathways, increasing antioxidants like SOD and GSH, while reducing inflammatory responses mediated by NF- κ B and NLRP3. Additionally, PCs modulate cellular stress and autophagy, mitigating endoplasmic reticulum stress and promoting metabolic homeostasis. These mechanisms collectively address glucotoxicity, lipotoxicity, and insulin resistance in diabetes.

et al., 2021). Additionally, a randomized controlled trial revealed that a combination of flavan-3-ols and isoflavones enhanced insulin sensitivity and lipoprotein profiles compared to placebo, further lowering the estimated 10-year CVD risk in women with type 2 diabetes (Peter et al., 2012).

In summary, under insulin-resistant conditions, polyphenolic PCs can effectively bolster cellular insulin sensitivity. However, prior investigations have yet to establish the ideal PCs concentration and dose for mitigating insulin resistance or to clarify the therapeutic distinctions among active metabolites from diverse sources. Future studies should center on identifying effective concentrations and characterizing botanical metabolites derived from multiple sources.

4.2 Reduced glucotoxicity and lipotoxicity

Glucotoxicity is characterized by irreversible tissue and cell damage resulting from insulin resistance and persistently elevated glucose levels stemming from excessive carbohydrate intake (Mota et al., 2016). The primary cause of glucotoxicity is insulin resistance, which arises from defective islet cell function and damage caused by reduced insulin mRNA expression, associated with diminished transcription or activity of transcription factors involved in insulin production (Daniël and Michaëla, 2011). Insulin resistance significantly contributes to hyperglycemia-induced

glucotoxicity. Excess carbohydrates are metabolized into free fatty acids and triglycerides, promoting adipogenesis and lipotrophy through the activation of enzymes like acetyl coenzyme A carboxylase (ACC), fatty acid synthase (FAS), and SCD-1 (Mota et al., 2016). These processes are influenced by endoplasmic reticulum (ER) stress, oxidative stress, mitochondrial dysfunction, and islet inflammation (Maria et al., 2020; Wenqian et al., 2018; Jiwon and Kun-Ho, 2011).

Prolonged exposure to elevated fatty acid levels triggers lipotoxicity, compromising pancreatic β -cell functionality and viability. This condition activates multiple stress pathways, resulting in β -cell impairment and mortality. ER stress and oxidative stress are especially well-documented contributors to this effect (Kerry et al., 2005; Eloisa Aparecida et al., 2021; Andrei et al., 2007). Cellular lipotoxicity, also known as glycolipotoxicity, is exacerbated by elevated glucose levels (Yiqi et al., 2022). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), a producer of reactive oxygen species (ROS), acts as a key generator of oxidative stress within pancreatic islet β -cells, significantly affecting glucose-induced insulin release and β -cell viability in Type 1 and Type 2 diabetes (Eloisa Aparecida et al., 2021). Animal studies demonstrate that palmitate impairs insulin secretion by upregulating the p47phox NOX subunit protein within rat pancreatic islets (Marta et al., 2010). Shuang et al. (2017) demonstrated that PCs from lychee pericarp decrease mRNA levels

of cellular NADPH oxidase subunits (p47phox, p67phox, NOX2/gp91phox, and NOX4) and enhance superoxide dismutase (SOD) activity, thereby providing a strong antioxidant effect. Additionally, Xinyi et al. (2020) found that cinnamon tannin D1, an A-type PCs oligomer derived from *Cinnamomum cinnamomi*, protects pancreatic β -cells against glucotoxicity induced by high glucose and palmitic acid, both *in vitro* and *in vivo*. The key process entails CD-1 initiating autophagy in pancreatic β -cells via the AMPK/mTOR/UNC-52-like kinase 1 (ULK1) pathway. This autophagic response reduces cell damage by activating the Keap1/Nrf2 antioxidant pathway, which is associated with Kelch-like ECH protein 1 and nuclear factor erythroid 2-related factor 2, thereby mitigating inflammation, endoplasmic reticulum stress, and apoptosis. Consequently, this lowers hyperglycemia and reduces glucotoxicity in diabetic db/db mice (Figure 5). A clinical study found (Hadi et al., 2020) that supplementation with epigallocatechin-3-gallate significantly increased serum total antioxidant capacity (TAC) levels in patients with type 2 diabetes, thereby enhancing the body's overall antioxidant capacity.

In summary, this section systematically elucidates the mechanisms through which glucotoxicity and lipotoxicity impact pancreatic β -cell function and survival, leveraging both literature and experimental evidence to underscore the potential application of PCs in mitigating these pathological processes. In particular, PCs extracted from lychee pericarp and A-type PCs oligomers (CD-1) derived from cinnamon exhibit promising effects on autophagy activation, mitigation of β -cell damage, and enhancement of glucose metabolism. However, a notable gap remains between these findings and their clinical application. First, many uncertainties exist regarding the absorption, distribution, and metabolism of PCs in humans, including their bioavailability and potential side effects. Moreover, given the trend towards precision medicine, which accounts for individual differences, factors such as a patient's disease stage, comorbidities, and genetic background must also be considered to fully assess the clinical translational potential of these active compounds in diabetes management. Only by bridging laboratory research with evidence-based medicine can we fully harness the potential of these active components in suppressing glucolipotoxicity and reducing the risk of diabetic complications.

4.3 Maintains glucose homeostasis

Maintaining glucose homeostasis is crucial for providing energy to vital organs and sustaining overall health. The liver is key in this dynamic, participating in processes such as glucose synthesis, glycogenolysis, glycolysis, gluconeogenesis, and glucose metabolism. Insulin, primarily stimulated by glucose, is secreted by beta cells under normal physiological conditions. During fasting, the liver generates glucose to fuel the brain, muscles, and adipose tissues, collectively regulating glucose uptake (Xinyi et al., 2020; Wei et al., 2017). PCs regulate glucose uptake, effectively lowering glucose levels through this mechanism (Montserrat et al., 2012). Recent research has underscored the importance of AMPK in managing metabolic conditions, including diabetes, obesity, and fatty liver disease (Sébastien and Reuben, 2017). Furthermore, AMPK boosts glucose absorption in insulin-responsive tissues

such as adipocytes, muscle cells, and hepatocytes, proving effective in enhancing glucose uptake *in vitro* (Zhang et al., 2009; Yuta et al., 2013; Montserrat et al., 2004; Isabel et al., 2015). Elevated phosphorylation levels of AMPK were noted in the liver, muscle tissue, and adipocytes of mice subjected to insulin resistance from high-fat diets and streptozotocin (STZ)-induced diabetes models (Masahito et al., 2010; Peiling et al., 2013). Yuta et al. (2013), Ken-yu et al. (2022) utilized anthocyanins extracted from black beans to treat type 2 diabetic mice, activating AMPK in skeletal muscle cells to improve glucose utilization and decrease gluconeogenesis, while concurrently down-regulating phosphoenolpyruvate carboxykinase (PEPCK) and glucokinase (GK) activities—crucial enzymes in glycolysis that boost intracellular glucose catabolism.

Glucose Transporter Type 4 (GLUT4), a crucial glucose transport regulator, is predominantly found in adipose, skeletal, and heart muscles. Significantly, skeletal muscle serves as a crucial target for managing hyperglycemia, accounting for roughly 80% of postprandial insulin-mediated glucose absorption and is essential for maintaining glucose equilibrium (Nia et al., 2002; Alan and Kahn, 2001). PCs enhance glucose absorption, facilitate GLUT4 translocation in mouse L6 myotubes, and promote glucose uptake within skeletal muscle via insulin and AMPK-dependent pathways (Miki et al., 2011). G Montagut et al. and HH Lee et al. showed that enhanced GLUT4 translocation increases Akt phosphorylation in adipocytes, further boosting a critical pathway in the insulin signaling cascade (Gemma et al., 2010b; Hee-Hyun et al., 2010). Additionally, PCs affect glucose synthesis and metabolism by boosting the functions of enzymes including glucokinase, hexokinase, and glycogen synthase, and reducing the functions of liver enzymes like glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, and fructose-1,6-bisphosphatase (Zhang et al., 2009; Gopalsamy Rajiv et al., 2011) (Figure 5).

GLP-1, a crucial hormone linked to intestinal insulin, is secreted by L-cells within the intestinal lining and remains vital for human glucose metabolism. Studies suggest that polyphenols can stimulate GLP-1 secretion, helping to manage insulin resistance, hyperglycemia, and type 2 diabetes (Dao et al., 2011). Recent studies have demonstrated that botanical extracts emulate the actions of gut insulinotropic hormones. For example, PCs inhibit DPP-4 (the catabolic enzyme of GLP-1) expression, and tetrameric PCs cinnamon tannin A2 enhances GLP-1 secretion within 1 hour of ingestion (Noemi et al., 2012; Eun-Jung et al., 2011). Meanwhile, researchers noted that oligomers and polymers of PCs enhance GLP-1 activity and insulin secretion independently of glucose loading. This finding indicates that PCs may target L cells in the intestines as a crucial regulator of blood glucose, though the exact mechanism is yet to be elucidated and warrants further investigation (Yoko et al., 2019).

In summary, PCs regulate the function of glucose-targeting organs, modulate glucose metabolism and synthesis, and maintain glucose homeostasis through multiple pathways. However, the above studies have not clarified the differences in efficacy between PCs structures and total extracts, nor the specific targets of individual metabolites. Therefore, future research should focus on these aspects to provide more targeted options for clinical applications.

4.4 Regulation of pancreatic beta cell function

Insulin secretion by pancreatic β -cells is crucial for preserving glucose metabolic homeostasis. Research indicates that PCs modulate islet fibrosis, enhance pancreatic β -cell function and morphology, and promote insulin release in Wistar rats with high-fat-diet-induced diabetes (Anna et al., 2012). The amount of insulin secreted by β -cells hinges on the number of insulin-producing cells. Under insulin-resistant conditions, a direct relationship emerges between β -cell count and insulin demand. Often, a persistent imbalance between β -cell proliferation and cell death sets the stage for type 2 diabetes (Laura et al., 2007). The influence of PCs on apoptosis varies among different cell types. Research has shown that PCs display chemopreventive properties in cancer cells by enhancing apoptosis and suppressing proliferation (Giovanna et al., 2024). Similarly, PCs demonstrate parallel effects on pancreatic β -cell lines. Lídia et al. (2013) established an *in vitro* model of insulin resistance and diabetes using the pancreatic INS-1E β -cell line. This approach involved subjecting INS-1E β -cells to high glucose and fatty acid conditions to induce dysfunction. The researchers investigated how elevated glucose, fatty acids, and PCs affect glucose- and palmitate-induced apoptosis in INS-1E cells. They found that PCs amplified glucose-induced apoptosis yet did not alter palmitate-induced β -cell apoptosis. This discrepancy likely arises because these two triggers engage different mechanisms underlying INS-1E cell dysfunction. Research indicates that elevated glucose levels diminish glucokinase (Gck) protein expression in pancreatic islet cells, limiting its interaction with voltage-dependent anion channels (VDAC) in the mitochondrial outer membrane. Conversely, palmitic acid triggers apoptosis via LC-CoA or other metabolites, in conjunction with endoplasmic reticulum stress and mitochondrial dysfunction. The results suggest that PCs augment high glucose-induced apoptosis in pancreatic β -cells by increasing glucose uptake under high glucose conditions, potentially via a mechanism that downregulates Gck and promotes Bax protein translocation and oligomerization at the mitochondrial membrane. Furthermore, the study showed that PCs curtail cell proliferation induced by glucose, insulin, and palmitate, although the precise mechanism remains unclear. Meanwhile, epigallocatechin gallate (EGCG), used alone or together with GLP-1 agonist exendin-4, was shown to enlarge islet area and number, expand β -cell area, and boost pancreatic insulin content in diabetic and obese mouse models, thus demonstrating favorable therapeutic outcomes (Nupur et al., 2018).

The onset of diabetes and its associated complications are tightly linked to oxidative stress and inflammation. Elevated amounts of oxidative stressors and inflammatory cytokines are closely associated with pancreatic harm in diabetic laboratory rats. Therefore, reducing oxidative stress and cytokines could represent one pathway through which PCs safeguard pancreatic islet cells. Nrf2 is pivotal in the regulation of intracellular antioxidant defense mechanisms. Mahmoud MF and his team (Mona et al., 2021) noted significant elevations in Nrf2 and HO-1 levels within the pancreatic tissues of rats suffering from STZ-induced diabetes. Studies have demonstrated that catechin-rich PCs improve the functionality of isolated pancreatic β -cells from Wistar rats and primary rat islet cells. This improvement is realized by enhancing

insulin secretion through a non-oxidative stress pathway involving the activation of MAPK/PI3K to phosphorylate Nrf2, facilitating its nuclear translocation, binding to the ARE promoter, and ultimately boosting antioxidant gene expression (Thomas et al., 2017). Ji-Hyun et al. (2009) showed that cytokines intensify inflammatory damage in isolated pancreatic islet cells, leading to disrupted insulin secretion. This result is attained by increasing nitric oxide (NO) production, enhancing NF- κ B DNA binding, boosting inducible nitric oxide synthase (iNOS) expression, and activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) inflammatory pathway, leading to DNA damage and elevated levels of FAS and IL-1 β . Wild PCs has successfully inhibited the phosphorylation of MAPKs and PI3K/Akt, thereby preventing lipopolysaccharide (LPS)-induced NF κ B nuclear translocation. As a result, this leads to diminished production of NO, prostaglandin E2 (PGE2), and ROS, along with decreased levels of inducible iNOS, cyclooxygenase-2 (COX-2), and cytokines (Min-Ji et al., 2013).

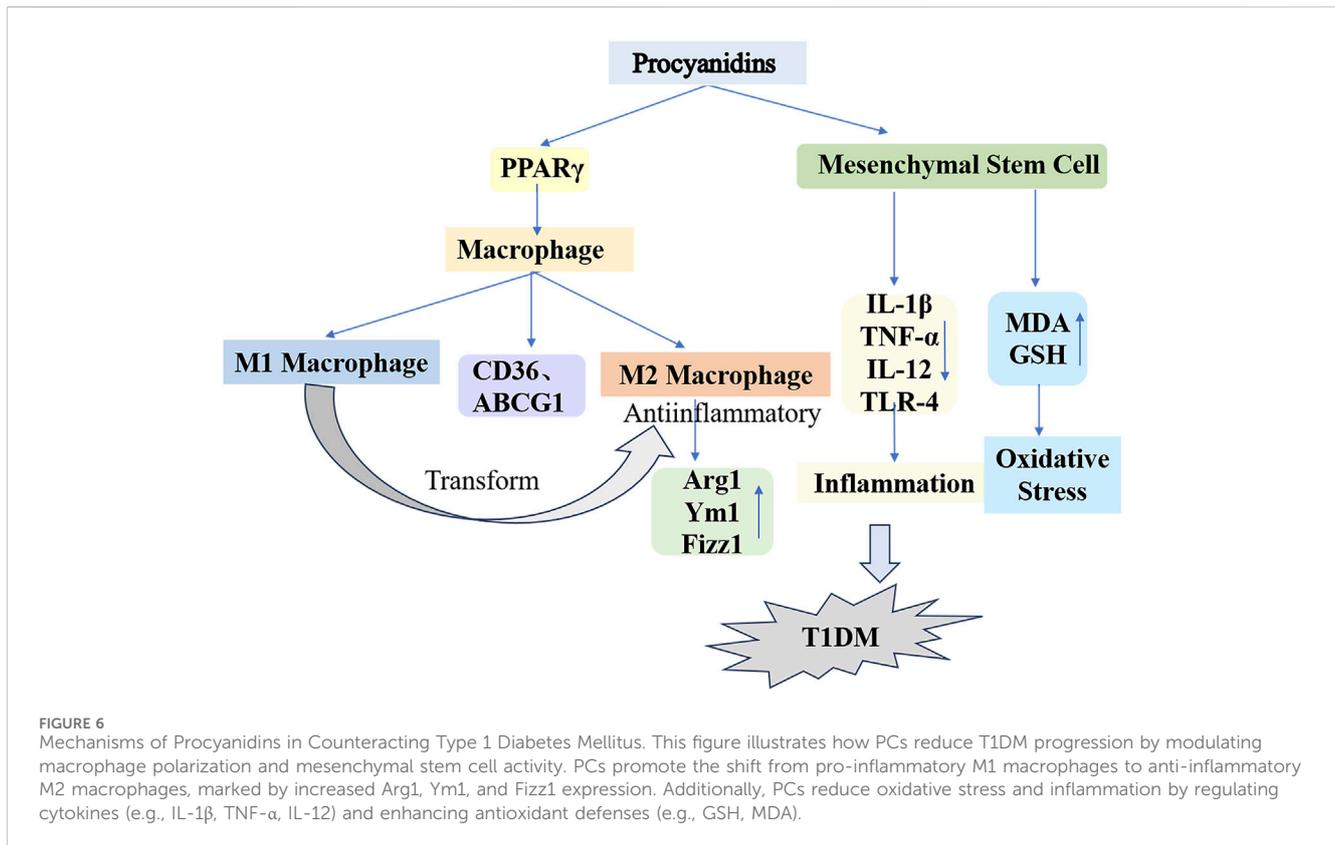
The NOD-like receptor family pyrin domain containing 3 (NLRP3) comprises a large molecular weight protein assembly, incorporating NLRP3, ASC, and caspase-1, which forms an inflammatory vesicle. This complex is responsible for releasing proinflammatory cytokines Interleukin-1 β (IL-1 β) and Interleukin-18 (IL-18), fulfilling a critical function in regulating insulin resistance (Bo-Zong et al., 2015). Research has shown that silencing NLRP3 inhibits obesity-induced activation of inflammatory vesicles in adipose and hepatic tissues, thereby improving insulin sensitivity—a significant finding in this area (Bolormaa et al., 2011). Initiation of the NF- κ B pathway is crucial for regulating the NLRP3 inflammasome, a vital element of the innate immune system. NF- κ B is acknowledged as the primary mediator responsible for transcribing NLRP3 and generating precursors of IL-1 β and IL-18 (Yuan et al., 2016). Yao et al. (2022) demonstrated that PCs treatment effectively reduces NF- κ Bp65 nuclear translocation and NLRP3 inflammasome activation, thereby inhibiting excessive NF- κ B pathway activation due to high in sugar and fat. The intervention led to a marked decrease in the concentrations of inflammatory markers like IL-6, tumor necrosis factor- α , (TNF- α), IL-17, and CRP, and notably improved insulin sensitivity in gestational diabetic mice.

