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REVIEW ARTICLE

Dietary polyphenols as antidiabetic agents: Advances and opportunities

Chongde Sun[1] | Chao Zhao[2,3] | Esra Capanoglu Guven[4] | Paolo Paoli[5] | Jesus Simal-Gandara[6] | Kunka Mohanram Ramkumar[7,8] | Shengpeng Wang[3] | Florina Buleu[9] | Ana Pah[9] | Vladiana Turi[9] | Georgiana Damian[9] | Simona Dragan[9] | Merve Tomas[10] | Washim Khan[11] | Mingfu Wang[12] | Dominique Delmas[13,14,15] | Maria Puy Portillo[16,17] | Parsa Dar[3] | Lei Chen[2] | Jianbo Xiao[3]

[1]Zhejiang Provincial Key Laboratory of Horticultural Plant Integrative Biology, Zhejiang University, Hangzhou, China

[2]College of Food Science, Fujian Agriculture and Forestry University, Fuzhou, China

[3]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

[4]Department of Food Engineering, Faculty of Chemical and Metallurgical Engineering, İstanbul Technical University, Istanbul, Turkey

[5]Department of Biomedical, Experimental, and Clinical Sciences, University of Florence, Florence, Italy

[6]Nutrition and Bromatology Group, Department of Analytical Chemistry and Food Science, Faculty of Food Science and Technology, University of Vigo - Ourense Campus, Ourense, Spain

[7]Life Science Division, SRM Research Institute, SRM University, Kattankulathur, India

[8]Department of Biotechnology, School of Bio-engineering, SRM University, Kattankulathur, India

[9]Centre for Interdisciplinary Research & Department of Cardiology, University of Medicine and Pharmacy Victor Babes, Timisoara, Romania

[10]Faculty of Engineering and Natural Sciences, Food Engineering Department, Istanbul Sabahattin Zaim University, Istanbul, Turkey

[11]National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, Mississippi

[12]School of Biological Sciences, The University of Hong Kong, Pokfulam, Hong Kong

[13]INSERM U866 Research Center, Université de Bourgogne Franche-Comté, Dijon, France

[14]INSERM Research Center U1231 – Cancer and Adaptive Immune Response Team, Bioactive Molecules and Health Research Group, Dijon, France

[15]Centre Anticancéreux Georges François Leclerc Center, Dijon, France

[16]Nutrition and Obesity Group, Department of Nutrition and Food Science, Faculty of Pharmacy and Lucio Lascaray Research Institute, University of País Vasco (UPV/EHU), Vitoria-Gasteiz, Spain

[17]CIBEROBN Physiopathology of Obesity and Nutrition, Institute of Health Carlos III (ISCIII), Vitoria-Gasteiz, Spain

Correspondence
Jianbo Xiao, Institute of Chinese Medical Sciences, State Key Laboratory of Quality Research in Chinese Medicine, University of Macau, Macau, China.
Email: jianboxiao@yahoo.com
Lei Chen, College of Food Science, Fujian Agriculture and Forestry University, Fuzhou 350002, China.
Email: chenlei841114@hotmail.com

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Abstract

Dietary polyphenols have been widely investigated as antidiabetic agents in cell, animals, human study, and clinical trial. The number of publication (Indexed by Web of Science) on "polyphenols and diabetes" significantly increased since 2010. This review highlights the advances and opportunities of dietary polyphenols as antidiabetic agents. Dietary polyphenols prevent and manage Type 2 diabetes mellitus via the insulin-dependent approaches, for instance, protection of pancreatic islet β-cell, reduction of β-cell apoptosis, promotion of β-cell proliferation, attenuation of oxidative stress, activation of insulin signaling, and stimulation of pancreas to secrete insulin, as well as the

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insulin-independent approaches including inhibition of glucose absorption, inhibition of digestive enzymes, regulation of intestinal microbiota, modification of inflammation response, and inhibition of the formation of advanced glycation end products. Moreover, dietary polyphenols ameliorate diabetic complications, such as vascular dysfunction, nephropathy, retinopathy, neuropathy, cardiomyopathy, coronary diseases, renal failure, and so on. The structure–activity relationship of polyphenols as antidiabetic agents is still not clear. The individual flavonoid or isoflavone has no therapeutic effect on diabetic patients, although the clinical data are very limited. Resveratrol, curcumin, and anthocyanins showed antidiabetic activity in human study. How hyperglycemia influences the bioavailability and bioactivity of dietary polyphenols is not well understood. An understanding of how diabetes alters the bioavailability and bioactivity of dietary polyphenols will lead to an improvement in their benefits and clinical outcomes.

KEYWORDS

bioavailability, clinical study, diabetes, diabetic complication, dietary polyphenols, glucose absorption, intestinal microbiota, pancreatic islet β-cell

1 | NATURAL PRODUCTS BASED ANTIDIABETIC DRUG DISCOVERY

Historically, natural products have been playing an important role in human health. Plants have been traditionally used to combat diseases in the medical traditions of different societies. Therefore, not surprisingly many modern drugs represent plant-derived substances for treating Type 2 diabetes (T2D) mellitus, with multiple prominent examples, such as acarbose, andrographolide, and galegine, which contributed to the discovery of biguanides (Figure 1).