In summary, PCs can regulate pancreatic β -cell function and influence insulin secretion through apoptosis, oxidative stress, and inflammatory pathways. However, the retrieved literature mainly focuses on pancreatic cell lines, with limited studies on other cell lines. Future research could establish diverse cell models to investigate whether PCs exhibit similar effects on other cell lines (Figure 5).

5 Protective effects of PCs on diabetes mellitus and complications

5.1 PCs and type 1 diabetes mellitus

Type 1 diabetes originates as an autoimmune disease involving the targeted destruction of pancreatic islet β -cells due to specific immune reactions. The β -cell primarily serves as the organ responsible for insulin secretion. Besides producing insulin, β -cells sense glucose levels and release insulin to maintain these levels within the normal physiological range



(Jeffrey et al., 2010). Consequently, β -cells function not only as insulin producers but also as regulators—or “thermostats”—of glucose levels. Research indicates that key factors behind pancreatic islet β -cell dysfunction and structural damage include the presence of infiltrating CD4⁺ and CD8⁺ T cells, along with macrophages (Alan et al., 1991). When β -cells are depleted, individuals with type 1 diabetes lose glycemic control, resulting in acute conditions like ketoacidosis and severe hypoglycemia, as well as chronic complications such as heart disease, blindness, and kidney failure (Maahs and Rewers, 2006). Hence, targeting macrophages may represent a promising strategy for managing type 1 diabetes.

Macrophages, key components of the innate immune system, maintain immune homeostasis and contribute to overall health. This regulatory function occurs via macrophage polarization in response to both internal and external environmental or pathological stimuli (Guillermo Arango and Albert, 2014). Ying et al. (2019) applied different concentrations of PCs to macrophages from db/db diabetic mice. Their findings indicated that PCs reduced M1 macrophage counts while elevating M2 macrophage markers such as Arginase 1, Ym1, and Fizz1. The proposed mechanism involves PCs activating peroxisome proliferator-activated receptor γ (PPAR γ) in macrophages, upregulating PPAR γ target genes (CD36 and ABCG1) and driving the transition from M1 to M2 phenotypes. Recently, bone marrow mesenchymal stem cells (MSCs) have been recognized as a promising treatment alternative for diabetes. However, challenges such as oxidative stress and inflammation significantly limit the efficacy of bone marrow MSC transplantation therapy. The antioxidant and anti-inflammatory

properties of PCs were validated through *ex vivo* experiments (Shuang et al., 2017; Min-Ji et al., 2013). Alyaa et al. (2022) administered a daily 300 mg/kg dose of PCs combined with bone marrow MSC transplantation to STZ-induced type 1 diabetic rats over a 30-day period, resulting in successful blood glucose management and enhanced insulin secretion. Furthermore, PCs mitigated oxidative stress and lowered the concentrations of inflammatory markers such as IL-1 β , TNF- α , IL-12, and TLR-4, which were elevated by MSCs, while upregulating critical antioxidant enzymes, notably glutathione (GSH). This finding demonstrates that PCs provide substantial protection against oxidative stress and inflammatory responses triggered by diabetes and MSC differentiation (Figure 6).

In conclusion, the pathogenesis of type 1 diabetes involves the immune-mediated destruction of β -cells and abnormal activation of immune cells, with macrophage polarization playing a critical role in immune regulation, making it a promising therapeutic target. PCs, with their antioxidant and anti-inflammatory properties, can amplify the therapeutic effects of bone marrow mesenchymal stem cell combination therapy, alleviating oxidative stress and inflammatory responses. Although existing studies support its therapeutic potential, further investigation is necessary to clarify its mechanisms, optimize bioavailability, and identify specific targets, while large-scale clinical trials remain imperative to validate its efficacy.

5.2 PCs and type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is recognized as a metabolic syndrome, primarily marked by insufficient insulin caused by

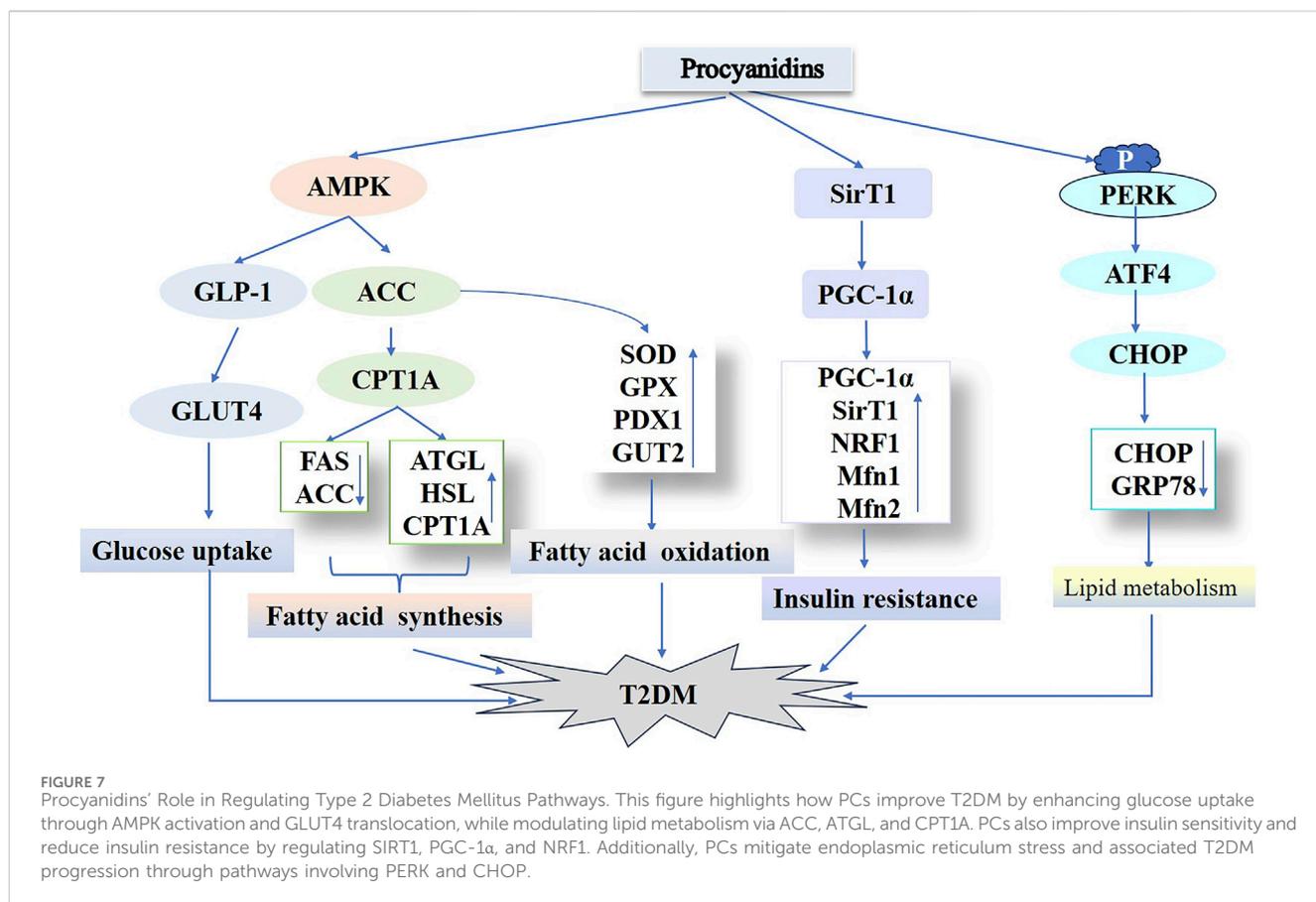
pancreatic β -cell dysfunction and insulin resistance in target organs (NCD Risk Factor Collaboration NCD-RisC, 2016; Sudesna et al., 2017). Multiple genes govern β -cell differentiation and function—for instance, GLP-1, which enhances insulin secretion while reducing glucagon secretion; PAX4, essential for islet development; and PDX1, vital for β -cell differentiation, growth, and the maintenance of mature function. Furthermore, elements including NF- κ B, Toll-like receptors, and bone bridging proteins significantly affect insulin resistance, all of which are regulated by epigenetic mechanisms (Karina et al., 2021). Yoko et al. (2019) administered various doses of cocoa-derived proanthocyanidin extracts to ICR mice, observing that PCs with distinct structures enhanced GLP-1 secretion and reduced postprandial hyperglycemia. The probable pathway likely involves PCs augmenting GLUT4 translocation and glucose uptake in skeletal muscle through an AMPK-dependent mechanism, subsequently enhancing GLP-1-activated insulin signaling and lowering postprandial hyperglycemia. *In vitro* studies show that a 10 μ M concentration of PCs optimally attenuates bisphenol-induced islet cell damage, suppresses apoptosis, and improves insulin secretion. In bisphenol-induced T2DM mice, PCs reduced lipid peroxidation, boosted antioxidant enzymes (SOD and Gpx), upregulated mRNA levels of PDX1 and GUT2, and preserved glucose homeostasis. Furthermore, combined catechin and quercetin therapy demonstrated a stronger impact on elevating key enzymatic activities in hepatic glucose metabolism in diabetic rats relative to monotherapy (Byoung Rai and Pyoung Sim, 2022). Additionally, a double-blind clinical trial reported that continuous intake of a PCs-rich beverage, largely composed of catechin, stimulated insulin secretion and enhanced blood glucose control in individuals with type 2 diabetes (Tomonori et al., 2009). Collectively, these findings prevented BPA-induced islet cell apoptosis, hyperglycemia, and diabetic onset (Ahangarpour et al., 2016).

Insulin resistance is a major contributor to the development of type 2 diabetes. Furthermore, mitochondrial dysfunction plays a pivotal role in the progression of insulin resistance. Essential for maintaining normal mitochondrial function, mitochondrial biosynthesis is regulated by key factors such as Peroxisome receptor gamma coactivator 1-alpha (PGC-1 α) and silent information regulator factor 2-related enzyme1 (SirT1). PGC-1 α acts as a coactivator for transcription factors that regulate mitochondrial genes, including nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM). Conversely, SirT1-mediated deacetylation activates PGC-1 α (Helena et al., 2009; Bor Luen, 2016). In a dexamethasone-induced insulin resistance model using 3T3-L1 adipocytes, flavan-3-ols from PCs enhanced the expression of genes involved in mitochondrial biosynthesis (PGC-1 α , SirT1, NRF1) and fusion proteins (Mfn1 and Mfn2). Furthermore, PCs reduced the expression of the fission protein Drp1, thereby improving mitochondrial defects in 3T3-L1 adipocytes by enhancing mitochondrial biosynthesis, dynamics, membrane potential, and antioxidant capacities, ultimately mitigating insulin resistance (Fangfang et al., 2020).

Hyperlipidemia substantially contributes to type 2 diabetes susceptibility. This condition arises from disrupted hepatic lipid metabolism, characterized by elevated triglyceride synthesis, increased cholesterol production, and reduced fatty acid

oxidation. These processes drive excessive hepatic fat accumulation, culminating in steatosis (Lewis et al., 2002; David et al., 2007). Thus, optimizing lipid metabolism represents a viable strategy for both preventing and managing type 2 diabetes. In their research, Fangfang et al. (2020) used PCs to treat a T2DM mouse model induced by a high-fat diet (HFD) and STZ. PCs treatment significantly decreased hyperglycemia and hyperinsulinemia, as well as serum triglycerides, total cholesterol, LDL cholesterol, and AST-associated lipokines in T2DM mice compared to controls. PCs treatment enhanced diabetic hyperlipidemia and liver function in mice. Additionally, PCs suppressed adipogenic proteins (FAS, ACC) while upregulating lipolytic proteins (ATGL, HSL, CPT1A). The results indicate that PCs may suppress lipogenesis while enhancing lipid hydrolysis and β -oxidation processes for fatty acids. This effect likely occurs via AMPK/ACC/CPT1A pathway activation, enhancing hepatic lipid metabolism in HFD/STZ-induced diabetic mice. The degree of polymerization in PCs correlates with their biological potency. Zhao et al. (2024) administered equivalent doses of PCs exhibiting varying polymerization levels to HFD/STZ-induced diabetic mice. These PCs significantly lowered fasting blood glucose, improved glucose/insulin tolerance, and optimized lipid profiles (total cholesterol, triglycerides, LDL cholesterol), while reducing oil-red staining in hepatic and serum tissues. They significantly downregulated CHOP and GRP78 expression in diabetic mouse livers, implying a link between hepatic lipid dysregulation and endoplasmic reticulum stress. Furthermore, *in vitro* experiments showed that administering PCs of different polymerization degrees to palmitic acid-induced HepG2 cells markedly diminished intracellular GRP78 expression. Additionally, this approach activated the protein kinase R-like endoplasmic reticulum kinase (PERK)/active transcription factor 4 (ATF4) signaling pathway, crucial for endoplasmic reticulum stress regulation, and partially mitigated hepatic lipid accumulation. These findings align with earlier investigations in high glucose-induced C57BL/6 mice treated with PB2, indicating that PCs regulate lipid metabolism in diabetes by targeting endoplasmic reticulum sensors such as PERK, IRE1, and ATF6 (Liu Z. et al., 2023; Nie et al., 2020). GSPE with varying polymerization degrees exhibit protective activity on blood glucose, lipid levels, and hepatic oxidative stress in diabetic rats (Zhaoxia et al., 2014). Notably, oligomers outperformed polymers, implying that the oligomeric form of GSPE might provide superior benefits over other forms. In conclusion, PCs and their derivatives, spanning different polymerization degrees, may influence the initiation and progression of T2DM via multiple pathways. Hence, these plant metabolites show promise as active agents for type 2 diabetes management (Figure 7).

In summary, PCs participate in T2DM pathophysiology via multiple mechanisms, such as enhancing insulin secretion, safeguarding pancreatic β -cells, optimizing mitochondrial function and insulin resistance, and regulating hepatic lipid metabolism. Their polyphenolic metabolites display significant potential in regulating endoplasmic reticulum stress and lipid metabolism. As natural plant metabolites, PCs hold considerable promise as a therapeutic option for T2DM, but their specific mechanisms and clinical applications demand further research.



5.3 PCs and gestational diabetes mellitus

Gestational diabetes mellitus (GDM) emerges exclusively during pregnancy or is diagnosed when abnormal glucose tolerance is first identified (Sweeting et al., 2022). The pathogenesis of GDM is intricate, primarily involving impaired insulin secretion and reduced functionality. Insulin resistance gradually intensifies during pregnancy, ultimately leading to hyperglycemia (Jasmine et al., 2018; Kimber-Trojnar et al., 2018). Glucose, which traverses the placenta, serves as the primary energy source for the developing fetus (Ruszała et al., 2022). Furthermore, the overactivation of adipose tissue, which produces monocytes and macrophages that secrete inflammatory factors, contributes to the pathogenesis of GDM by initiating inflammatory responses. Growing evidence indicates that abnormal inflammatory responses are major contributors to the development of insulin resistance (Skórzyńska-Dzidusko et al., 2016; Akash et al., 2018; Gao et al., 2016). In a study utilizing a GDM mouse model induced by a high-fat diet and sugar, PCs (27.8 mg/kg/d) were administered from 4 weeks before pregnancy until delivery to evaluate their impact on insulin resistance, including during the postnatal period and in offspring. PCs effectively managed weight gain during pregnancy, decreased serum fasting blood glucose (FBG), fasting insulin, oral glucose tolerance test area under the curve, and insulin tolerance test area under the curve levels, and enhanced the Homeostatic Model Assessment (HOMA) insulin sensitivity index. These interventions positively affected fasting glucose and insulin levels. Additionally, PCs improved glucose metabolism and reduced concentrations of inflammatory mediators such as IL-6, TNF- α , IL-17, and CRP, thereby diminishing inflammation

and hepatic inflammatory infiltration in mice 4 weeks postnatally. However, these treatments did not significantly impact the offspring. In a related observation, PCs were used in a GDM mouse model with gut flora defects induced by a combination of broad-spectrum antibiotics and a high-fat, high-sugar diet. This treatment enhanced insulin resistance by inhibiting the NF- κ B/NLRP3 activation pathway, thereby altering the levels of gut flora metabolites 4-hydroxyphenylacetic acid and 3-(4-hydroxyphenyl) propionic acid (Yao et al., 2022). In a double-blind, randomized, controlled trial on gestational diabetes (Zhang et al., 2017), it was observed that mothers in the epigallocatechin 3-gallate group showed significant improvements in diabetes parameters, with fewer cases of neonatal complications compared to the placebo group.