With so many successful records, the advantages of natural products-based drug discovery highlight biodiversity of resources, structural and chemical diversity, drug-likeness and biological friendliness, biocompatibility and biological validation, hints on efficacy and safety from application of traditional medicines, opportunities for use as scaffolds for chemical modifications to optimize potency, multi-targeted mechanism of action for diseases of complex etiology, and available to large-scale production by biotechnological approaches.

Biodiversity of resources of natural products from rich ecosystems includes plants, fungi, bacteria, algae, animals, minerals, and their metabolites, which provide a unique and renewable resource for the discovering of potential new polyphenols with novel bioactivities (Hoffmann et al., 2018). One key advantage of natural products is their enormous structural diversity; they typically have higher molecular weights, more sp^3 carbon atoms, and less nitrogen and halogen elements; a greater number of chiral centers increased steric complexity and greater molecular rigidity than either synthetic drugs or combinatorial libraries (Li & Vederas, 2009). The significance of natural products chemistry is the introduction of novel molecular skeletons and functionalities, which may change their bioavailability and bio-efficacy. Moreover, natural polyphenols produced by living organisms are evolutionarily optimized as drug-likeness and biological friendliness than totally synthetic chemicals. Application of biotechnology including transgenic plants, microbial fermentation, and enzyme engineering enables the large-scale production of specific natural bioactive polyphenols (Atanasov et al., 2015; Cao, Chen, Jassbi, & Xiao, 2015; Xiao, Muzashvili, & Georgiev, 2014).

The medicinal herbs usually contain multiple bioactive compounds including with multiple targets diabetic therapy. In traditional Chinese medicine, purslane, Fenugreek seeds, and mulberry leaves were widely applied to treat diabetes (Figure 2). Fenugreek seeds contained soluble dietary fibers (galactomannan), diosgenin, trigonelline, flavone *C*-glycosides, and other ingredients that showed hypoglycemic activity. Galactomannan can delay gastric emptying of carbohydrates, inhibit digestive enzymes, and regulate intestinal flora (Zentek et al., 2013). Diosgenin protects pancreatic islet β-cells and upregulates hepatic glucose kinase (Fuller & Stephen, 2015). Trigonelline improves insulin signaling pathway (Aldakinah, Al-Shorbagy, Abdallah, & El-Abhar, 2017), attenuates the endoplasmic reticulum stress and oxidative stress in type 2 diabetic rats (Mayakrishnan et al., 2015), and affects the regeneration of pancreatic islet β-cells, the secretion of insulin, and glucose metabolizing enzymes (Zhou, Chan, & Zhou, 2012). Flavone *C*-glycosides can inhibit digestive enzymes, activate insulin signaling, and reduce the formation of advanced glycation end products (Xiao, Capanoglu, Jassbi, & Miron, 2016). Dietary polyphenols have been widely investigated as antidiabetic agents in cell, animals, human study, and clinical trial. The number of publication (Indexed by Web of Science) on "polyphenols and diabetes" significantly increased since 2010 (Figure 3). This review will focus on the advances and opportunities of dietary polyphenols as antidiabetic agents.

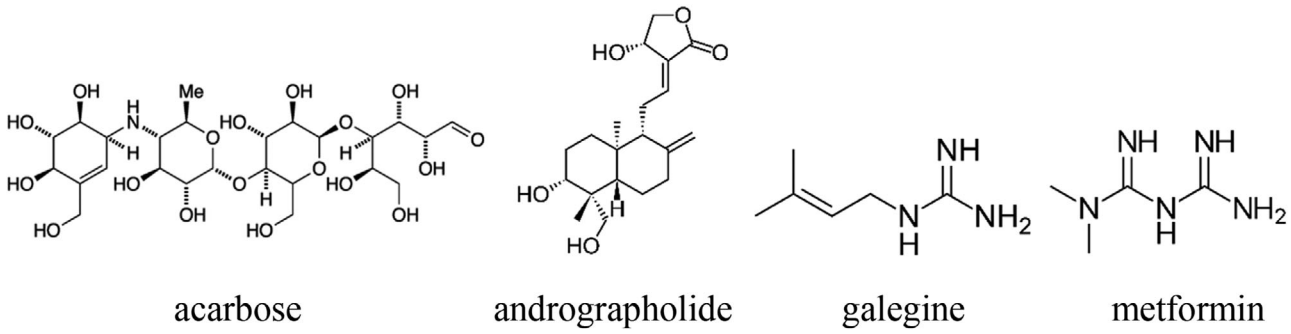


FIGURE 1 Natural antidiabetic drugs

FIGURE 2 Purslane, fenugreek seeds, and mulberry leaves were applied to treat diabetes in Traditional Chinese Medicine

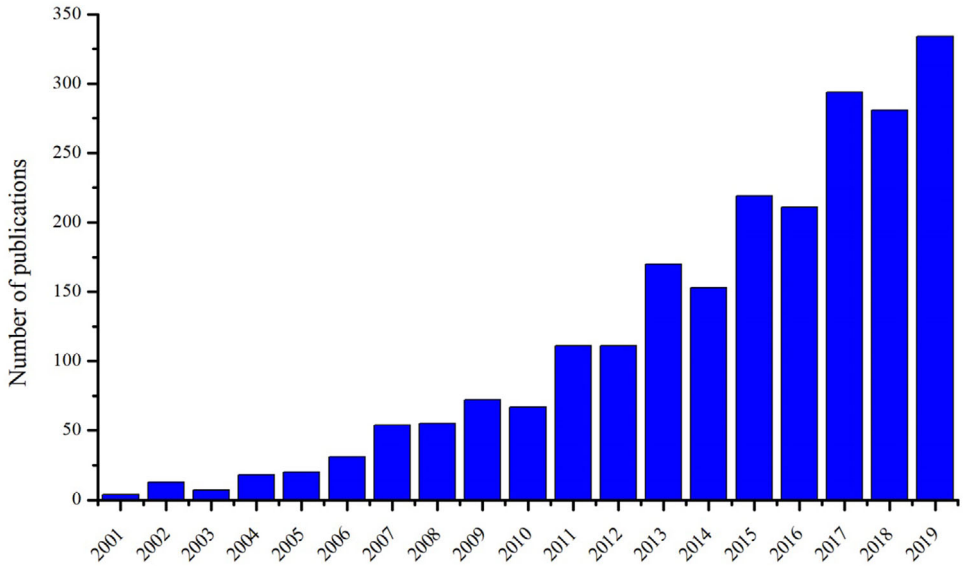


FIGURE 3 Increasing publications on "polyphenols and diabetes" since 2010 (Indexed by Web of Science)

2 | DIETARY POLYPHENOLS

Phenolics are the intricate category of bioactive molecules produced by shikimate and acetate pathways that occur naturally. Almost all medicinal and edible plants contain phenolic compounds. Among the richest dietary sources of phenolic and polyphenolic compounds are fruits, spices, seeds, and vegetables. Moreover, certain beverages like tea, coffee, and wine contribute significantly to the daily intake of phenolics (Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). Due to their structural diversity and possessing therapeutic activities, researchers have focused on phenolic compounds exploring their use as medicinal agents. Compounds with one phenolic ring are generally classified as simple phenols, whereas those with more than one phenolic ring referred to as polyphenols (Figure 4). There are four major groups

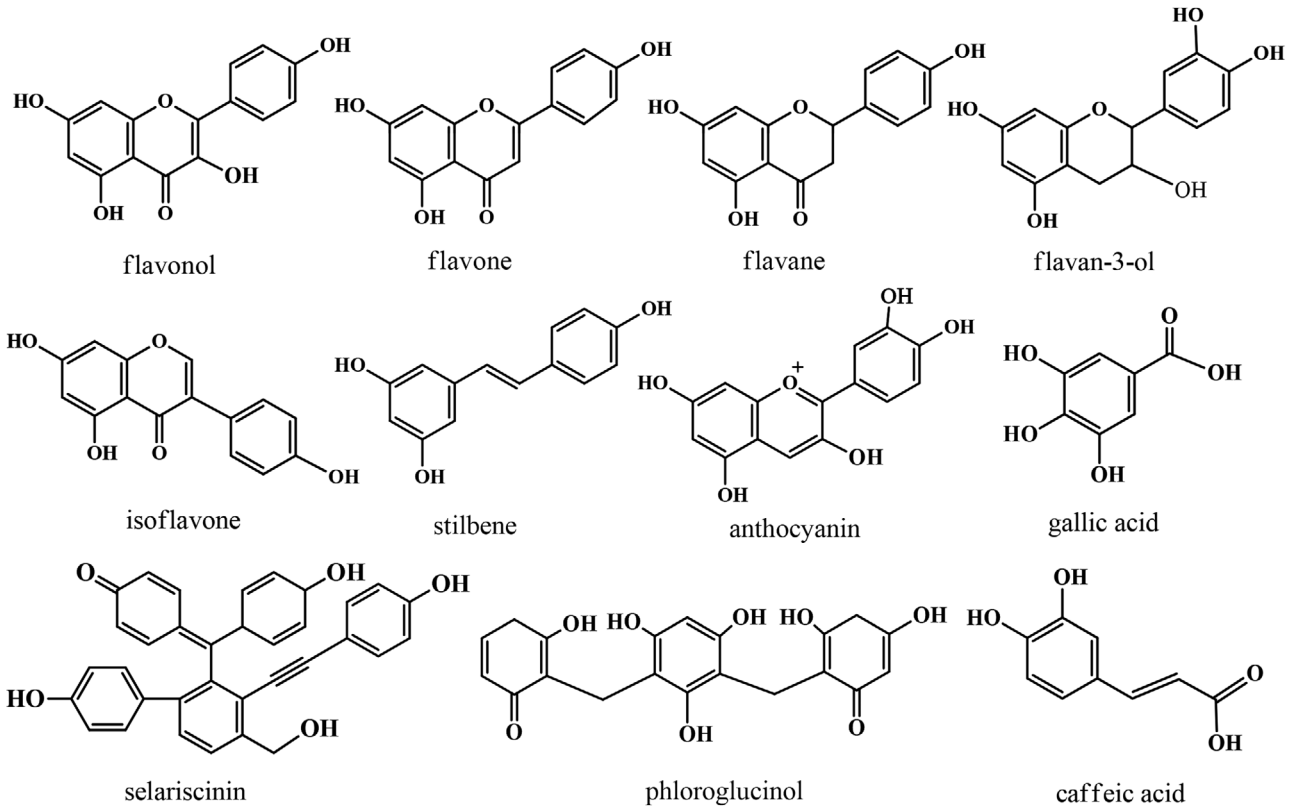


FIGURE 4 Chemical structures of natural polyphenols

of phenolic compounds: simple phenols (designated as phenolic acid), lignans, stilbenes, and polyphenols (referred to as flavonoids). Among polyphenols, flavonoids represent the wide-ranging metabolites, which include flavonols, flavones, flavanones, isoflavones, and anthocyanins (Figure 3).