In conclusion, PCs exert significant protective effects on the pathogenesis of GDM by enhancing insulin sensitivity, lowering levels of inflammatory factors, and alleviating liver inflammation, while effectively regulating glucose metabolism during pregnancy and *postpartum* stages. Despite limited effects on offspring mice, PCs continue to show potential as a treatment for GDM, but their long-term safety and mechanisms require further research and verification.

5.4 Effect of PCs on diabetic complications

5.4.1 PCs and diabetic nephropathy

Diabetic nephropathy (DN) is a primary microvascular complication of diabetes mellitus, characterized by proteinuria, glomerular enlargement, reduced tubular filtration, renal fibrosis,

and renal dysfunction, ultimately leading to end-stage renal disease (Samsu, 2021). The progression of diabetic nephropathy is multifaceted, influenced by factors such as renal hemodynamic abnormalities, dyslipidemia, oxidative stress, and hormone synthesis, including Angiotensin II (Ang II). Additionally, its progression is influenced by inflammation, the renin-angiotensin system (RAAS), advanced glycation end-product (AGE) formation, and signaling molecules, including transforming growth factor- β 1 (TGF- β 1), connective tissue growth factor (CTGF), PKC, MAPK, and ROS. Collectively, these factors accelerate the progression of diabetic nephropathy, making it a leading cause of end-stage renal disease (Javier et al., 2020; Su Woong and Jae-Young, 2021; Majid, 2013; Wei-Jian et al., 2015; Yashpal et al., 2011; Mandeep Kumar and Umesh Kumar, 2013). In a rat model induced by STZ, a 12-week regimen of PCs treatment resulted in improvements in proteinuria and podocyte injury. Its probable mechanism includes activation of renal AGE-RAGE signaling pathways, decreasing levels of monocyte chemoattractant protein-1 (MCP-1) and PKC-A, which consequently reduces the production of slit diaphragm proteins such as nephrin and podocin, thereby mitigating the impact of AGE-mediated DN pathogenesis (Muthenna et al., 2014). Oral administration of PCs significantly enhanced kidney function and reduced pathological alterations in db/db mice. Proteomic evaluation revealed that following PCs administration, 53 proteins were downregulated and 60 upregulated, with milk fat globule-epidermal growth factor 8, (MFG-E8) as the most notably upregulated protein in diabetic kidneys. Inhibition of MFG-E8 via shRNA transfection decreased phosphorylation levels of ERK1/2, Akt, and GSK-3 β in the kidneys of db/db mice, improving renal histopathology. Conversely, overexpression of MFG-E8 had opposite effects. PCs treatment reduced MFG-E8, phospho-ERK1/2, phospho-Akt, and phospho-GSK-3 β levels in db/db mouse kidneys, indicating MFG-E8's influence on the progression of diabetic nephropathy. PCs appear to mitigate diabetic nephropathy by reducing MFG-E8 levels and modulating the ERK1/2, Akt, and GSK-3 β pathways (Zhang et al., 2013).

Diabetic glomerulosclerosis is a defining feature of diabetic nephropathy. A key process in glomerulosclerosis and tubular epithelial fibrosis involves the epithelial-to-mesenchymal transition (EMT) induced by high glucose levels (Xu et al., 2017). PCs mitigate high glucose-triggered EMT within HK-2 cells by activating the TGF- β /Smads and P38/MAPK pathways, upregulating α -SMA, FN, and Waveform proteins, and downregulating E-cadherin levels (Li et al., 2015). Oxidative stress plays a crucial role in the progression of diabetic kidney injury. Research shows that PCs protect cells from the systemic high glucose impacts on mitochondria, preventing cellular dysfunction and cell death by activating the AMPK-SIRT1-PGC-1 α pathway. This compound reduces ROS levels, enhances SOD antioxidant activity, and increases the expression of NRF-1 and TFAM genes (Cai et al., 2016). In diabetic nephropathy models, PCs attenuated renal cell apoptosis by enhancing p38 MAPK and ERK1/2 activities and reducing Bcl-2 expression. GSPE also reduced thioredoxin-interacting protein expression, facilitating intracellular ROS catabolism via the sulfhydryl antioxidant pathway to mitigate oxidative stress in diabetic kidneys (Wei et al., 2018). Additionally, PCs alleviated DN pathology, such as glomerular basement membrane thickening and central dilatation, by

modulating mimecan protein expression through the NF- κ B p65 pathway (Zhou et al., 2016) (Figure 8). The combined treatment of perindopril and catechin significantly improved mesangial matrix and podocyte function in diabetic rats, effectively preventing glomerular injury, with greater efficacy compared to monotherapy (Salime Pelin et al., 2014). A clinical study demonstrated (Tung-Sheng et al., 2011) that a 1:1 mixture of epigallocatechin-3-gallate and Amla (*Embllica officinalis*) significantly enhanced antioxidant defenses in patients with diabetic nephropathy, synergistically improving clinical outcomes.

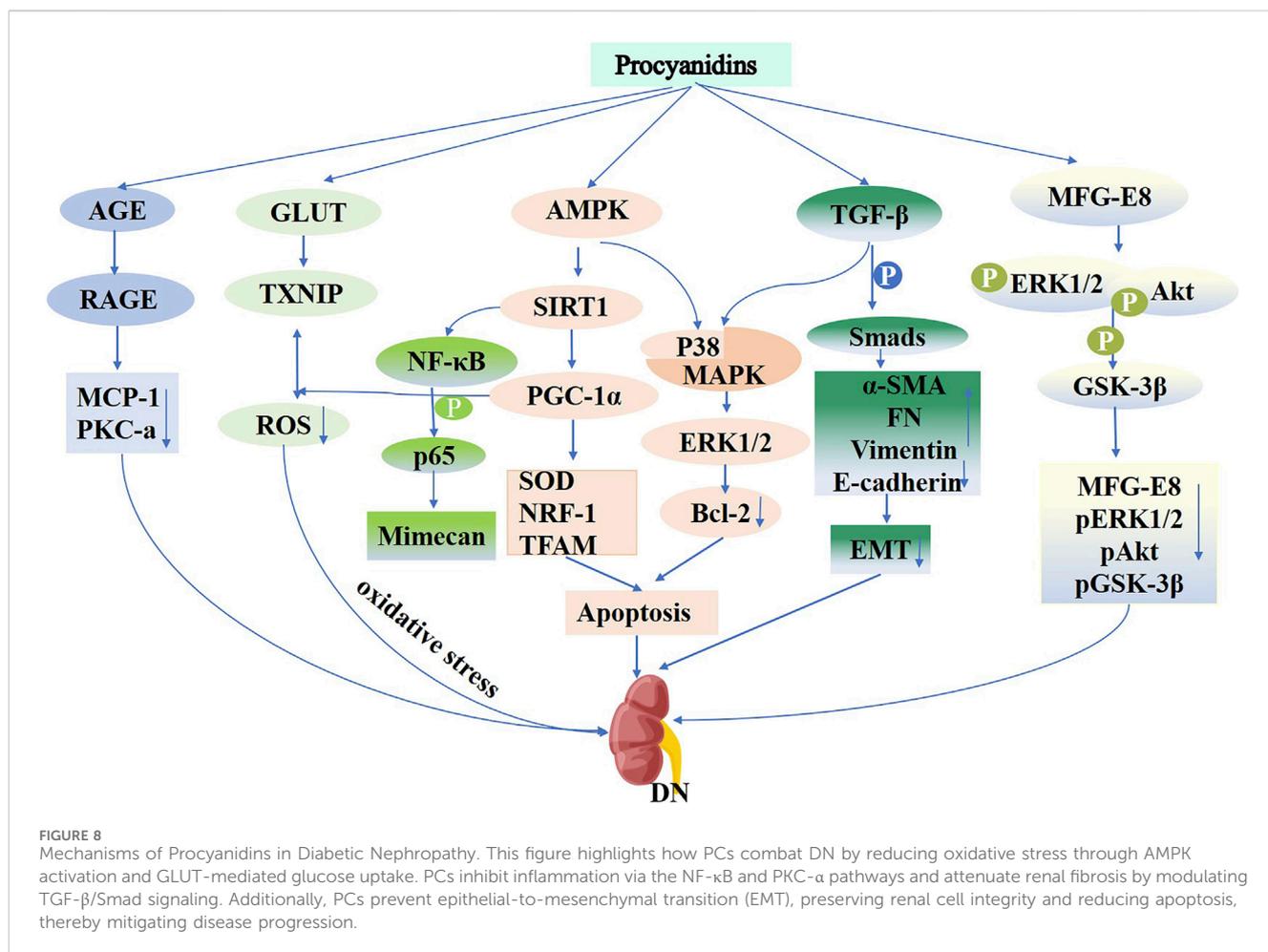
PCs and their metabolites exhibit significant therapeutic potential in the pathogenesis of diabetic nephropathy through multiple mechanisms, including antioxidant and anti-fibrotic effects, as well as the regulation of key signaling pathways. They are particularly effective in reducing proteinuria, protecting mitochondrial function, and inhibiting inflammatory responses. Despite these promising findings, current research is largely confined to animal models and *in vitro* studies, with limited clinical investigations available. Therefore, further large-scale clinical trials are essential to confirm the safety and efficacy of PCs in managing diabetic nephropathy, thereby establishing a foundation for their clinical application.

5.4.2 PCs and diabetic retinopathy

Diabetic retinopathy (DR) is a significant microvascular complication of diabetes mellitus and a leading cause of vision loss worldwide (Tan and Wong, 2022; Liu and Wu, 2021; Joanne et al., 2012). DR stems from a complex pathology involving oxidative stress, inflammatory lesions, and the polyol pathway. Activation of hexosamine flux and advanced glycation end product (AGE) formation, driven by PKC isoform activation and related pathways, contributes to vascular dysfunction and tissue injury in the retina (Yau et al., 2012; Al-Shabrawey et al., 2015; Lu et al., 2018). Early and timely intervention is crucial to prevent retinal damage and vision impairment in individuals with diabetes.

Recent studies indicate that PCs exert protective effects on retinal cells by modulating autophagy, reducing oxidative stress, and attenuating inflammation (Rodríguez-Carrizalez et al., 2014; John et al., 2020). In high-glucose-challenged retinal pigment epithelial cells, PCs activate the p53/mTOR autophagy pathway, lowering apoptosis-related factors (e.g., Bax, Caspase-3, LC3-II/LC3-I, and phosphorylated p53) and elevating the levels of survival proteins (Bcl-2, p62, and phosphorylated mTOR) (Li et al., 2022). Additionally, the application of PCs to rat retinal capillary endothelial cells (TR-iBRB2) decreases oxidative stress and inflammasome activation, suggesting involvement of the oxidase/NF- κ B/NLRP3 axis in mediating their cytoprotective effects (Zou et al., 2023). Further research reveals that PCs, alone or in combination with other phytoalexins, can activate the AMPK/SIRT1/NF- κ B pathway and inhibit the miR-34a/SIRT1/p53 axis, thereby mitigating hyperglycemia-induced inflammation, oxidative stress, and apoptosis in retinal cells (Liu et al., 2021) (Figure 9).

Moreover, mounting evidence highlights the anti-glycation and anti-dicarbonyl properties of PCs, which inhibit the formation of AGEs by scavenging reactive carbonyl species (e.g., methylglyoxal) (Qian et al., 2013). By reducing the burden of these glycation intermediates, PCs help maintain retinal integrity and limit the progression of DR.



In conclusion, PCs safeguard retinal cells and mitigate diabetic retinopathy through various molecular mechanisms, including autophagy activation, oxidative stress reduction, anti-glycation activity, and anti-inflammatory modulation. These pleiotropic actions underscore the potential of PCs as promising therapeutics for DR and warrant further investigation in both preclinical and clinical settings.

5.4.3 PCs and diabetic neuropathy

Diabetic neuropathy (DN), commonly presenting as a distal symmetrical polyneuropathy, is characterized by sensory deficits and pain in the extremities (Eva et al., 2019). Hyperglycemia-driven pathways accelerate DN progression, with AGEs and reactive dicarbonyl compounds exacerbating nerve injury through chronic inflammation and neuronal apoptosis (Stella et al., 2021; Ryuichi et al., 2001).

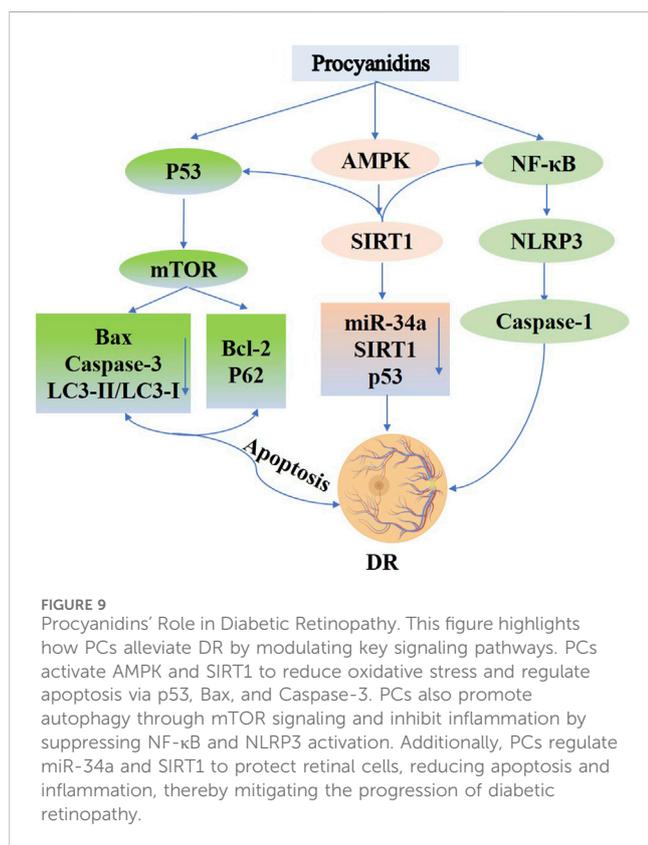
PCs have shown promising neuroprotective effects by reducing oxidative stress, preventing the accumulation of AGEs and other toxic intermediates, and mitigating glycation-induced damage. Moreover, their anti-glycation and anti-dicarbonyl properties lessen the accumulation of AGEs and other toxic intermediates, consequently protecting peripheral nerves from glyceamic damage (Xiao-Fang et al., 2008; Xiao-Fang et al., 2010). Notably, in models of type 2 diabetes, PCs confer neuroprotection by modulating NF-E2/STAT1 signaling, attenuating Janus kinase activity, and inhibiting cell apoptosis, thereby

reducing cerebrovascular lesions and associated neurological deficits (Wu et al., 2015; Yin et al., 2021) (Figure 10).

In summary, PCs offer a multifaceted neuroprotective effect in DN by targeting oxidative and inflammatory pathways, preventing glycation-related damage, and reducing neuronal apoptosis. Further clinical studies are needed to validate these findings and establish optimal dosing regimens for maximizing the therapeutic efficacy of PCs in managing DN.

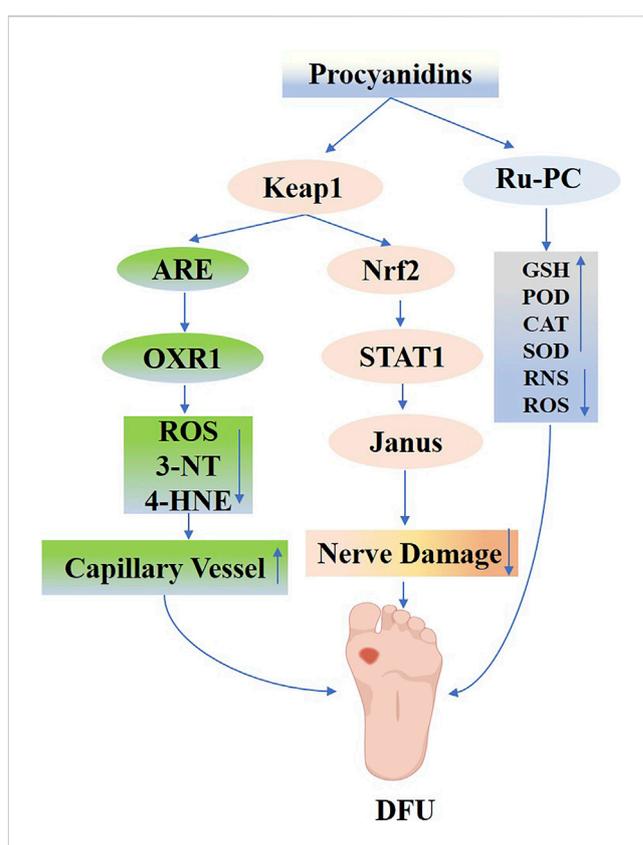
5.4.4 PCs and diabetic foot ulcer

Diabetic foot ulcers (DFU) are severe and common complications stemming from a multifactorial interplay of sensory, motor, autonomic, and vascular abnormalities, along with altered foot biomechanics (McDermott et al., 2023). Approximately 50%–60% of diabetic ulcer patients develop infections, and about 20% of these cases, involving moderate to severe infections, require lower extremity amputation (David et al., 2023). Patients with DFU face a 5-year mortality rate of about 30%, which rises to over 70% for those undergoing major amputations. Moreover, infected diabetic ulcers significantly heighten the risk of disability and mortality among these patients (Armstrong et al., 2020). Diabetic ulcer wounds that are resistant to healing markedly increase the risk of bacterial invasion and subsequent infection. Thus, prompt treatment and intervention aimed at promoting wound healing in diabetic ulcers are crucial for reducing



infections and preventing amputations in diabetic patients. The wound healing process encompasses hemostasis, inflammation, proliferation, and wound remodeling. Hyperglycemia-induced cellular dysfunction, prolonged low-grade inflammation, and tissue ischemia and hypoxia are well-documented barriers to wound healing, further decelerating the repair of refractory diabetic wounds (Matoori et al., 2021).