Phenolic acids are the aromatic carboxylic acid with hydroxyl derivatives that have only one phenolic ring in their structure and are of two types, for example, hydroxybenzoic acid and hydroxycinnamic acid derivatives (Kondratyuk & Pezzuto, 2004). Caffeic, *p*-coumaric, ferulic, and sinapic acids are the hydroxycinnamic acid derivatives that are more abundant in plant as compared to benzoic acid derivatives such as gallic acid, protocatechuic acid, and *p*-hydroxybenzoic acid.

With 1,2-diphenylethylene nucleus, stilbenes consist of two phenolic rings connected by a methylene bridge (Rivière, Pawlus, & Mérillon, 2012). Stilbenes are not found abundantly in plants, and thus our diet always deficit with it. Resveratrol (3,4′,5-trihydroxy stilbene), a well-known stilbenes class of polyphenol, found mainly in grapes skin, mulberries, peanuts, and red wine (Burns, Yokota, Ashihara, Lean, & Crozier, 2002). Anthocyanidins are present in red wine, cereals, and certain vegetables (e.g., beans, cabbage, and onions), but the primary source of these polyphenols is red fruits (Lee, Durst, & Wrolstad, 2005). Cyanidine, delphinidine, malvidin, petunidine, pelargonidine, and peonidine are the common anthocyanidin aglycones in the human diet (Kähkönen & Heinonen, 2003).

The most common group of polyphenols in the human diet are flavonoids. It contains two phenolic rings, which are connected by three carbon atoms of an oxygen-containing heterocyclic ring. Flavonols, flavones, flavanones, isoflavones, flavan-3-ols, and anthocyanidins are the different types of flavonoids found in the plant-based human diet. Flavonoids with 3-hydroxy pyran-4-one group on the C-ring known as flavonols are prevalent in human diet, especially in tea, fruits, and vegetables (Xiao, 2017). The dietary flavonoids in nature almost all exist as their glycosides, such as glucoside, galactoside, rhamnoside, arabinoside, and rutinoside. The most abundant flavonoid glycosides in plants are flavone *O/C*-glycosides and flavonol *O*-glycosides. The flavonoid *O*-glycosides are found mainly as their 3- or 7-*O*-glycosides (Xiao, 2017); however, most flavonoid *C*-glycosides are in 6- and 8-*C*-glycosidic forms (Xiao et al., 2016).

Caffeoylquinic acids are members of a larger family of chlorogenic acids. The subfamily of caffeoylquinic acids includes several isomers of which the most famous are 3-*O*-caffeoylquinic acid, crypto-chlorogenic acid, chlorogenic acid, 1,5-di-O-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, and 4,5-di-O-caffeoylquinic acid. Plants use caffeoylquinic acids as precursors to sustain the lignin biosynthesis, to defend plants from the attack of pathogens (bacteria and fungi), or as protecting agents against damages induced by oxidative stress and UV rays (Clifford, Jaganath, Ludwig, & Crozier, 2017). Depending on the plant species, the amount of caffeoylquinic acids produced changes, varying from micrograms to grams per kilogram of dry weight. Due to their chemical structure, caffeoylquinic acids show a good solubility in water and can easily be extracted from natural sources (Clifford, 2000; Meinhart et al., 2017).

Proanthocyanidins are a class of polyphenols found in a variety of plants. Chemically, they are oligomeric flavonoids. Many are oligomers of catechin and epicatechin and their gallic acid esters. More complex polyphenols, having the same polymeric building block, form the group of tannins. Anthocyanidins are a class of water-soluble pigments that are widely found in plant tissues such as flowers, leaves, fruits, and stems. Structurally, anthocyanidins are phenolic compounds belonging to the flavonoids, usually in the form of glycosides, composed of aglycones and glycosyl groups. More than 600 anthocyanidins have been reported, of which six anthocyanins (aglycones) including cyanidin, malvidin, delphinidin, petunidin, peonidin, and pelargonidin accounted for 95% of them. Anthocyanidins differ in the number and position of hydroxyl groups on the ring, the degree of methylation of the hydroxyl groups, and the number and location of glycosyl ligands.