Research increasingly indicates that plant-derived active ingredients support the differentiation and functional capabilities of various cell types, thereby promoting wound healing (Kisseih et al., 2015). Specifically, PCs have exhibited notable efficacy. Pimentel EF and their group (Pimentel et al., 2024) employed resonance mass spectrometry to analyze seed hulls, noting that PCs enhanced fibroblast functionality and migration, and increased the levels of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These improvements supported the healing of wounds infected with *Staphylococcus aureus*. Subsequent experiments showed that PCs significantly enhanced the angiogenic, survival, and migration capabilities of human umbilical cord blood endothelial progenitor cells under high-glucose conditions, thus reducing glucose-induced damage. This protective action likely involves regulating antioxidant gene expression via Nrf2 activation, diminishing excessive ROS accumulation, and reducing oxidative damage markers (e.g., 3-NT and 4-HNE), as evidenced by J Fan et al.'s study on STZ-induced diabetic mouse wounds treated with PCs (Fan et al., 2021). They found that PCs not only reduce oxidative stress in damaged skin via Nrf2 activation but also stimulate capillary formation and facilitate endothelial progenitor cell migration to the wound site, thereby accelerating wound healing and promoting neoangiogenesis.



The integration of nanomaterials and hydrogels with plant-derived active ingredients for wound healing has recently attracted significant interest among researchers. PCs, polyphenolic compounds derived from plants, exhibit antioxidant, antibacterial, and anti-inflammatory properties. When combined with ruthenium-liganded nano-enzymes, PCs are converted into potent antimicrobial agents that could potentially replace antibiotics in treating bacterial-infected wounds. Shan et al. (2024) combined RuCl₃ with polyvinylpyrrolidone to synthesize Ru-PVP, then mixed it with PCs in a methanol solution to formulate Ru-PC nano-enzymes exhibiting four enzymatic activities. The functional pathways of Ru-PC nano-enzymes varied significantly across different environments. In acidic environments, these nanoenzymes demonstrated effective antimicrobial properties through GSH reduction and peroxidase (POD) -mimetic activity. Under neutral conditions, Ru-PC nanoenzymes break down H₂O₂ into O₂ via catalase (CAT) activity, thus alleviating wound healing complications due to hypoxia. Concurrently, Ru-PC exhibits SOD-like activity, efficiently eliminating excessive reactive oxygen and nitrogen species in neutral environments, thereby preserving antioxidant balance. Additionally, Ru-PC modulates the transition from M1 to M2 macrophage polarization, aiding in the management

of inflammatory wound repair challenges. In conclusion, Ru-PC nanoenzymes expedite the healing of infected wounds by stimulating cell proliferation, eradicating bacteria, reducing inflammation, neutralizing free radicals, supplying oxygen, and promoting blood vessel growth. Liu K. et al. (2023) created a versatile PBOF hydrogel dressing composed of poly (vinyl alcohol) (P), borax (B), oligomeric PCs (O), and ferric ions (F). This hydrogel is characterized by its adhesive, shape-adapting, stretchable, self-healing, detachable, antioxidant, photothermal antimicrobial, hemostatic, and biocompatible properties, making it exceptionally suitable for managing wounds in highly active areas. In a mouse model with *Staphylococcus aureus*-induced cervical wound infections, the PBOF hydrogel dressing showed antimicrobial activity, utilizing the photothermal properties of ferric ions and polyphenol chelates, together with the hemostatic, antimicrobial, and anti-inflammatory qualities of PCs. These features aid in wound healing by minimizing oxidative stress, curbing inflammation, and enhancing angiogenesis (Figure 10).

In conclusion, the occurrence of DFU is closely related to cell dysfunction, low-grade inflammation, and tissue hypoxia induced by hyperglycemia. PCs significantly promote wound healing by alleviating oxidative stress, promoting endothelial progenitor cell migration, improving angiogenesis, and exerting anti-inflammatory and antibacterial effects. Moreover, the combination of nanomaterials and hydrogels with plant bioactive metabolites further enhances the therapeutic effect, suggesting that PCs hold great promise for the treatment of DFU.

5.5 The effects of PCs on atypical complications of diabetes

5.5.1 PCs and diabetic encephalopathy

Diabetic encephalopathy (DE), a diabetes-related complication marked by central nervous system damage, primarily results from cerebral microangiopathy, including conditions such as stroke, dementia, and depression (van Sloten et al., 2020). Numerous studies have confirmed that DM independently increases the risk of conditions such as ischemic stroke, transient ischemia, and vascular dementia (Antal et al., 2022). People with type 2 diabetes have a 2.5-fold increased risk of ischemic stroke and are 1.5 times more likely to experience hemorrhagic stroke and dementia than those without diabetes (Sarwar et al., 2010; Cheng et al., 2012). Potential mechanisms linking diabetes to stroke include vascular endothelial dysfunction, atherosclerosis, inflammatory responses, oxidative stress, and alterations in blood-brain barrier permeability (van Sloten et al., 2020; Chen et al., 2016). Wu et al. (2015) employed PCs using a mouse model of middle cerebral artery occlusion (MCAO) to examine its impact. They observed that PCs reduced infarct size, cerebral swelling, and neurological impairments following MCAO. This effect is attributed to PCs' role in facilitating nuclear translocation, enhancing levels of HO-1, GST α , NQO1, and ZO-1 proteins in the ischemic zone to maintain blood-brain barrier integrity and mitigate damage to the nervous system. Similarly, PCs activated the TLR4-p38-NF- κ B-NLRP3 signaling pathway, which decreases the production of inflammatory cytokines in response to MCAO/R and OGD/R both *in vivo* and *in vitro*. Furthermore, it exhibited neuroprotective properties by lessening cerebral edema,

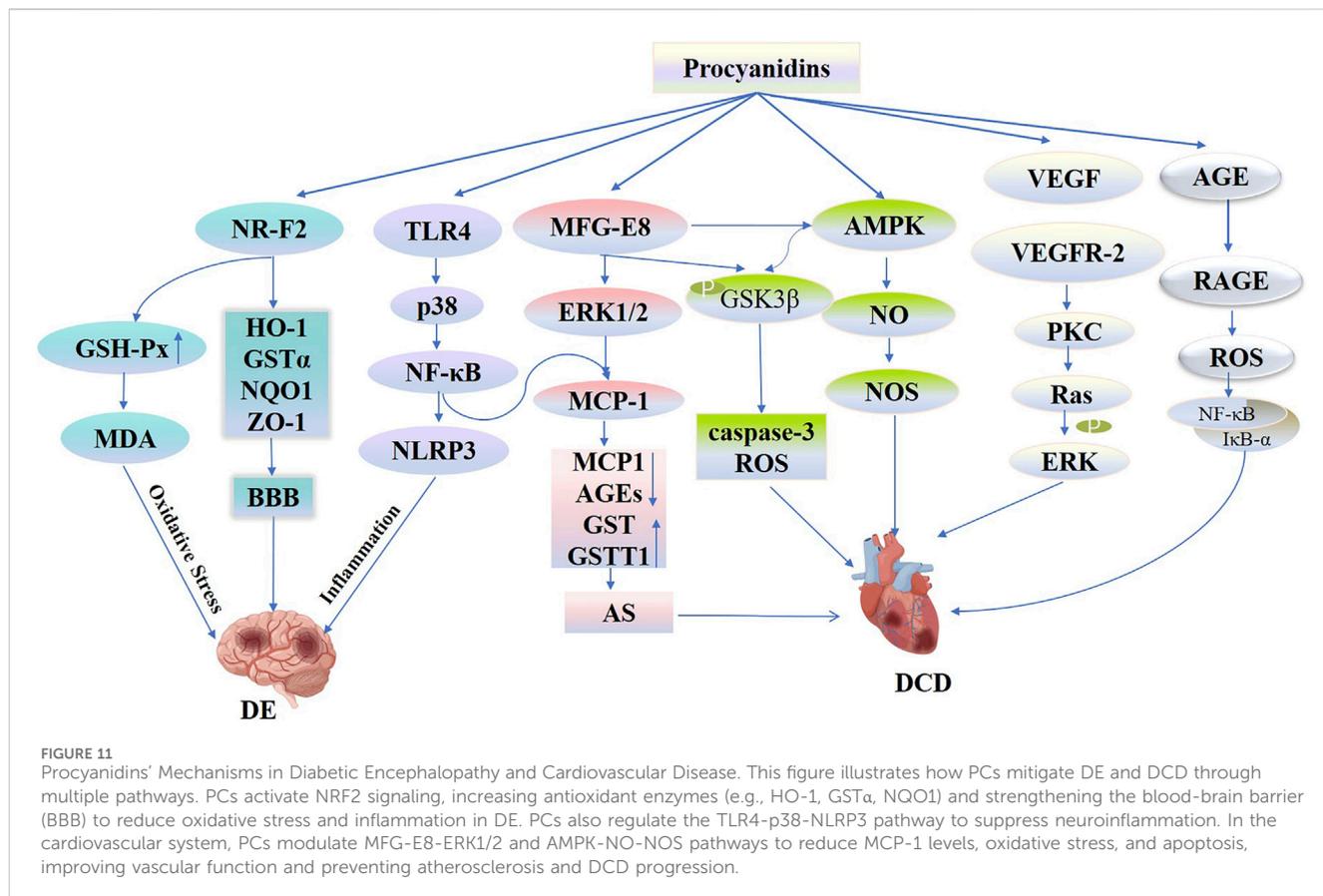
reducing infarct size, minimizing histological damage, and decreasing microglial cell death (Yang et al., 2020).

Oxidative stress acts as a critical factor in the onset of ischemic reperfusion damage. PCs derived from grape seeds significantly modulate oxidative stress responses. In experiments employing the MCAO/R model, PCs significantly reduced neurological impairment scores at various intervals—1, 24, 72 h, and 7 days post-MCAO. Additionally, PCs effectively reduced the volume of cerebral infarcts and curbed malondialdehyde (MDA) levels in brain tissues. Significantly, PCs lowered MDA levels and boosted glutathione peroxidase (GSH-Px) activity in brain tissues relative to the control group. This protective effect was achieved by mitigating oxidative stress and apoptosis, promoting angiogenesis, and triggering the GSH-Px antioxidant pathway, thus defending against ischemia-reperfusion brain injury (Kong et al., 2017) (Figure 11).

In conclusion, PCs demonstrate significant neuroprotective effects through their antioxidant, anti-inflammatory properties, and maintenance of blood-brain barrier function. Additionally, PCs provide effective protection against cerebral ischemia-reperfusion injury by alleviating oxidative stress, promoting angiogenesis, and activating antioxidant enzyme pathways. Both provide potential therapeutic strategies for treating brain injury caused by diabetes, but their clinical application requires further validation.

5.5.2 PCs and diabetic cardiovascular disease

Diabetic cardiovascular disease (DCD) remains the primary cause of mortality among individuals with type 2 diabetes. Dysfunction of vascular endothelial cells is an initial contributor to cardiovascular disease (Strain and Paldánus, 2018). Nitric oxide is critical for regulating vasodilation. A diminished availability of nitric oxide can lead to endothelial dysfunction (Jeong et al., 2022). Elevated glucose levels activate the enzyme aldose reductase (AR), which transforms glucose to sorbitol, with NADPH serving as a coenzyme for this process. Depletion of NADPH impairs NO synthesis and lowers glutathione levels, causing an overproduction of oxygen free radicals, which compromises endothelial cell function in blood vessels (Belenichev et al., 2023). Clinical research has shown that PCs raise endothelial nitric oxide synthase (eNOS) levels, subsequently reducing systolic and diastolic blood pressure values (Odai et al., 2019; Schön et al., 2021). Simultaneously, PCs stimulate AMPK, which increases eNOS levels and nitric oxide production, thereby enhancing vascular endothelial performance (Cui et al., 2012). Research indicates that microRNAs (miRNAs) are involved in endothelial cell dysfunction and apoptosis (Silambarasan et al., 2016). PCs modulate glucose metabolism by regulating microRNA expression in the pancreas (Castell-Auví et al., 2013). Elevated blood sugar levels impair vasodilation by activating PKC in vascular cells, affecting the activities of ET-1, VEGF, NO, PDGF, ROS, and NF- κ B in pericytes, leading to capillary myelopoietic thickening and increased endothelial cell proliferation (Barrett et al., 2017). Liu et al. (2016) demonstrated that PCs and their oligomers enhance cell proliferation, reducing oxidative damage in endothelial cells under high glucose conditions. This outcome is realized by enhancing VEGFR-2 expression and activating its downstream signaling pathways. Furthermore, glycated LDL, common in diabetic patients, substantially contributes to vascular endothelial cell dysfunction and apoptosis. Proteomic research



reveals that extracts from grape seed PCs suppress apoptosis in vascular endothelial cells, initiated by glycated LDL, through the modulation of PIMT, a methyltransferase involved in protein repair (Li et al., 2013).

Considerable evidence indicates that the expansion of vascular endothelial and smooth muscle cells, induced by AGEs, is vital for diabetic vasculopathy (Barbosa et al., 2008). The NF-κB signaling pathway substantially affects the movement, invasion, and growth of vascular smooth muscle cells (VSMCs). The interaction of AGEs with their receptor (RAGE) on VSMCs triggers intracellular oxidative stress by activating the transcription factor NF-κB (Yamagishi, 2011; San Martin et al., 2007). Experimental research has demonstrated that PCs therapy diminishes the proliferation and migration of human aortic smooth muscle cells (HASMCs) triggered by AGEs by elevating UCH-L1 protein levels, reducing IκB-α degradation, and curtailing NF-κB nuclear translocation in a dose-responsive manner (Qian et al., 2011). GSK-3β, a pro-apoptotic kinase, is crucial in managing cell survival and apoptosis. Overexpression of GSK-3β increases cellular susceptibility to apoptosis, while inhibition of GSK-3β diminishes the release of cytochrome c from mitochondria (Ryu et al., 2021). Li et al. (2011) showed that low concentrations of PCs (<12.5 mmol/L) enhance cell viability and proliferation in HUVECs, while higher concentrations (>25.00 mmol/L) induce apoptosis. This effect is attributed to PCs dose-dependently enhancing GSK-3β phosphorylation, attenuating caspase-3 activation, and inhibiting lactin adhesion protein expression, thereby mitigating oxidative stress and apoptosis induced by AGEs in HUVECs. These protective mechanisms lead to decreased intracellular ROS production and reduced apoptotic damage.

Atherosclerosis is a key marker of diabetic cardiovascular lesions. Oxidative stress, induced by hyperglycemia, plays a significant role in advancing atherosclerosis (Chen et al., 2011). In individuals with diabetes, ROS facilitate atherosclerosis by damaging endothelial cells while promoting proliferation, movement, and phenotypic changes in smooth muscle cells (Jay et al., 2006). MFG-E8, also known as lactoadhesin, adversely affects diabetic vascular disease by playing a role in oxidative stress and inflammatory responses (Silvestre et al., 2005). Prior studies have demonstrated that elevated glucose levels enhance ROS production by increasing MFG-E8 expression in adipose tissue (Aoki et al., 2007). Within the db/db mouse model, PCs effectively reduced VSMC proliferation and endothelial cell damage by decreasing MCP-1 and AGEs in mouse serum. Additionally, it reduced oxidative stress in vascular endothelial cells and decelerated atherosclerosis progression by enhancing aortic glutathione S-transferase theta 1 (GSTT1) activity. The suggested mechanism includes PCs impacting MFG-E8 expression, which subsequently mitigates atherosclerosis in db/db mice by reducing the secretion of chemokines involved in inflammation and oxidative stress via the pathways of ERK1/2 and MCP-1 (Yu et al., 2012) (Figure 11). Clinical studies have found (Peter et al., 2013) that the combined intake of isoflavones and flavan-3-ols improves vascular function and arterial stiffness in postmenopausal patients with type 2 diabetes, thereby slowing disease progression.

In conclusion, PCs improve diabetes-induced cardiovascular diseases through various mechanisms, particularly by regulating endothelial function, reducing oxidative stress, inhibiting inflammation, and modulating vascular smooth muscle cell

proliferation, exhibiting significant neuroprotective and cardiovascular protective effects. PCs can slow the formation of atherosclerosis and vascular endothelial cell damage by regulating multiple signaling pathways, including AGEs, MFG-E8, and GSK-3 β . Although these studies support the application of PCs in diabetes-related cardiovascular diseases, further clinical trials and validation are required to promote their clinical application.

5.5.3 PCs and diabetic cardiomyopathy

Diabetic cardiomyopathy (DC) presents as abnormal cardiac structure and function in individuals with diabetes, occurring in the absence of significant coronary artery disease, hypertension, or valvular heart conditions (Jia et al., 2018; Dillmann, 2019). Recent research indicates that endothelial dysfunction is a key factor in the advancement of diabetic cardiomyopathy (Knapp et al., 2019). Several factors, including hyperglycemia, hyperinsulinemia, lipid metabolism imbalances due to insulin resistance, mitochondrial dysfunction, decreased NO activity, elevated ROS, and inflammatory dysregulation, adversely affect endothelial function (Moran et al., 2022). This dysfunction can lead to cardiac fibrosis and structural changes through disrupted myocardial metabolism. The involved processes include improper handling of intracellular Ca²⁺, ER stress, mitochondrial dysfunction, the accumulation of AGEs, and the buildup of the extracellular matrix (ECM). These alterations can ultimately lead to both diastolic and systolic cardiac dysfunction, potentially resulting in heart failure (Moran et al., 2022). Quantitative proteomic analysis using iTRAQ revealed that PCs reverse s100A11 protein expression, a component in the S100 calcium-binding protein family involved in cellular regulation, and lower serum AGE levels in db/db mice. The hypothesis suggests that PCs activate the S100A11/RAGE/PPAR γ signaling pathway, resulting in reduced RAGE expression and alleviation of cardiac fibrosis triggered by AGEs in type 2 diabetic rats (Luan et al., 2014). Mitochondria act as the primary sources of cellular energy and also produce ROS. A notable correlation exists between ROS production and the deterioration of cardiac function and structure (Bou-Teen et al., 2021). Dysfunctional mitochondrial activity due to hyperglycemia serves as an early sign of endothelial dysfunction, hastening the advancement of cardiovascular disease (Yuan et al., 2019). Normal mitochondrial function reduces myocardial oxidative damage, while abnormal mitochondrial function can cause chronic myocardial hypoxia and exacerbate myocardial fibrotic degeneration by impairing respiratory function. PCs stimulate myocardial mitochondrial phosphorylation, modulating mitochondrial uncoupling rates and affecting respiratory function (Kopustinskiene et al., 2015).

In conclusion, PCs can alleviate diabetes-induced myocardial hypertrophy, cardiac fibrosis, and heart failure, demonstrating potential cardioprotective effects by regulating the S100A11/RAGE/PPAR γ signaling pathway, improving mitochondrial function, reducing oxidative stress, and inhibiting the formation of AGEs.

6 Advantages, limitations, and future directions

As a potent antioxidant, PCs exhibit significant therapeutic potential in the treatment of diabetes and its complications through their anti-inflammatory, antioxidant, and anti-glycation

properties. These plant metabolites improve endothelial function, reduce insulin resistance, and protect pancreatic β -cell function, offering a multidimensional strategy for diabetes treatment. However, current studies face several limitations. Most studies are restricted to *in vitro* experiments or animal models, lacking clinical trials in humans, particularly long-term efficacy and safety evaluations. Additionally, the low bioavailability of PCs, primarily due to poor gastrointestinal absorption, poses challenges for clinical application. The precise mechanisms of PCs remain unclear, necessitating further investigation into their molecular pathways.

Future research should focus on enhancing the bioavailability and pharmacokinetics of PCs, potentially through novel delivery systems like nanoparticles or their combination with other plant bioactive metabolites, to optimize therapeutic outcomes. Large-scale randomized controlled trials are essential to validate their efficacy in patients with diabetic complications, particularly for clinical assessments of diabetic retinopathy, nephropathy, and neuropathy. Additionally, investigating the synergistic effects of PCs with other natural compounds or conventional drugs may unveil more comprehensive therapeutic strategies. More importantly, greater emphasis should be placed on studying their molecular mechanisms, especially their effects on inflammatory pathways and oxidative stress, to develop more targeted therapeutic approaches. Personalized medicine approaches, considering individual genetic and metabolic variations, may further optimize the clinical application of PCs in diabetes and its complications.

7 Prospectives and conclusion

PCs are versatile bioactive compounds with significant potential in the prevention and management of diabetes and its related complications. They not only regulate glucose metabolism but also exhibit strong antioxidant and anti-inflammatory properties, which enhance insulin sensitivity and improve endothelial function. Experimental studies have shown that PCs offer protective effects against diabetic nephropathy, neuropathy, and cardiovascular diseases. Despite these promising findings, most research has been limited to *in vitro* and animal models, highlighting the need for clinical validation.

Future research should prioritize comprehensive clinical trials to confirm the efficacy and safety of PCs in human subjects. Investigating synergistic interactions between PCs and existing antidiabetic therapies could lead to more effective treatment protocols with minimized side effects. Furthermore, advancements in delivery systems and the development of standardized formulations are crucial for enhancing the bioavailability and therapeutic effectiveness of PCs. Establishing uniform criteria for PC purity, composition, and dosage will not only ensure reproducible and effective results but also streamline clinical trials and future regulatory approval processes.

In summary, PCs present a promising adjunctive option for diabetes management, contributing to better glycemic control and the mitigation of complications. Continued research and clinical investigations are essential to fully realize the therapeutic benefits of PCs, ultimately aiming to improve long-term outcomes and the quality of life for individuals with diabetes.

Author contributions

YZ: Writing–review and editing, Writing–original draft. ML: Writing–review and editing, Writing–original draft. HaL: Writing–review and editing, Writing–original draft. YF: Writing–review and editing, Validation. HuL: Writing–review and editing, Writing–original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We acknowledge Figdraw for the creation of the figures, and we extend our gratitude to all staff members who contributed to this study for their dedicated efforts and support.

References

- Abdur, R., Muhammad, I., Tareq, A. I., Iahisham-Ul, H., Seema, P., Xiaohong, P., et al. (2019). Proanthocyanidins: a comprehensive review. *Biomed. and Pharmacother.* 116, 108999. doi:10.1016/j.biopha.2019.108999
- Ahangarpour, A., Afshari, G., Mard, S. A., Khodadadi, A., and Hashemitabar, M. (2016). Preventive effects of procyanidin A2 on glucose homeostasis, pancreatic and duodenal homeobox 1, and glucose transporter 2 gene expression disturbance induced by bisphenol A in male mice. *J. Physiology Pharmacol. Official J. Pol. Physiological Soc.* 67 (2), 243–252.
- Akash, M. S. H., Rehman, K., and Liaqat, A. (2018). Tumor necrosis factor- α : role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *J. Cell. Biochem.* 119 (1), 105–110. doi:10.1002/jcb.26174
- Alan, K. F., Margaret, M., and Farquharson, M. A. (1991). Insulinitis in type 1 (insulin-dependent) diabetes mellitus in man—macrophages, lymphocytes, and interferon- γ containing cells. *J. Pathology.* doi:10.1002/path.1711650203
- Alan, R. S., and Kahn, C. R. (2001). Insulin signalling and the regulation of glucose and lipid metabolism. *Nature* 414, 799–806. doi:10.1038/414799a
- Aleksey, V. M., and Peter, C. B. (2008). Relationship between β -cell mass and diabetes onset. *Diabetes, Obes. Metabolism.* doi:10.1111/j.1463-1326.2008.00939.x
- Al-Shabrawey, M., Zhang, W., and McDonald, D. (2015). Diabetic retinopathy: mechanism, diagnosis, prevention, and treatment. *BioMed Res. Int.*, 2015, 854593. doi:10.1155/2015/854593
- Alyaa, F., Hebatallah, H., Salma, A., Selim, A., and Gehan, S. (2022). Co-treatment with grape seed extract and mesenchymal stem cells *in vivo* regenerated beta cells of islets of Langerhans in pancreas of type I-induced diabetic rats. *Stem Cell Res. and Ther.* 13, 528. doi:10.1186/s13287-022-03218-y
- André, S. (2019). SGLT2 inhibitor or GLP-1 receptor agonist in type 2 diabetes? *Lancet Diabetes and Endocrinol.* 7, 818–820. doi:10.1016/s2213-8587(19)30310-9
- Andrei, I. O., George, B., Anthony, E. N., Emma, M. A., Christine, T., Edward, P., et al. (2007). Free fatty acid–induced reduction in glucose-stimulated insulin secretion. *Diabetes* 56, 2927–2937. doi:10.2337/db07-0075
- Anna, A., Mari'a-José, M., Aida, S., Mayte, B., and Montserrat, P. (2013). Procyanidins target mesenteric adipose tissue in Wistar lean rats and subcutaneous adipose tissue in Zucker obese rat. *Food Chem.* doi:10.1016/j.foodchem.2013.02.104
- Anna, C.-A., Lidia, C., Víctor, P., Mayte, B., Montserrat, P., Mari'a-José, M., et al. (2012). Procyanidins modify insulinemia by affecting insulin production and degradation. *J. Nutr. Biochem.* 23, 1565–1572. doi:10.1016/j.jnutbio.2011.10.010
- Anoop, D. S., Claudia, L., Eleni, R., Spiros, D., Mar, P.-R., Chris, P. G., et al. (2015). Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes and Endocrinol.* 3, 105–113. doi:10.1016/s2213-8587(14)70219-0
- Antal, B., McMahon, L. P., Sultan, S. F., Lithen, A., Wexler, D. J., Dickerson, B., et al. (2022). Type 2 diabetes mellitus accelerates brain aging and cognitive decline: complementary findings from UK Biobank and meta-analyses. *ELife* 11, e73138. doi:10.7554/eLife.73138

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- Antoni, C., Josep Maria del, B., Anna, C., and Lluís, A. (2012). Low doses of grape seed procyanidins reduce adiposity and improve the plasma lipid profile in hamsters. *Int. J. Obes.* doi:10.1038/ijo.2012.75
- Antoni, C., Roger, M.-C., Noemí, B., Anna, C., Lluís, A., and Josep Maria del, B. (2017). Maternal intake of grape seed procyanidins during lactation induces insulin resistance and an adiponectin resistance-like phenotype in rat offspring. *Sci. Rep.* 7, 12573. doi:10.1038/s41598-017-12597-9
- Aoki, N., Jin-no, S., Nakagawa, Y., Asai, N., Arakawa, E., Tamura, N., et al. (2007). Identification and characterization of microvesicles secreted by 3T3-L1 adipocytes: redox- and hormone-dependent induction of milk fat globule-epidermal growth factor 8-associated microvesicles. *Endocrinology* 148 (8), 3850–3862. doi:10.1210/en.2006-1479
- Armstrong, D. G., Swerdlow, M. A., Armstrong, A. A., Conte, M. S., Padula, W. V., and Bus, S. A. (2020). Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. *J. Foot Ankle Res.* 13 (1), 16. doi:10.1186/s13047-020-00383-2
- Aurèle, B. P., Stewart, J., Philpa, L.-D., Blandine, S., Mathieu, L., and Jennifer, L. E. (2019). *PGC1A regulates the IRS1:IRS2 ratio during fasting to influence hepatic metabolism downstream of insulin.* doi:10.1073/pnas.1815150116
- Aya, A. G., Nayira, A. A. B., Eman, A. M., and Heba, S. Z. (2020). Cardioprotective effect of pioglitazone and curcumin against diabetic cardiomyopathy in type 1 diabetes mellitus: impact on CaMKII/NF- κ B/TGF- β 1 and PPAR- γ signaling pathway. *Naunyn-Schmiedeberg's Archives Pharmacol.* 394, 349–360. doi:10.1007/s00210-020-01979-y
- Barbara Di, C., Azzurra, C., Federica, E., and Gianna, T. (2016). A rule-based model of insulin signalling pathway. *BMC Syst. Biol.* doi:10.1186/s12918-016-0281-4
- Barbosa, J. H. P., Oliveira, S. L., and Seara, L. T. e. (2008). O papel dos produtos finais da glicação avançada (AGEs) no desencadeamento das complicações vasculares do diabetes. *Arq. Bras. Endocrinol. Metabol.* 52 (6), 940–950. doi:10.1590/s0004-27302008000600005
- Barrett, E. J., Liu, Z., Khamaisi, M., King, G. L., Klein, R., Klein, B. E. K., et al. (2017). Diabetic microvascular disease: an endocrine society scientific statement. *J. Clin. Endocrinol. Metabolism* 102 (12), 4343–4410. doi:10.1210/je.2017-01922
- Belenichev, I., Aliyeva, O., Popazova, O., and Bukhtiyarova, N. (2023). Molecular and biochemical mechanisms of diabetic encephalopathy. *Acta Biochim. Pol.* 70 (4), 751–760. doi:10.18388/abp.2020_6953
- Benedetta, R., Fabiana, P., Ilaria, M., and Simona, F. (2019). Flavonoids and insulin-resistance: from molecular evidences to clinical trials. *Int. J. Mol. Sci.* 20, 2061. doi:10.3390/ijms20092061
- Bolormaa, V., Yun-Hee, Y., Anthony, R., José, E. G., Krisztián, S., Randall, L. M., et al. (2011). The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat. Med.* 17, 179–188. doi:10.1038/nm.2279
- Bor Luen, T. (2016). Sirt1 and the mitochondria. *Mol. Cells.* doi:10.14348/molcells.2016.2318