3 | EVIDENCE FROM THE EPIDEMIOLOGICAL INVESTIGATION

Significant evidence from epidemiological investigations has shown that dietary polyphenols might control and prevent T2D while contrary opinions also exist. A high intake of total polyphenols, total flavonoids (specifically flavanones and dihydroflavonols), and stilbenoids is associated with a reduced risk of diabetes in elderly persons at high risk of cardiovascular disease in the Prevencion con Dieta Mediterranea trial (Tresserra-Rimbau et al., 2016). Dietary flavonoids were regarded as a related factor of reduced risk of T2D (Liu, Li, Zhang, Sun, & Xia, 2014), for example, van Dam, Naidoo, and Landberg (2013) highlighted that anthocyanidins and flavan-3-ols could reduce the risk of T2D and a 20-year investigation conducted in the United States received similar effects through higher consumption of anthocyanins or anthocyanin-rich food. Intake of dietary flavones has benefits in prevalence of T2D in Korean women aged ≥30 years (Oh et al., 2017). Furthermore, a study involving 4,186 Korean individuals even illustrated that the consumption of flavones and flavonols was inversely associated with insulin resistance among male subjects (Wedick et al., 2015). Quercetin intake was inversely related to the prevalence of T2D in the Chinese population investigated by a validated 100-item food frequency questionnaire (Yao et al., 2019). However, this study is not convinced because the effects of co-existed other flavonoids are not considered. Flavonoid intake from fruit and vegetables during adolescence is linked with a favorable risk factor profile for T2D in early adulthood (Penczynski et al., 2019). Contradictory results, however, indicated that uptake of flavonoids might not link to a lower risk of T2D. A prospective cross-sectional study conducted on 38,018 women suggested that there was no relationship between flavonols or flavones consumption and the risk of T2D (Song, Manson, Buring, Sesso, & Liu, 2005). In addition, the intake of anthocyanidins was not linked with the risk of diabetes in women in Iowa (Nettleton et al., 2006). In summary, the results from different epidemiological studies are inconsistent, which may be due to the large variation between different populations and measurement errors in dietary intake (Talaei & Pan, 2015).

4 | MECHANISMS OF DIETARY POLYPHENOLS AS ANTIDIABETIC AGENTS

Accumulated evidences from in vivo and in vitro investigations suggest a significant function of dietary polyphenols in the prevention and management of T2D through the insulin dependent approaches, for instance, protection of pancreatic islet β-cell, reduction of β-cell apoptosis, promotion of β-cell proliferation, attenuation of oxidative stress, activation of insulin signaling, and stimulation of pancreas to secrete insulin, as well as the insulin independent approaches including inhibition of glucose absorption, inhibition of digestive enzymes, regulation of intestinal microbiota, modification of inflammation response, and inhibition of the formation of advanced glycation end products (Table 1). Moreover, dietary polyphenols ameliorates diabetic complications, such as vascular dysfunction, nephropathy, retinopathy, neuropathy, cardiomyopathy, coronary diseases, renal failure, and so on (Figure 5).

4.1 | Flavonoids

Flavonoids and extracts rich in flavonoids from coffee, guava tea, whortleberry, olive oil, propolis, chocolate, and cocoa have been widely studied as possible antidiabetic agents. Quercetin was the most widely investigated flavonoid in the literatures for the in vivo and cellular antidiabetic effects in animal and cell models (Shi et al., 2019), followed by kaempferol (Alkhalidy et al., 2018), luteolin (Sangeetha, 2019), myricetin (Li et al., 2017), and naringenin (Den Hartogh & Tsiani, 2019). Compared with these aglycones, flavonoid *O*-glycosides shown less antidiabetic potential (Xiao, 2017). However, flavonoid *C*-glycosides, such as vitexin, isovitexin, swertisin, apigenin 6-*C*-β-fucopyranoside, and apigenin 6-*C*-(2″-*O*-α-rhamnopyranosyl)-β-fucopyranoside, exhibited positive antidiabetic activity in hyperglycemic animals (Xiao et al., 2016).

Dietary flavonoids showed significant hypoglycemic effect via regulation of glucose absorption (Loureiro & Martel, 2019), inhibition of digestive enzymes (Xiao, Ni, Kai, & Chen, 2013; Xiao, Kai, Yamamoto, & Chen, 2013), regulation of intestinal microbiota (Gowd, Karim, Shishir, Xie, & Chen, 2019), inhibition of advanced glycation end products formation (Xie a& Chen, 2013), and so on. Flavonoids improve the pathogenesis of diabetes and its complications through the regulation of glucose metabolism, hepatic enzymes activities, and a lipid profile (Al-Ishaq, Abotaleb, Kubatka, Kajo, & Büsselberg, 2019; Zhao et al., 2019). The hydroxyl groups attached to ring B and ring C and an unsaturated 2,3-bond in conjugation with a 4-carbonyl group of flavonoids are in favor of the inhibition of digestive enzymes and advanced glycation end products formation, whereas methyl and glycosidic moieties make against the inhibition (Xiao, Ni, et al., 2013; Xiao, Kai, et al., 2013; Xie & Chen, 2013). However, the structure–activity relationship of hypoglycemic effects of dietary flavonoids in animals was not clear. The antidiabetic activity of flavonoid *C*-glycosides in human and clinical study has been rarely reported.