- Bou-Teen, D., Kaludercic, N., Weissman, D., Turan, B., Maack, C., Di Lisa, F., et al. (2021). Mitochondrial ROS and mitochondria-targeted antioxidants in the aged heart. *Free Radic. Biol. and Med.* 167, 109–124. doi:10.1016/j.freeradbiomed.2021.02.043
- Bo-Zong, S., Zuojun, X., Baohui, H., Ding-Feng, S., and Chong, L. (2015). NLRP3 inflammasome and its inhibitors: a review. *Front. Pharmacol.* doi:10.3389/fphar.2015.00262
- Brigitte, V., Denis, G., Henri, P., Pourrat, A., Bastide, P., and Jeanine, B. (1989). *Anti-ulcer activity of procyanidins preparation of water-soluble procyanidin-cimetidine complexes.*
- Byoung Rai, L., and Pyoung Sim, P. (2022). Effect of combined treatment with catechin and quercetin on hepatic glucose metabolism in diabetic rats. *J. Korean Soc. Food Sci. Nutr.* doi:10.3746/jkfn.2022.51.1.12
- Cai, X., Bao, L., Ren, J., Li, Y., and Zhang, Z. (2016). Grape seed procyanidin B2 protects podocytes from high glucose-induced mitochondrial dysfunction and apoptosis via the AMPK-SIRT1-PGC-1 α axis *in vitro*. *Food and Funct.* 7 (2), 805–815. doi:10.1039/c5fo01062d
- Castell-Auvi, A., Cedó, L., Movassat, J., Portha, B., Sánchez-Cabo, F., Pallarès, V., et al. (2013). Procyanidins modulate microRNA expression in pancreatic islets. *J. Agric. Food Chem.* 61 (2), 355–363. doi:10.1021/jf303972f
- Chao, X., Mingxia, Z., Jiahui, W., and Zhenyu, W. (2021). Hawthorn polyphenols, D-chiro-inositol, and epigallocatechin gallate exert a synergistic hypoglycemic effect. *J. Food Biochem.* 45, e13771. doi:10.1111/jfbc.13771
- Chen, J., Chen, X., Lei, Y., Wei, H., Xiong, C., Liu, Y., et al. (2011). Vascular protective potential of the total flavanol glycosides from *Abacopteris penangiana* via modulating nuclear transcription factor- κ B signaling pathway and oxidative stress. *J. Ethnopharmacol.* 136 (1), 217–223. doi:10.1016/j.jep.2011.04.052
- Chen, R., Ovbiagele, B., and Feng, W. (2016). Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. *Am. J. Med. Sci.* 351 (4), 380–386. doi:10.1016/j.amjms.2016.01.011
- Cheng, G., Huang, C., Deng, H., and Wang, H. (2012). Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern. Med. J.* 42 (5), 484–491. doi:10.1111/j.1445-5994.2012.02758.x
- Christian, K. R., Andrea, L. H., and Barnard, R. J. (2013). Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. *Compr. Physiol.* 3, 1–58. doi:10.1002/cphy.c110062
- Chunhui, D. (2014). Protective effect of proanthocyanidins in cadmium induced neurotoxicity in mice. *Drug Res.* doi:10.1055/s-0034-1395544
- Chuntang, M., Xuanzi, Z., Jianxin, Z., and Xiaoyan, H. (2022). Procyanidins regulate colonic metabolome, inflammatory response and antioxidant capacity in lambs fed a high-concentrate diet. *J. Animal Physiology Animal Nutr.* 107, 1006–1018. doi:10.1111/jpn.13790
- Claudine, M., Gary, W., Christine, M., Augustin, S., and Christian, R. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* 81, 230S–242S. doi:10.1093/ajcn/81.1.230S
- Constanze, C. M., Dina, C. S., Marco, G. A., Pedro, F. O., David Morrirtz de, K., and Thomas, L. (2017). Diabetes-induced hyperglycemia impairs male reproductive function: a systematic review. *Hum. Reprod. Update* 24, 86–105. doi:10.1093/humupd/dmx033
- Cui, X., Liu, X., Feng, H., Zhao, S., and Gao, H. (2012). Grape seed proanthocyanidin extracts enhance endothelial nitric oxide synthase expression through 5'-AMP activated protein kinase/Sirtuin 1-Krüppel like factor 2 pathway and modulate blood pressure in ouabain induced hypertensive rats. *Biol. and Pharm. Bull.* 35 (12), 2192–2197. doi:10.1248/bpb.12-00598
- Dandan, H., Guangjiang, S., Yaping, J., Chao, Y., and Chuanbing, Z. (2020). A review on the potential of Resveratrol in prevention and therapy of diabetes and diabetic complications. *Biomed. and Pharmacother.* doi:10.1016/j.biopha.2019.109767
- Daniël, H. v. R., and Michaëla, D. (2011). Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? *Diabetes Res. Clin. Pract.* 93, S37–S46. doi:10.1016/s0168-8227(11)70012-2
- Daniel, J. D., and Michael, A. N. (2006). The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368, 1696–1705. doi:10.1016/s0140-6736(06)69705-5
- Dao, T.-M. A., Waget, A., Klopp, P., Serino, M., Vachoux, C., Pechere, L., et al. (2011). Resveratrol increases glucose induced GLP-1 secretion in mice: a mechanism which contributes to the glycemic control. *PLoS One* 6 (6), e20700. doi:10.1371/journal.pone.0020700
- David, B. S., Kitt Falk, P., and Gerald, I. S. (2007). Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol. Rev.* 87, 507–520. doi:10.1152/physrev.00024.2006
- David, G. A., Tze-Woei, T., Andrew, J. M. B., and Sicco, A. B. (2023). Diabetic foot ulcers. *Jama* 330, 62. doi:10.1001/jama.2023.10578
- Décio, L. E., Lorenzo, P., and Miriam, C. (2020). Pancreatic β -cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nat. Rev. Endocrinol.* 16, 349–362. doi:10.1038/s41574-020-0355-7
- Diagnosis and Classification of Diabetes Mellitus (2013). Diagnosis and classification of diabetes mellitus. *Diabetes Care* 37, S81–S90. doi:10.2337/dc14-s081
- Dillmann, W. H. (2019). Diabetic cardiomyopathy. *Circulation Res.* 124 (8), 1160–1162. doi:10.1161/CIRCRESAHA.118.314665
- Eloisa Aparecida, V.-B., Davidson Correa, A., Leticia Prates, R., Fernanda, O., and Ângelo Rafael, C. (2021). Lipotoxicity and β -cell failure in type 2 diabetes: oxidative stress linked to NADPH oxidase and ER stress. *Cells.* doi:10.3390/cells10123328
- Eskandar, Q., Marwan, A., Bandar, A.-H., Abdullah, Q., Haneen, A., Ahmed, A.-M., et al. (2023). Procyanidins: a promising anti-diabetic agent with potential benefits on glucose metabolism and diabetes complications. *Wound Repair Regen.* 31, 688–699. doi:10.1111/wrr.13115
- Eun-Jung, B., Hong Gyu, P., Choong Hwan, L., Tong Il, L., Gye Hyeong, W., Younghwa, N., et al. (2011). Effects of novel chalcone derivatives on α -glucosidase, dipeptidyl peptidase-4, and adipocyte differentiation *in vitro*. *J. Biochem. Mol. Biol.* doi:10.5483/bmbrep.2011.44.6.410
- Eva, L. F., Brian, C. C., Rodica, P. B., Douglas, W. Z., Douglas, E. W., David, B., et al. (2019). Diabetic neuropathy. *Nat. Rev. Dis. Prim.* 5, 41. doi:10.1038/s41572-019-0092-1
- Fan, J., Liu, H., Wang, J., Zeng, J., Tan, Y., Wang, Y., et al. (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. doi:10.1111/jcmm.16111
- Fangfang, T., Jifei, W., Yuexin, L., Shujun, Z., Zhenhua, W., Gang, L., et al. (2020). Proanthocyanidins ameliorated deficits of lipid metabolism in type 2 diabetes mellitus via inhibiting adipogenesis and improving mitochondrial function. *Int. J. Mol. Sci.* 21, 2029. doi:10.3390/ijms21062029
- Feng, J., Xiaolu, Z., Yingyu, L., Yingyu, C., and Yihan, C. (2016). Pinus massoniana Bark extract: structure-activity relationship and biomedical potentials. *Am. J. Chin. Med.* 44, 1559–1577. doi:10.1142/s0192415x16500877
- Gao, L., Gu, Y., and Yin, X. (2016). High serum tumor necrosis factor- α levels in women with polycystic ovary syndrome: a meta-analysis. *PLoS One* 11 (10), e0164021. doi:10.1371/journal.pone.0164021
- Gaochao, Z., Robert, W. M., Ying, L., Yuli, C., Xiaolan, S., Judy, F.-M., et al. (2001). Role of AMP-activated protein kinase in mechanism of metformin action. *J. Clin. Investigation* 108, 1167–1174. doi:10.1172/jci13505
- Gary, F. L., and Patricia, L. B. (2021). The discovery of insulin revisited: lessons for the modern era. *J. Clin. Investigation* 131, e142239. doi:10.1172/jci142239
- Gary, W., and Claudine, M. (2005). Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. *Am. J. Clin. Nutr.* 81, 243S–255S. doi:10.1093/ajcn/81.1.243S
- Gemma, M., Cinta, B., Mayte, B., Juan, F.-L., Gerard, P., Salvadó, M. J., et al. (2010a). Effects of a grapeseed procyanidin extract (GSPE) on insulin resistance. *J. Nutr. Biochem.* 21, 961, 967. doi:10.1016/j.jnutbio.2009.08.001
- Gemma, M., Sheela, O., Montserrat, V., Cinta, B., Mayte, B., Juan, F.-L., et al. (2010b). 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, 476–481. doi:10.1016/j.jnutbio.2009.02.003
- Giovanna, B., Alessandra, A., Luca Della, V., Francesca, G., Quagliano, O., Sara, C., et al. (2024). Unraveling the parahormetic mechanism underlying the health-protecting effects of grapeseed procyanidins. *Redox Biol.* doi:10.1016/j.redox.2023.102981
- Gopalsamy Rajiv, G., Savarimuthu, I., and Michael Gabriel, P. (2011). Solanum torvum Swartz. fruit containing phenolic compounds shows antidiabetic and antioxidant effects in streptozotocin induced diabetic rats. *Food Chem. Toxicol.* doi:10.1016/j.fct.2011.08.005
- Guillermo Arango, D., and Albert, D. (2014). Macrophage cytokines: involvement in immunity and infectious diseases. *Front. Immunol.* doi:10.3389/fimmu.2014.00491
- Hadi, B., Seyed Ahmad, H., Sirous, S., Delsa, M., Mohammad, A., Maryam, L., et al. (2020). Effects of epigallocatechin-3-gallate of *Camellia sinensis* leaves on blood pressure, lipid profile, atherogenic index of plasma and some inflammatory and antioxidant markers in type 2 diabetes mellitus patients: a clinical trial. *J. Complementary Integr. Med.* 18, 405–411. doi:10.1515/jcim-2020-0090
- Hee-Hyun, L., Kui-Jin, K., Ok-Hwan, L., and Boo-Yong, L. (2010). Effect of pycnogenol[®] on glucose transport in mature 3T3-L1 Adipocytes. *Phytotherapy Res.* doi:10.1002/ptr.3193
- Helena, Q., Josep Maria del, B., David, P., Sabina, D., Juan, F.-L., Montserrat, P., et al. (2009). Grape seed proanthocyanidins correct dyslipidemia associated with a high-fat diet in rats and repress genes controlling lipogenesis and VLDL assembling in liver. *Int. J. Obes.* doi:10.1038/ijo.2009.136
- Hong, S., Pouya, S., Suvi, K., Moritz, P., Katherine, O., Bruce Bartholow, D., et al. (2022). IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.* 183, 109119. doi:10.1016/j.diabres.2021.109119
- Hsiang-Jung, T., Liang-Yi, W., and Lucy Sun, H. (2008). Effect of a proanthocyanidin-rich extract from longan flower on markers of metabolic syndrome in fructose-fed rats. *J. Agric. Food Chem.* doi:10.1021/jf801966y
- Ill-Min, C., Govindasamy, R., Umadevi, S., Baskar, V., Venkatesan Gopiesh, K., and Muthu, T. (2020). Insights on the current status and advancement of diabetes mellitus type 2 and to avert complications: an overview. *Biotechnol. Appl. Biochem.* doi:10.1002/bab.1853

- Isabel, C.-H., María Ángeles, M., Luis, G., and Sonia, R. (2014). Cocoa flavonoids attenuate high glucose-induced insulin signalling blockade and modulate glucose uptake and production in human HepG2 cells. *Food Chem. Toxicol.* 64, 10–19. doi:10.1016/j.fct.2013.11.014
- Isabel, C.-H., María Ángeles, M., Luis, G., and Sonia, R. (2015). Cocoa flavonoids protect hepatic cells against high-glucose-induced oxidative stress: relevance of MAPKs. *Mol. Nutr. and Food Res.* 59, 597–609. doi:10.1002/mnfr.201400492
- Janika, S., Zi Yu, C., Bingyao, T., Damon Wing Kee, W., Xinyu, L., and Jacqueline, C. (2022). Dietary intake and diabetic retinopathy: a systematic review of the literature. *Nutrients* 14, 5021. doi:10.3390/nu14235021
- Jasmine, F. P., John, C. S., Philip, N. B., Clare, M. R., and Mark, H. V. (2018). The pathophysiology of gestational diabetes mellitus. *Int. J. Mol. Sci.* 19, 3342. doi:10.3390/ijms19113342
- Javier, D.-C., Desirée, L.-R., Ernesto, M. N., Víctor, G. T., Carolina, H.-C., Carla, F., et al. (2020). Inflammatory targets in diabetic nephropathy. *J. Clin. Med.* 9, 458. doi:10.3390/jcm9020458
- Javier, I. O., Christian, H., Jeremy, P. E. S., Malte, K., and Hagen, S. (2018). Recommending flavanols and procyanidins for cardiovascular health: revisited. *Mol. Aspects Med.* 61, 63–75. doi:10.1016/j.mam.2018.02.001
- Jay, D., Hitomi, H., and Griendling, K. K. (2006). Oxidative stress and diabetic cardiovascular complications. *Free Radic. Biol. and Med.* 40 (2), 183–192. doi:10.1016/j.freeradbiomed.2005.06.018
- Jeffrey, A. B., Kevan, C. H., and George, S. E. (2010). Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature* 464, 1293–1300. doi:10.1038/nature08933
- Jeong, H., Choi, D., Oh, Y., Heo, J., and Hong, J. (2022). A nanocoating Co-localizing nitric oxide and growth factor onto individual endothelial cells reveals synergistic effects on angiogenesis. *Adv. Healthc. Mater.* 11 (6), e2102095. doi:10.1002/adhm.202102095
- Jia, G., Hill, M. A., and Sowers, J. R. (2018). Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circulation Res.* 122 (4), 624–638. doi:10.1161/CIRCRESAHA.117.311586
- Ji-Hyun, L., Mi-Young, S., Eunkyung, S., Min Jung, K., Woo Sung, M., Myung-Kwan, H., et al. (2009). Overexpression of SIRT1 protects pancreatic β -cells against cytokine toxicity by suppressing the nuclear factor- κ B signaling pathway. *Diabetes*. doi:10.2337/db07-1795
- Jiwon, K., and Kun-Ho, Y. (2011). Glucolipotoxicity in pancreatic β -cells. *Diabetes and Metabolism J.* doi:10.4093/dmj.2011.35.5.444
- Joanne, Y., Sophie, R., Ryo, K., Ecosse, L. L., Jonathan, W. K., Toke, B., et al. (2012). Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 35, 556–564. doi:10.2337/dc11-1909
- John, V. F., Lucia, K., and Mirela, D. (2020). The role of inflammation in diabetic retinopathy. *Front. Immunol.* 11, 583687. doi:10.3389/fimmu.2020.583687
- Justin, B. E. T., Haolin, X., Adam, D. D., Phillip, J. S., Javed, B., Clyde, W. Y., et al. (2016). Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: findings from Get with the Guidelines–Heart Failure registry. *Am. Heart J.* 182, 9–20. doi:10.1016/j.ahj.2016.07.025
- Karina, R. A., Montserrat, V., Lorena, M., Marcelo, V., Ahmed, A. H., Ahmed, A. R., et al. (2021). Phytochemicals as potential epidrugs in type 2 diabetes mellitus. *Front. Endocrinol.* 12, 656978. doi:10.3389/fendo.2021.656978
- Kathryn, P., Clara, W. R., Agnieszka, K. A., Garth, L. W., and Verchere, C. B. (2013). Death and dysfunction of transplanted β -cells: lessons learned from type 2 diabetes? *Diabetes* 63, 12–19. doi:10.2337/db12-0364
- Kaul, R. K. (1996). Pflanzliche procyanidine vorkommen, klassifikation and pharmakologische wirkungen. *Pharmazie unserer Zeit* 25, 175–185. doi:10.1002/pauz.19960250406
- Ken-yu, H., Hitoshi, A., and Yoko, Y. (2022). Black soybean seed coat polyphenol ameliorates the abnormal feeding pattern induced by high-fat diet consumption. *Front. Nutr.* doi:10.3389/fnut.2022.1006132
- Kerry, L. D., Coleman, I. S., Sarah Jane, S., José, J., Mark, D. B., and Elizabeth, J. P. (2005). Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J. Clin. Investigation* 115, 1343–1351. doi:10.1172/jci23621
- Kimber-Trojnar, Ž., Patro-Mahysza, J., Skórzyńska-Dziduszko, K. E., Oleszczuk, J., Trojnar, M., Mierzyński, R., et al. (2018). Ghrelin in serum and urine of post-partum women with gestational diabetes mellitus. *Int. J. Mol. Sci.* 19 (10), 3001. doi:10.3390/ijms19103001
- Kisseih, E., Lechtenberg, M., Petereit, F., Sendker, J., Zacharski, D., Brandt, S., et al. (2015). Phytochemical characterization and *in vitro* wound healing activity of leaf extracts from *Combretum mucronatum* Schum. and Thonn.: oligomeric procyanidins as strong inducers of cellular differentiation. *J. Ethnopharmacol.* 174, 628–636. doi:10.1016/j.jep.2015.06.008
- Knapp, M., Tu, X., and Wu, R. (2019). Vascular endothelial dysfunction, a major mediator in diabetic cardiomyopathy. *Acta Pharmacol. Sin.* 40 (1), 1–8. doi:10.1038/s41401-018-0042-6
- Kong, X., Guan, J., Gong, S., and Wang, R. (2017). Neuroprotective effects of grape seed procyanidin extract on ischemia-reperfusion brain injury. *Chin. Med. Sci. J. = Chung-kuo I Hsueh K'o Hsueh Tsa Chih* 32 (2), 92–99. doi:10.24920/J1001-9294.2017.020
- Kopustinskiene, D. M., Savickas, A., Vetchý, D., Masteikova, R., Kasauskas, A., and Bernatoniene, J. (2015). Direct effects of (-)-epicatechin and procyanidin B2 on the respiration of rat heart mitochondria. *BioMed Res. Int.* 2015, 232836. doi:10.1155/2015/232836
- Kyle, D. C., and Morris, F. W. (2012). Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. *Diabetologia*. doi:10.1007/s00125-012-2644-8
- Laura, A., Takuya, Y., Pili, Z., Donald, K. S., Seung, K. K., Christopher, P. O. D., et al. (2007). Glucose infusion in mice. *Diabetes* 56, 1792–1801. doi:10.2337/db06-1513
- Lewis, G. F., Carpentier, A., Adeli, K., and Giacca, A. (2002). Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr. Rev.* 23 (2), 201–229. doi:10.1210/edrv.23.2.0461
- Li, B.-y., Li, X.-l., Gao, H.-q., Zhang, J.-h., Cai, Q., Cheng, M., et al. (2011). Grape seed procyanidin B2 inhibits advanced glycation end product-induced endothelial cell apoptosis through regulating GSK3 β phosphorylation. *Cell Biol. Int.* 35 (7), 663–669. doi:10.1042/CBI20100656
- Li, D., Zhao, T., Meng, J., Jing, Y., Jia, F., and 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. doi:10.3892/mmr.2015.4445
- Li, R., Li, H., and Zhang, Q. (2022). Procyanidin protects human retinal pigment epithelial cells from high glucose by inhibiting autophagy. *Environ. Toxicol.* 37 (2), 201–211. doi:10.1002/tox.23389
- Li, X.-l., Li, B.-y., Cheng, M., Yu, F., Yin, W.-b., Cai, Q., et al. (2013). PIMT prevents the apoptosis of endothelial cells in response to glycated low density lipoproteins and protective effects of grape seed procyanidin B2. *PLoS One* 8 (7), e69979. doi:10.1371/journal.pone.0069979
- Liang, C., Peng, S., Ting, W., Kaixian, C., Qi, J., He-Yao, W., et al. (2012). Diverse mechanisms of antidiabetic effects of the different procyanidin oligomer types of two different cinnamon species on db/db mice. *J. Agric. Food Chem.* 60, 9144–9150. doi:10.1021/jf3024535
- Liang, Z., Yijun, W., Daxiang, L., Chi Tang, H., Junsong, L., and Xiaochun, W. (2016). The absorption, distribution, metabolism and excretion of procyanidins. *Food and Funct.* 7, 1273–1281. doi:10.1039/c5fo01244a
- Lidia, C., Anna, C.-A., Victor, P., Mayte, B., Anna, A., Lluís, A., et al. (2013). Grape seed procyanidin extract modulates proliferation and apoptosis of pancreatic beta-cells. *Food Chem.* 138, 524–530. doi:10.1016/j.foodchem.2012.10.088
- Linards, K., Ingus, P. r., Märcis, M., Artūrs, V., and Māris, K. (2022). Procyanidins from cranberry press residues—extraction optimization, purification and characterization. *Plants* 11, 3517. doi:10.3390/plants11243517
- Liu, K., Zhang, C., Chang, R., He, Y., Guan, F., and Yao, M. (2023b). Ultra-stretchable, tissue-adhesive, shape-adaptive, self-healing, on-demand removable hydrogel dressings with multiple functions for infected wound healing in regions of high mobility. *Acta Biomater.* 166, 224–240. doi:10.1016/j.actbio.2023.05.025
- Liu, S., Fang, Y., Yu, J., and Chang, X. (2021). Hawthorn polyphenols reduce high glucose-induced inflammation and apoptosis in ARPE-19 cells by regulating miR-34a/SIRT1 to reduce acetylation. *J. Food Biochem.* 45 (2), e13623. doi:10.1111/jfbc.13623
- Liu, Y., Liao, W. J., Zhu, Z., Zeng, H., He, H. Q., Sun, X. L., et al. (2016). Effect of procyanidine on VEGFR-2 expression and transduction pathway in rat endothelial progenitor cells under high glucose conditions. *Genet. Mol. Res. GMR* 15 (1). doi:10.4238/gmr.15016925
- Liu, Y., and Wu, N. (2021). Progress of nanotechnology in diabetic retinopathy treatment. *Int. J. Nanomedicine* 16, 1391–1403. doi:10.2147/IJN.S294807
- Liu, Z., Liu, G., Ha, D. P., Wang, J., Xiong, M., and Lee, A. S. (2023a). ER chaperone GRP78/BiP translocates to the nucleus under stress and acts as a transcriptional regulator. *Proc. Natl. Acad. Sci. U. S. A.* 120 (31), e2303448120. doi:10.1073/pnas.2303448120
- Liwei, G., Mark, A. K., John, F. H., Gary, R. B., David, C., Sarah, V., et al. (2002). Fractionation of polymeric procyanidins from lowbush blueberry and quantification of procyanidins in selected foods with an optimized normal-phase HPLC–MS fluorescent detection method. *J. Agric. Food Chem.* 50, 4852–4860. doi:10.1021/jf020214v
- Lu, L., Lu, Q., Chen, W., Li, J., Li, C., and Zheng, Z. (2018). Vitamin D3 protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway. *J. Diabetes Res.*, 2018, 8193523. doi:10.1155/2018/8193523
- Luan, S.-s., Yu, F., Li, B.-y., Qin, R.-j., Li, X.-l., Cai, Q., et al. (2014). Quantitative proteomics study of protective effects of grape seed procyanidin B2 on diabetic cardiomyopathy in db/db mice. *Biosci. Biotechnol. Biochem.* 78 (9), 1577–1583. doi:10.1080/09168451.2014.930320
- Maahs, D. M., and Rewers, M. (2006). Editorial: mortality and renal disease in type 1 diabetes mellitus—progress made, more to be done. *J. Clin. Endocrinol. Metabolism* 91 (10), 3757–3759. doi:10.1210/ajc.2006-1730
- Maaik, M. A., Jean-Paul, V., Anna-Marja, A., Hollman, P. C. H., and Harry, G. (2009). Procyanidin dimers are metabolized by human microbiota with 2-(3,4-dihydroxyphenyl)acetic acid and 5-(3,4-dihydroxyphenyl)- γ -valerolactone as the major metabolites. *J. Agric. Food Chem.* 57, 1084–1092. doi:10.1021/jf803059z

- Majid, T. (2013). Diabetic nephropathy and antioxidants. *J. Nephrothol.* 2, 20–27. doi:10.5812/nephrothol.9093
- Mandeep Kumar, A., and Umesh Kumar, S. (2013). Molecular mechanisms in the pathogenesis of diabetic nephropathy: an update. *Vasc. Pharmacol.* doi:10.1016/j.vph.2013.01.001
- Maria, L., Anne-Laure, C., Vincent, P., and Miriam, C. (2020). Recent insights into mechanisms of β -cell lipo- and glucolipotoxicity in type 2 diabetes. *J. Mol. Biol.* 432, 1514–1534. doi:10.1016/j.jmb.2019.09.016
- Marinko, M., Matej, P., Mia, K., and Ana-Marija Liberati, P. (2021). NAFLD, insulin resistance, and diabetes mellitus type 2. *Can. J. Gastroenterology and Hepatology* 2021, 6613827. doi:10.1155/2021/6613827
- Marta, M., Gabriele, W., Reinhard, W., and Philip, N. (2010). Effects of pharmacological inhibition of NADPH oxidase or iNOS on pro-inflammatory cytokine, palmitic acid or H2O2-induced mouse islet or clonal pancreatic β -cell dysfunction. *Biosci. Rep.* 30, 445–453. doi:10.1042/bsr20090138
- Mary, T. K. (2004). Sulfonylurea treatment of type 2 diabetes mellitus: focus on glimepiride. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* 24, 606–620. doi:10.1592/phco.24.6.606.34752
- Mary, W.-L., Xiaohui, L. W., Brian, K. L., Robert, K. H., Masao, N., and Daryl, K. G. (2002). Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. *J. Biol. Chem.* 277, 34933–34940. doi:10.1074/jbc.m204672200
- Masahito, T., Seiya, I., Fumihiko, H., and Takanori, T. (2010). Dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. *J. Nutr.* 140, 527–533. doi:10.3945/jn.109.118216
- Matoori, S., Veves, A., and Mooney, D. J. (2021). Advanced bandages for diabetic wound healing. *Sci. Transl. Med.* 13 (585), eabe4839. doi:10.1126/scitranslmed.abe4839
- McDermott, K., Fang, M., Boulton, A. J. M., Selvin, E., and Hicks, C. W. (2023). Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. *Diabetes Care* 46 (1), 209–221. doi:10.2337/dci22-0043
- Michael, N. C. (2004). Diet-derived phenols in plasma and tissues and their implications for health. *Planta Medica.* doi:10.1055/s-2004-835835
- Miki, M., Atutoshi, K., Yutaka, M., and Kazumi, Y. (2011). Hypoglycemic effect of resveratrol in type 2 diabetic model db/db mice and its actions in cultured L6 myotubes and RIN-5F pancreatic β -cells. *J. Clin. Biochem. Nutr.* 48, 237–244. doi:10.3164/jcbn.10-119
- Min, L., Bijun, H., Li, W., Qun, L., and Rui, L. (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, 5935–5947. doi:10.1002/jsfa.11945
- Min-Ji, B., Van Long, T., Hey-Sook, K., Mira, J., and Woo-Sik, J. (2013). Anti-inflammatory effect of procyanidins from wild grape (*Vitis amurensis*) seeds in LPS-induced RAW 264.7 cells. *Oxidative Med. Cell. Longev.* doi:10.1155/2013/409321
- Mona, F. M., Shima, A., Heba, O. S., Assem, M. E.-S., Rachid, D., Mohamed, A. O. A., et al. (2021). Syzygium aqueum (Burm.f.) alston prevents streptozotocin-induced pancreatic beta cells damage via the TLR-4 signaling pathway. *Front. Pharmacol.* 12, 769244. doi:10.3389/fphar.2021.769244
- Montserrat, P., Lúcia, C., Gemma, M., Mayte, B., and Anna, A. (2012). Procyanidins improve some disrupted glucose homeostatic situations: an analysis of doses and treatments according to different animal models. *Crit. Rev. Food Sci. Nutr.* 52, 569–584. doi:10.1080/10408398.2010.501533
- Montserrat, P., Mayte, B., Cinta, B., Salvadó, M. J., Lluís, A., and Anna, A. (2004). Grape seed-derived procyanidins have an antihyperglycemic effect in streptozotocin-induced diabetic rats and insulinomimetic activity in insulin-sensitive cell lines. *Endocrinology.* doi:10.1210/en.2004-0764
- Moran, W., Yongsheng, L., Sheng, L., and Jiagao, L. (2022). Endothelial dysfunction and diabetic cardiomyopathy. *Front. Endocrinol.* 13, 851941. doi:10.3389/fendo.2022.851941
- Mota, M., Banini, B. A., Cazanave, S. C., and Sanyal, A. J. (2016). Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease. *Metabolism Clin. Exp.* 65 (8), 1049–1061. doi:10.1016/j.metabol.2016.02.014
- Muthenna, P., Raghu, G., Kumar, P. A., Surekha, M. V., and Reddy, G. B. (2014). Effect of cinnamon and its procyanidin-B2 enriched fraction on diabetic nephropathy in rats. *Chemico-biological Interact.* 222, 68–76. doi:10.1016/j.cbi.2014.08.013
- Najim, A.-A., Caroline, A., Aurélie, B., Sandrine, D., Jean-Paul, C., Nathalie, L., et al. (2004). Extracts enriched in different polyphenolic families normalize increased cardiac NADPH oxidase expression while having differential effects on insulin resistance, hypertension, and cardiac hypertrophy in high-fructose-fed rats. *J. Agric. Food Chem.* 53, 151–157. doi:10.1021/jf048919f
- NCD Risk Factor Collaboration NCD-RisC (2016). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet London, Engl.* 387 (10027), 1513–1530. doi:10.1016/S0140-6736(16)00618-8
- Nia, J. B., Roland, G., and David, E. J. (2002). Regulated transport of the glucose transporter GLUT4. *Nat. Rev. Mol. Cell Biol.* 3, 267–277. doi:10.1038/nrm782
- Nie, X., Tang, W., Zhang, Z., Yang, C., Qian, L., Xie, X., et al. (2020). Procyanidin B2 mitigates endothelial endoplasmic reticulum stress through a PPAR δ -Dependent mechanism. *Redox Biol.* 37, 101728. doi:10.1016/j.redox.2020.101728
- Noemi, G.-A., Neus, M.-M., Mayte, B., Gerard, P., Santiago, G. a.-V., Montserrat, P., et al. (2012). Grape seed-derived procyanidins decrease dipeptidyl-peptidase 4 activity and expression. *J. Agric. Food Chem.* 60, 9055–9061. doi:10.1021/jf3010349
- Nupur, P., Paul, M., Varun, P., Peter, R. F., and Victor, G. (2018). Beneficial metabolic effects of dietary epigallocatechin gallate alone and in combination with exendin-4 in high fat diabetic mice. *Mol. Cell. Endocrinol.* 460, 200–208. doi:10.1016/j.mce.2017.07.024
- Odai, T., Terauchi, M., Kato, K., Hirose, A., and Miyasaka, N. (2019). Effects of grape seed proanthocyanidin extract on vascular endothelial function in participants with prehypertension: a randomized, double-blind, placebo-controlled study. *Nutrients* 11 (12), 2844. doi:10.3390/nu11122844
- Peiling, H., Chin-Wen, C., and Tsung-Yun, L. (2013). Areca nut procyanidins ameliorate streptozotocin-induced hyperglycemia by regulating gluconeogenesis. *Food Chem Toxicol.* doi:10.1016/j.fct.2012.12.057
- Peter, J. C., John, F. P., Paul, A. K., Paddy, W., Ketan, D., Mike, S., et al. (2013). Vascular function and atherosclerosis progression after 1 y of flavonoid intake in statin-treated postmenopausal women with type 2 diabetes: a double-blind randomized controlled trial. *Am. J. Clin. Nutr.* 97, 936–942. doi:10.3945/ajcn.112.043745
- Peter, J. C., Mike, S., John, F. P., Ketan, D., Paul, A. K., and Aedin, C. (2012). Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes. *Diabetes Care* 35, 226–232. doi:10.2337/dc11-1443
- Pimentel, E. F., de Oliveira, B. G., Pereira, A. C. H., Figueira, M. M., Portes, D. B., Scherer, R., et al. (2024). Polyphenols, antioxidants, and wound healing of *Lecythis pisonis* seed coats. *Planta Medica* 90 (3), 243–251. doi:10.1055/a-2212-0262
- Qian, C., Baoying, L., Haiqing, G., Jianhua, Z., Junfu, W., Fei, Y., et al. (2011). Grape seed procyanidin B2 inhibits human aortic smooth muscle cell proliferation and migration induced by advanced glycation end products. *Biosci. Biotechnol. Biochem.* 75, 1692–1697. doi:10.1271/bbb.110194
- Qian, W., Fen, Z., Mengyao, N., Yan, J., Lin, S., Yinggang, L., et al. (2023). Extraction methods, properties, functions, and interactions with other nutrients of *Lotus* procyanidins: a review. *J. Agric. Food Chem.* 71, 14413–14431. doi:10.1021/acs.jafc.3c05305
- Qian, W., Hengye, C., Zhejuan, L., Shuyi, L., Bei, H., Yan-Qing, G., et al. (2013). Oligomeric procyanidins of lotus seedpod inhibits the formation of advanced glycation end-products by scavenging reactive carbonyls. *Food Chem.* 138, 1493–1502. doi:10.1016/j.foodchem.2012.10.111
- Ramesh, C. K., Luke, R. H., Samuel, E. W., Theodore, J. R., and Ronald, L. P. (2012). Effect of dietary blueberry pomace on selected metabolic factors associated with high fructose feeding in growing sprague-dawley rats. *J. Med. Food* 15, 802–810. doi:10.1089/jmf.2011.0212
- Ramesh, C. K., Theodore, J. R., Samuel, E. W., Luke, R. H., and Ronald, L. P. (2010). Effects of dietary consumption of cranberry powder on metabolic parameters in growing rats fed high fructose diets. *Food and Funct.* 1, 116–123. doi:10.1039/c0fo00089b
- Rebecca, A. H., Timothy, E. M., and Domenico, A. (2017). Biochemical and cellular properties of insulin receptor signalling. *Nat. Rev. Mol. Cell Biol.* 19, 31–44. doi:10.1038/nrm.2017.89
- Reuben, J. S., Katja, L., Debbie, S. V., Seung Hoi, K., Nabeel, B., Ronald, A. D., et al. (2005). The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 310, 1642–1646. doi:10.1126/science.1120781
- Rodríguez-Carrizalez, A. D., Castellanos-González, J. A., Martínez-Romero, E. C., Miller-Arreavillaga, G., Villa-Hernández, D., Hernández-Godínez, P. P., et al. (2014). Oxidants, antioxidants and mitochondrial function in non-proliferative diabetic retinopathy. *J. Diabetes* 6 (2), 167–175. doi:10.1111/1753-0407.12076
- Rosalyn, S. Y., and Solomon, A. B. (1960). Plasma insulin concentrations in nondiabetic and early diabetic subjects: determinations by a new sensitive immunoassay technic. *Diabetes* 9, 254–260. doi:10.2337/diab.9.4.254
- Rui, X., Xiuling, W., Jianming, W., Yong, T., Wen-Qiao, Q., Xin, S., et al. (2020). Polyphenols isolated from lychee seed inhibit Alzheimer's disease-associated Tau through improving insulin resistance via the IRS-1/PI3K/Akt/GSK-3 β pathway. *J. Ethnopharmacol.* 251, 112548. doi:10.1016/j.jep.2020.112548
- Ruszała, M., Pilszyk, A., Niebrzydowska, M., Kimber-Trojnar, Ż., Trojnar, M., and Leszczyńska-Gorzela, B. (2022). Novel biomolecules in the pathogenesis of gestational diabetes mellitus 2.0. *Int. J. Mol. Sci.* 23 (8), 4364. doi:10.3390/ijms23084364
- Ryu, H. Y., Kim, L. E., Jeong, H., Yeo, B. K., Lee, J.-W., Nam, H., et al. (2021). GSK3B induces autophagy by phosphorylating ULK1. *Exp. and Mol. Med.* 53 (3), 369–383. doi:10.1038/s12276-021-00570-6
- Ryuichi, W., Yusuke, N., Norito, Y., Masayoshi, T., Yuichi, I., Koichi, Y., et al. (2001). Effects of OPB-9195, anti-glycation agent, on experimental diabetic neuropathy. *Eur. J. Clin. Investigation.* doi:10.1046/j.1365-2362.2001.00826.x
- Salime Pelin, E., Murat, B., Matem, T. r., and İsmail, S. (2014). The comparative effects of perindopril and catechin on mesangial matrix and podocytes in the streptozotocin induced diabetic rats. *Pharmacol. Rep.* doi:10.1016/j.pharep.2013.09.010
- Samsu, N. (2021). Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. *BioMed Res. Int.*, 2021, 1497449. doi:10.1155/2021/1497449