TABLE 1 Antidiabetic effects of dietary phenolic compounds

Phenolic compounds	Foods	Promoting effect	Inhibiting effect	Refs.
Flavonoids	Coffee, guava tea, whortleberry, olive oil, propolis, chocolate, and cocoa	Intestinal microbiota	Glucose absorption; digestive enzymes; inhibition of advanced glycation end products (AGEs) products formation	Loureiro & Martel, 2019; Xiao, Ni, Kai, & Chen, 2013; Xiao, Kai, Yamamoto, & Chen 2013; Gowd et al., 2019; Xie & Chen, 2013
Isoflavones	Soybean	Hypoglycemic effects via improving insulin resistance and sensitivity, protecting pancreatic β-cells; exerting anti-inflammation activity	Carbohydrate digestion and glucose uptake in small intestine; the process of renal interstitial fibrosis in diabetic nephropathic rats; oxidative stress; Maillard reaction and AGEs formation	Jin et al., 2018; Liu et al., 2018; Chen et al., 2018; Chen et al., 2018
Catechins	Tea leaves and red wine	Insulin sensitivity; AMPK activation; fecal excretion of bile acids and cholesterol	Glycaemia; blood lipid; white fat depots; pancreatic α-glucosidase, and also α-amylase and maltase; Na+-dependent glucose transporter; reactive oxygen species production	Thielecke & Boschmann , 2009; Park et al., 2014; Xu et al., 2019; Kobayashi et al., 2000; Li et al., 2018; Matsui et al., 2007; Shimizu et al., 2000; Solinas & Becattini, 2016; Li et al., 2018
Hydroxycinnamic acids	Fruits and vegetables, especially the outer part of ripe fruits	Glucose intolerance and insulin resistance; glucokinase activity; β-cell function; activating AMP-activated protein kinase; antioxidant potential and anti-inflammation effects	Glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities in liver; adipogenesis and gluconeogenesis	Kasetti et al., 2012; Jung et al., 2007; Son et al., 2011; Pei et al., 2016
Caffeoylquinic acids	Potatoes, eggplants, peaches, prunes, and coffee beans	insulin response	Human salivary and pancreatic α-amylase; hepatic glucose-6-phosphatase	Narita & Inouye, 2009; Nurul Islam et al., 2013; Arion et al., 1997; Hemmerle et al., 1997; Henry-Vitrac et al., 2010; Reis et al., 2018
Anthocyanins, and anthocyanidins	Berries, eggplants, avocado, oranges, olives, red onion, fig, sweet potato, mango, and purple corn	Antioxidant; anti-inflammatory; blood glucose regulation	Oxidative stress; the levels of cholesterol, triglycerides, and low-density cholesterol	Zhu et al., 2012; Crozeir, Jaganath & Clifford, 2009; Roy et al., 2008; Tsuda et al., 1999; Shi et al., 2017
Stilbenoids	Grapevine, berries, and peanuts	Metabolic control; DNA integrity; insulin sensitivity; pancreatic β-cell and hepatoprotective activity	Oxidative damage and inflammation; digestive enzymes	Bahmanzadeh et al., 2019; Rašković et al., 2019; Sadi et al., 2015; Yan et al., 2018; Zhao et al., 2019; Bhakkiyalakshmi et al., 2014; El-Sayed et al., 2015
Procyanidins	Berries, red cabbage, apple, cocoa, cinnamon, wine, and nuts	Insulin and AMPK signaling pathways; cellular NAD+ and SIRT1 concentrations	Pro-inflammatory cytokine expression; target digestive enzymes	Ogura et al., 2016; Yamashita et al., 2016; Aragones et al., 2016; Vazquez-Flores et al., 2018
Tannins	Coffee, tea, wine, grapes, berries, apples, apricots, barley, peaches, dry fruits, mint, basil, and rosemary	AMPK phosphorylation; glucose uptake in adipose tissue via IRS-1 phosphorylation	α-Amylase and α-glucosidase activity; AGEs formation and enzymatic activity of maltase, lactase and sucrose	Hosoyama et al., 2003; Matsui et al., 2007; Miranda Pedroso et al., 2019
Curcumin	Turmeric-flavored foods and beverages	Protecting pancreatic β-cells	Insulin resistance; diabetic cardiomyopathy; oxidative stress	Jin et al., 2018; Pivari et al., 2019; Rashid et al., 2017; Zha et al., 2018