- San Martin, A., Foncea, R., Laurindo, F. R., Ebensperger, R., Griendling, K. K., and Leighton, F. (2007). Nox1-based NADPH oxidase-derived superoxide is required for VSMC activation by advanced glycation end-products. *Free Radic. Biol. and Med.* 42 (11), 1671–1679. doi:10.1016/j.freeradbiomed.2007.02.002
- Sarwar, N., Gao, P., Seshasai, S. R. K., Gobin, R., Kaptoge, S., Di Angelantonio, E., et al. (2010). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet London, Engl* 375 (9733), 2215–2222. doi:10.1016/S0140-6736(10)60484-9
- Schön, C., Allegrini, P., Engelhart-Jentsch, K., Riva, A., and Petrangolini, G. (2021). Grape seed extract positively modulates blood pressure and perceived stress: a randomized, double-blind, placebo-controlled study in healthy volunteers. *Nutrients* 13 (2), 654. doi:10.3390/nu13020654
- Sébastien, H., and Reuben, J. S. (2017). AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat. Rev. Mol. Cell Biol.* 19, 121–135. doi:10.1038/nrm.2017.95
- Shan, J., Jin, X., Zhang, C., Huang, M., Xing, J., Li, Q., et al. (2024). Metal natural product complex Ru-procyanidins with quadruple enzymatic activity combat infections from drug-resistant bacteria. *Acta Pharm. Sin. B* 14 (5), 2298–2316. doi:10.1016/j.apsb.2023.12.017
- Suang, R., Xueqiang, H., Siqi, Z., Yong, Z., Xiao, X., Wei, B., et al. (2017). Procyanidins extracted from the litchi pericarp ameliorate atherosclerosis in ApoE knockout mice: their effects on nitric oxide bioavailability and oxidative stress. *Food and Funct.* 8, 4210–4216. doi:10.1039/c7fo00747g
- Silambarasan, M., Tan, J. R., Karolina, D. S., Armugam, A., Kaur, C., and Jayaseelan, K. (2016). MicroRNAs in hyperglycemia induced endothelial cell dysfunction. *Int. J. Mol. Sci.* 17 (4), 518. doi:10.3390/ijms17040518
- Silvestre, J.-S., Théry, C., Hamard, G., Boddaert, J., Aguilar, B., Delcayre, A., et al. (2005). Lactadherin promotes VEGF-dependent neovascularization. *Nat. Med.* 11 (5), 499–506. doi:10.1038/nm1233
- Skórzyńska-Dziduszko, K. E., Kimber-Trojnar, Z., Patro-Malysza, J., Olszewska, A., Zaborowski, T., and Malecka-Massalska, T. (2016). An interplay between obesity and inflammation in gestational diabetes mellitus. *Curr. Pharm. Biotechnol.* 17 (7), 603–613. doi:10.2174/1389201017666160127105926
- Stella, P., Kalliopi, P., Grigoriou, T., Dimitrios, P., Konstantinos, V., and Νικόλαος, Π. (2021). Skin advanced glycation end products among subjects with type 2 diabetes mellitus with or without distal sensorimotor polyneuropathy. *J. diabetes Res.* 2021, 6045677. doi:10.1155/2021/6045677
- Stergios, A. P., Jannis, K., and Christos, Z. (2009). Nonalcoholic fatty liver disease: the pathogenetic roles of insulin resistance and adipocytokines. *Curr. Mol. Med.* 9, 299–314. doi:10.2174/156652409787847191
- Strain, W. D., and Paldanius, P. M. (2018). Diabetes, cardiovascular disease and the microcirculation. *Cardiovasc. Diabetol.* 17 (1), 57. doi:10.1186/s12933-018-0703-2
- Sudesna, C., Kamlesh, K., and Melanie, J. D. (2017). Type 2 diabetes. *Lancet* 389, 2239–2251. doi:10.1016/s0140-6736(17)30058-2
- Su Woong, J., and Jae-Young, M. (2021). The role of inflammation in diabetic kidney disease. *Korean J. Intern. Med.* doi:10.3904/kjim.2021.174
- Suzanne, M. B., William, T. M., Ryan, P. M., Melanie, R. D., Katheryn, M. G., Liyun, Y., et al. (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. doi:10.1016/j.jnutbio.2016.10.001
- Sweeting, A., Wong, J., Murphy, H. R., and Ross, G. P. (2022). A clinical update on gestational diabetes mellitus. *Endocr. Rev.* 43 (5), 763–793. doi:10.1210/endo/rev/bnac003
- Takako, Y., Hyun Ju, K., and Eun Ju, C. (2008). Gravinol ameliorates high-fructose-induced metabolic syndrome through regulation of lipid metabolism and proinflammatory state in rats. *J. Agric. Food Chem.* 56, 5026–5032. doi:10.1021/jf800213f
- Tan, T.-E., and Wong, T. Y. (2022). Diabetic retinopathy: looking forward to 2030. *Front. Endocrinol.* 13, 1077669. doi:10.3389/fendo.2022.1077669
- Teri, G. B., Steven, H. N., David, J. R., Nancy, Y. I., Elizabeth, R., Sharon, D. M., et al. (1991). ERKs: a family of protein-serine/threonine kinases that are activated and tyrosine phosphorylated in response to insulin and NGF. *Cell* 65, 663–675. doi:10.1016/0092-8674(91)90098-j
- Thomas, J. R., Benjamin, F. B., Jason, D. R., Daniel, R. L., Andrew, T. S., Blake, D., et al. (2017). Monomeric cocoa catechins enhance β -cell function by increasing mitochondrial respiration. *J. Nutr. Biochem.* 49, 30–41. doi:10.1016/j.jnutbio.2017.07.015
- Tomonori, N., Shu, M., Tadashi, H., Kazuhiro, O., Masanori, K., Ichiro, T., et al. (2009). A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. *Obesity* 17, 310–317. doi:10.1038/oby.2008.505
- Tung-Sheng, C., Show Yih, L., Hsi Chin, W., Fuu Jen, T., Chang Hai, T., Chih Yang, H., et al. (2011). Efficacy of epigallocatechin-3-gallate and Amla (emblica officinalis) extract for the treatment of diabetic-uremic patients. *J. Med. Food.* doi:10.1089/jmf.2010.1195
- Van Long, T., Min Ji, B., Mira, J., Ah Ng Tony, K., Chi Tang, H., and Woo-Sik, J. (2014). Antioxidant defense and hepatoprotection by procyanidins from almond (*Prunus amygdalus*) skins. *J. Agric. Food Chem.* doi:10.1021/jf5027247
- van Sloten, T. T., Sedaghat, S., Carnethon, M. R., Launer, L. J., and Stehouwer, C. D. A. (2020). Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet. Diabetes and Endocrinol.* 8 (4), 325–336. doi:10.1016/S2213-8587(19)30405-X
- Wei, J., Wu, H., Zhang, H., Li, F., Chen, S., Hou, B., et al. (2018). Anthocyanins inhibit high glucose-induced renal tubular cell apoptosis caused by oxidative stress in db/db mice. *Int. J. Mol. Med.* 41 (3), 1608–1618. doi:10.3892/ijmm.2018.3378
- Wei, T., Chen, L., Zhang, L., Wang, B., Li, X. B., Kai, F., et al. (2017). Effects of ginsenoside Rg1 on glucose metabolism and liver injury in streptozotocin-induced type 2 diabetic rats. *Genet. Mol. Res.* doi:10.4238/gmr16019463
- Wei-Jian, N., Hai-Hua, D., and Ling-Zhi, T. (2015). Berberine as a promising anti-diabetic nephropathy drug: an analysis of its effects and mechanisms. *Eur. J. Pharmacol.* 760, 103–112. doi:10.1016/j.ejphar.2015.04.017
- Wenqian, G., Andreas, R., Kjeld, H., Søren, G., and Per Bendix, J. (2018). The dynamic effects of isosteviol on insulin secretion and its inability to counteract the impaired β -cell formation during gluco-lipo- and aminoacidotoxicity: studies *in vitro*. *Nutrients* 10, 127. doi:10.3390/nu10020127
- Wu, S., Yue, Y., Li, J., Li, Z., Li, X., Niu, Y., et al. (2015). Procyanidin B2 attenuates neurological deficits and blood-brain barrier disruption in a rat model of cerebral ischemia. *Mol. Nutr. and Food Res.* 59 (10), 1930–1941. doi:10.1002/mnfr.201500181
- Xiao-Fang, P., Jinyu, M., Jianfei, C., Zheng, S., Raymond Chuen-Chung, C., Iris Mei Ying, T., et al. (2010). Beneficial effects of cinnamon proanthocyanidins on the formation of specific advanced glycation endproducts and methylglyoxal-induced impairment on glucose consumption. *J. Agric. Food Chem.* 58, 6692–6696. doi:10.1021/jf100538t
- Xiao-Fang, P., Ka-Wing, C., Jinyu, M., Bo, C., Chi-Tang, H., Clive, L., et al. (2008). Cinnamon bark proanthocyanidins as reactive carbonyl scavengers to prevent the formation of advanced glycation endproducts. *J. Agric. Food Chem.* 56, 1907–1911. doi:10.1021/jf073065v
- Xinyi, W., Bo-Rong, Z., Qi, J., Yiming, L., Ting, W., and He-Yao, W. (2020). Cinnamtannin D1 protects pancreatic β -cells from glucolipotoxicity-induced apoptosis by enhancement of autophagy *in vitro* and *in vivo*. *J. Agric. Food Chem.* doi:10.1021/acs.jafc.0c04898
- Xu, J., Hu, X. F., Huang, W., Shen, P. Y., Zhang, W., Ren, H., et al. (2017). The clinicopathological characteristics of diabetic nephropathy and non-diabetic renal diseases in diabetic patients. *Zhonghua Nei Ke Za Zhi* 56 (12), 924–929. doi:10.3760/cma.j.issn.0578-1426.2017.12.007
- Yamagishi, S.-i. (2011). Role of advanced glycation end products (AGEs) and receptor for AGEs (RAGE) in vascular damage in diabetes. *Exp. Gerontol.* 46 (4), 217–224. doi:10.1016/j.exger.2010.11.007
- Yang, B., Sun, Y., Lv, C., Zhang, W., and Chen, Y. (2020). Procyanidins exhibits neuroprotective activities against cerebral ischemia reperfusion injury by inhibiting TLR4-NLRP3 inflammasome signal pathway. *Psychopharmacology* 237 (11), 3283–3293. doi:10.1007/s00213-020-05610-z
- Yao, L., Ruifang, S., Xiaoping, L., Lei, W., Hengying, C., Siwen, S., et al. (2022). Procyanidins and its metabolites by gut microbiome improves insulin resistance in gestational diabetes mellitus mice model via regulating NF- κ B and NLRP3 inflammasome pathway. *Biomed. and Pharmacother.* 151, 113078. doi:10.1016/j.biopha.2022.113078
- Yashpal, S. K., Lin, S., Ping, X., Fu You, L., and Sheldon, C. (2011). A glimpse of various pathogenetic mechanisms of diabetic nephropathy. *Annu. Rev. Pathology-mechanisms Dis.* 6, 395–423. doi:10.1146/annurev.pathol.4.110807.092150
- Yau, J. W. Y., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T., et al. (2012). Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 35 (3), 556–564. doi:10.2337/dc11-1909
- Yin, Q., Wang, L., Yu, H., Chen, D., Zhu, W., and Sun, C. (2021). Pharmacological effects of polyphenol phytochemicals on the JAK-STAT signaling pathway. *Front. Pharmacol.* 12, 716672. doi:10.3389/fphar.2021.716672
- Ying, T., Chunmiao, Y., Qinyu, Y., Qian, L., Jia, L., Xinya, X., et al. (2019). Procyanidin B2 activates PPAR γ to induce M2 polarization in mouse macrophages. *Front. Immunol.* 10, 1895. doi:10.3389/fimmu.2019.01895
- Ying Yng, C., Paola, Q. R., Dirk, M. H., Steven, A. F., Calvert, C. C., David, A. M., et al. (2014). Phenolic metabolites and substantial microbiome changes in pig feces by ingesting grape seed proanthocyanidins. *Food and Funct.* doi:10.1039/c4fo00325j
- Yiqi, Y., Yixuan, L., Minqi, W., Kai, Y., Qishan, W., Pei, M., et al. (2022). Targeting ferroptosis suppresses osteocyte glucolipotoxicity and alleviates diabetic osteoporosis. *Bone Res.* 10, 26. doi:10.1038/s41413-022-00198-w
- Yoko, Y., Masaru, O., Mitsutaka, N., and Hitoshi, A. (2019). Cacao liquor procyanidins prevent postprandial hyperglycaemia by increasing glucagon-like peptide-1 activity and AMP-activated protein kinase in mice. *J. Nutr. Sci.* 8, e2. doi:10.1017/jns.2018.28
- Yu, F., Li, B.-y., Li, X.-l., Cai, Q., Zhang, Z., Cheng, M., et al. (2012). Proteomic analysis of aorta and protective effects of grape seed procyanidin B2 in db/db mice reveal a critical role of milk fat globule epidermal growth factor-8 in diabetic arterial damage. *PLoS One* 7 (12), e52541. doi:10.1371/journal.pone.0052541

- Yuan, H., Hideki, H., and Gabriel, N. (2016). Mechanism and regulation of NLRP3 inflammasome activation. *Trends Biochem. Sci.* 41, 1012–1021. doi:10.1016/j.tibs.2016.09.002
- Yuan, T., Yang, T., Chen, H., Fu, D., Hu, Y., Wang, J., et al. (2019). New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. *Redox Biol.* 20, 247–260. doi:10.1016/j.redox.2018.09.025
- Yue, W., Chi, L., Yuxu, N., Jiamin, X., Liwen, F., Yun, W., et al. (2021). Procyanidins mediates antineoplastic effects against non-small cell lung cancer via the JAK2/STAT3 pathway. *Transl. cancer Res.* 10, 2023–2035. doi:10.21037/tcr-20-3018
- Yuta, K., Yuki, S., Seiya, I., Minoru, S., Masahito, T., Chiaki, I., et al. (2013). Black soybean seed coat extract ameliorates hyperglycemia and insulin sensitivity via the activation of AMP-activated protein kinase in diabetic mice. *J. Agric. Food Chem.* 61, 5558–5564. doi:10.1021/jf401190y
- Zhang, H., Sheng-Chiang, S., Xiaoxi, Y., and Li, Y. (2017). Dietary epigallocatechin 3-gallate supplement improves maternal and neonatal treatment outcome of gestational diabetes mellitus: a double-blind randomised controlled trial. *J. Hum. Nutr. Dietetics* 30, 753–758. doi:10.1111/jhn.12470
- Zhang, H. J., Baoping, J., Chen, G., Feng, Z., Yangchao, L., Han-Qing, Y., et al. (2009). A combination of grape seed-derived procyanidins and gypenosides alleviates insulin resistance in mice and HepG2 cells. *J. Food Sci.* 74, H1–H7. doi:10.1111/j.1750-3841.2008.00976.x
- Zhang, Z., Li, B.-Y., Li, X.-L., Cheng, M., Yu, F., Lu, W.-d., et al. (2013). Proteomic analysis of kidney and protective effects of grape seed procyanidin B2 in db/db mice indicate MFG-E8 as a key molecule in the development of diabetic nephropathy. *Biochimica Biophysica Acta* 1832 (6), 805–816. doi:10.1016/j.bbdis.2013.02.022
- Zhao, T., Liu, D., Liu, Y., Deng, J., and Yang, H. (2024). Comparisons of procyanidins with different low polymerization degrees on prevention of lipid metabolism in high-fat diet/streptozotocin-induced diabetic mice. *Food Res. Int. Ott. Ont.* 188, 114508. doi:10.1016/j.foodres.2024.114508
- Zhaoxia, W., Siyao, S., Jiaqian, J., Tan, D., Donghua, J., Bing, B., et al. (2014). Protective effects of grape seed extract fractions with different degrees of polymerisation on blood glucose, lipids and hepatic oxidative stress in diabetic rats. *Nat. Prod. Res.* 29, 988–992. doi:10.1080/14786419.2014.965165
- Zhimei, L., Ning, L., Yaping, J., Jiamei, Y., Jie, Z., Miao, S., et al. (2019). Vitexin alleviates streptozotocin-induced sexual dysfunction and fertility impairments in male mice via modulating the hypothalamus–pituitary–gonadal axis. *Chemico-Biological Interact.* 297, 119–129. doi:10.1016/j.cbi.2018.10.013
- Zhiwei, Z., Xiaowei, Z., Lei, M., Mengqi, G., Jian, L., Wen, S., et al. (2021). Pioglitazone inhibits diabetes-induced atrial mitochondrial oxidative stress and improves mitochondrial biogenesis, dynamics, and function through the PPAR- γ /PGC-1 α signaling pathway. *Front. Pharmacol.* 12, 658362. doi:10.3389/fphar.2021.658362
- Zhou, Y., Li, B.-Y., Li, X.-L., Wang, Y.-J., Zhang, Z., Pei, F., et al. (2016). Restoration of mimecan expression by grape seed procyanidin B2 through regulation of nuclear factor-kappaB in mice with diabetic nephropathy. *Iran. J. Kidney Dis.* 10 (5), 325–331.
- Zou, W., Lu, Q., Zhu, X., Pan, Y., Xu, Q., and Wang, K. (2023). Procyanidin B2 protects TR-iBRB2 cells against hyperglycemia stress by attenuating oxidative stress and inflammasome activation via regulation of redoxosomes/NF-kB signaling. *Curr. Mol. Med.* 23 (10), 1095–1103. doi:10.2174/1566524023666221017120334