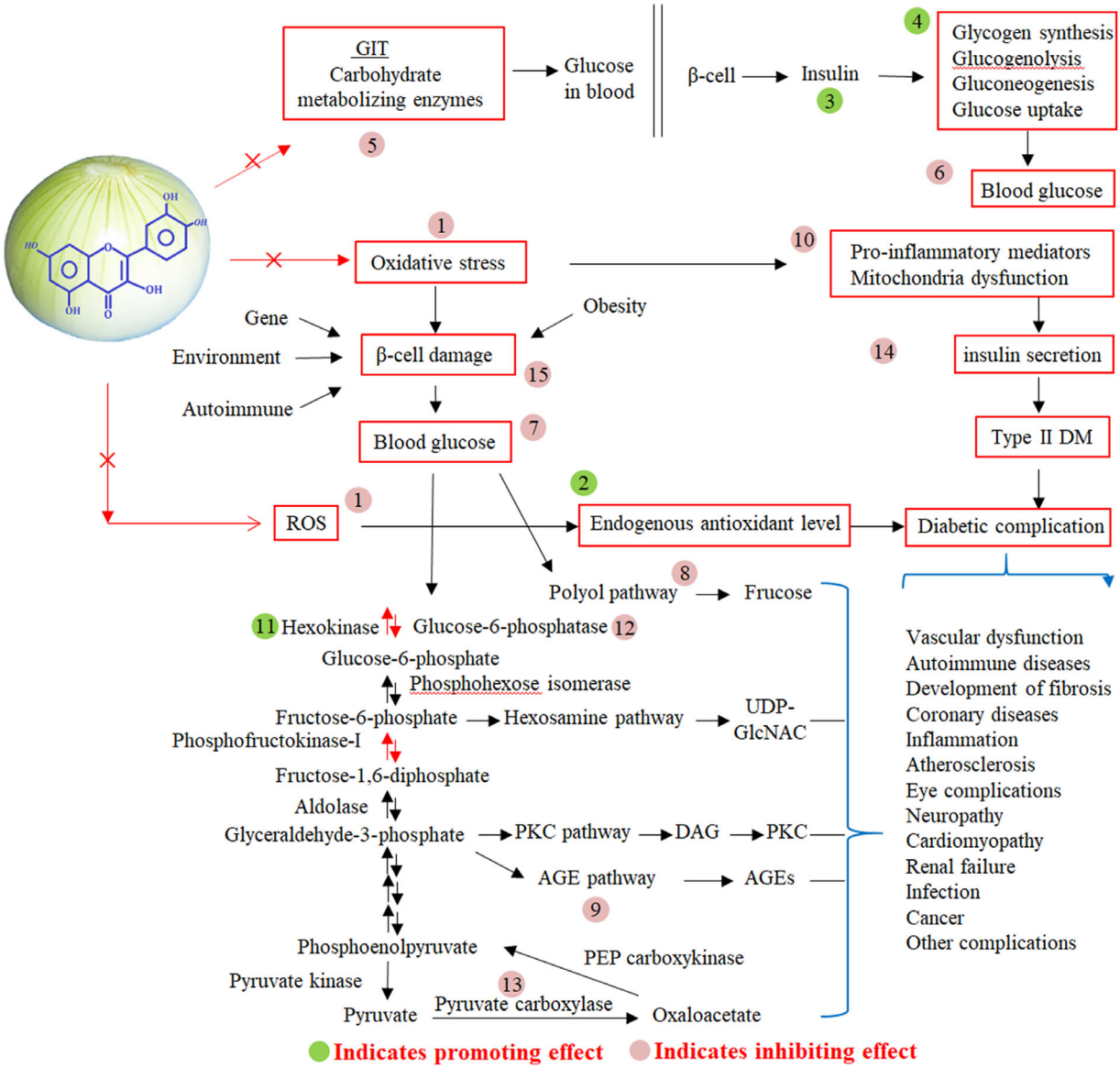


FIGURE 5 Antidiabetic mechanisms of dietary polyphenols

4.2 | Isoflavones

Significant evidence from epidemiological investigations has shown that soybean isoflavones intake is linked to a lower risk of diabetes (Konishi et al., 2019). Soy isoflavones perform hypoglycemic effects in Goto–Kakizaki diabetic rats via suppression of carbohydrate digestion and glucose uptake in small intestine (Jin et al., 2018) and delay the process of renal interstitial fibrosis in diabetic nephropathic rats (Liu et al., 2018). Among soy isoflavones, puerarin, the 8-*C*-glucoside of daidzein, showed best hypoglycemic effects via improving insulin resistance and sensitivity, protecting pancreatic β-cells, exerting anti-inflammation activity, decreasing oxidative stress, and inhibiting Maillard reaction and advanced glycation end products formation (Chen et al., 2018; Chen, Yu, & Shi, 2018). Moreover, puerarin ameliorates diabetic complications, such as cardiovascular complications, diabetic nephropathy, retinopathy, neuropathy, and so on. Genistein benefits type 2 diabetes via remarkably ameliorating hyperglycemia (Fu et al., 2012; Rockwood et al., 2019), enhancing β-cell proliferation and reducing apoptosis (Gilbert & Liu, 2013), ameliorating cardiac inflammation and oxidative stress (Gupta et al., 2015), improving fracture resistance (Odle, Dennison, Al-Nakkash, Broderick, & Plochocki, 2017), ameliorating vascular dysfunction (Valsecchi et al., 2011), and alleviating diabetic neuropathy, nephropathy, and retinopathy (Weng, Zhang, Wang, Ma, & Song, 2019).

Although daidzein does not affect the blood glucose level and glucose tolerance, but it induces an immunomodulatory effect in non-obese diabetic mice, the prophylactic effect of daidzein on the improvement of hyperglycemia, insulin resistance, dislipidemia, obesity, inflammation, and other complications associated with T2D was widely explored (Das et al., 2018; Huang, Xu, & Guo, 2019). Daidzein improves glucose homeostasis in Type 2 diabetic mice (Cheong et al., 2014). However, in a double-blind, randomized,

placebo-controlled trial, the 6-month supplementation of daidzein or genistein does not affect glycemic control and insulin sensitivity in Chinese women with impaired glucose regulation (Ye et al., 2015).

Biochanin A showed hypoglycemic effect on streptozotocin-diabetic rats (Harini, Ezhumalai, & Pugalendi, 2012). Biochanin A significantly reduced insulin resistance, improved inulin sensitivity and lipid profile, and attenuates neuropathic pain in diabetic rats (Chundi et al., 2016). Formononetin treatment reduces insulin resistance and attenuate hyperglycemia in T2D, which may be due to increasing expression of SIRT1 in pancreatic tissues (Oza & Kulkarni, 2018). Methylated isoflavones look like they exhibit better antidiabetic effect than nonmethyl forms. However, it needs further investigation in animals and human studies.

4.3 | Catechins

Catechins are natural polyphenols present in edible and medicinal plants, especially in tea leaves (Khan & Mukhtar, 2018). Catechins show a very low bioavailability. After consumption of a single cup of tea, plasma concentrations of catechins rinse quickly reaching a maximum after 2 hr, to then gradually decrease to reach the basal levels within 8 hr. Pharmacokinetic studies demonstrated that in human cells p-glycoprotein is responsible for both uptake and excretion of catechins (Vaidyanathan & Walle, 2003); however, due to the high individual variability existing between humans, the pharmacokinetics of catechins may change considerably from person to person (Ullmann et al., 2003).

There is a large agreement between researchers in sustaining that catechins have a positive impact on human health. Evidence suggested that the regular consumption of catechins could contribute to prevent gain of weight or the onset of chronic disease such as T2D or metabolic syndrome (Thielecke & Boschmann, 2009; Park, Bae, Im, & Song, 2014). In particular, catechins contribute to reduce glycaemia, enhance insulin sensitivity, decrease blood lipids, and reduce white fat depots.

It has been demonstrated that Epigallocatechin gallate acts as a reversible noncompetitive inhibitor of pancreatic α-glucosidase, showing an IC_{50} value lower than that calculated for acarbose. This explains why the assumption of a cup of tea before a meal is enough to delay intestinal glucose adsorption (Xu et al., 2019; Li et al., 2018). Interestingly, it has been observed that the inhibitory power of catechins varies depending on their chemical structure. Kamiyama and co-workers demonstrated that galloylated catechins are more effective than nongalloylated catechins in inhibiting α-glucosidase and α-amylase (Kamiyama et al., 2010). Moreover, other tea polyphenols, such as theaflavin-3-O-gallate, resulted to be potent inhibitors of maltase (Matsui et al., 2007). Besides acting as glucosidase inhibitors, catechins are able to interfere with the action mechanism of glucose transporters present onto plasma membrane of intestinal cells. Studies conducted using rabbit intestinal brush-border membrane vesicles showed that Epicatechin gallate and EGCG act as competitive inhibitor of the Na+-dependent glucose transporter (SGLT1). (Kobayashi et al., 2000; Shimizu, Kobayashi, Suzuki, Satsu, & Miyamoto, 2000). These data were also confirmed by tests conducted on healthy volunteers. It has been observed that administration of green tea powder or EGCG prior assumption of a glucose solution reduced intestinal carbohydrate absorption (Tsuneki et al., 2004; Zhong, Furne, & Levitt, 2006). Together, these results suggested that catechins modulated glucose absorption by two independent mechanisms: inhibiting glucosidase and/or interfering with the glucose transport through the plasma membrane of intestinal cells.

Another important question concerns the effect of catechins on glucose uptake by peripheral tissues. A plethora of data confirmed that in muscle cells, catechins stimulated either transcription or translocation of GLUT4 to plasma membrane through both PI3K- and AMPK-dependent pathways (Ashida et al., 2004; Li et al., 2011; Takagaki et al., 2019; Ueda et al., 2008; Ueda-Wakagi et al., 2018). Interestingly, in adipocytes catechins modulate glucose uptake in a different mode, depending from their chemical structure. In particular, nongallate-type catechins stimulate PI3K activity and GLUT4 translocation onto the plasma mebrane, recapitulating the results of studies conducted on muscle cells. Conversely, gallate-type catechins, including EGCG, seem to decrease insulin-induced glucose uptake (Ueda et al., 2010). It has been suggested that such an inhibitory effect could be the consequence of the EGCG-induced AMPK activation. In accord with this hypothesis, Li and co-workers showed that treatment of epididymal adipocytes with EGCG leads to AMPK activation, which, in turn, inhibits the expression of genes involved in de novo fatty acids synthesis, and, in the same moment, increases the expression of genes associated with lipolysis and lipid oxidization (Li et al., 2018).

Moreover, there is evidence that EGCG interferes also with the bile acid metabolism. In fact, it has been demonstrated that chronic assumption of EGCG favors fecal excretion of bile acids and cholesterol. This finding explain why in mice fed with a high-fat western-style diet, assumption of EGCG with the diet decreases intestinal lipids absorption, reduces adipose depots and contributes to normalize lipid profile (Li et al., 2018). Catechins have important effects also on liver cells. Kim and co-workers showed that low doses of EGCG stimulate glycogen synthesis and glucose uptake, whereas inhibit lipogenesis in liver cells (Kim, Tan, Xiao, Sun, & Qu, 2013). On the other hand, it has been demonstrated that treatment of hepatocytes with EGCG reduces reactive oxygen species production, thereby dampening JNK-activated signaling pathway. Thus, acting as antioxidant, EGCG protects insulin receptor and IRS proteins from phosphorylation on serine residues, a phenomenon that contributes to the onset of insulin resistance (Solinas & Becattini, 2016). Finally, it has been showed that treatment of HepG2 cells with EGCG stimulates nuclear translocation of Nrf2, which modulates the expression of antioxidant genes and reduces the expression of PTP1B, one the most important negative regulators of activated insulin receptor (Mi et al., 2018).

4.4 | Hydroxycinnamic acids

Several important hydroxycinnamic acids, such as cinnamic acid, *p*-coumaric acid, ferulic acid, caffeic acid, chlorgenic acid, and rosmarinic

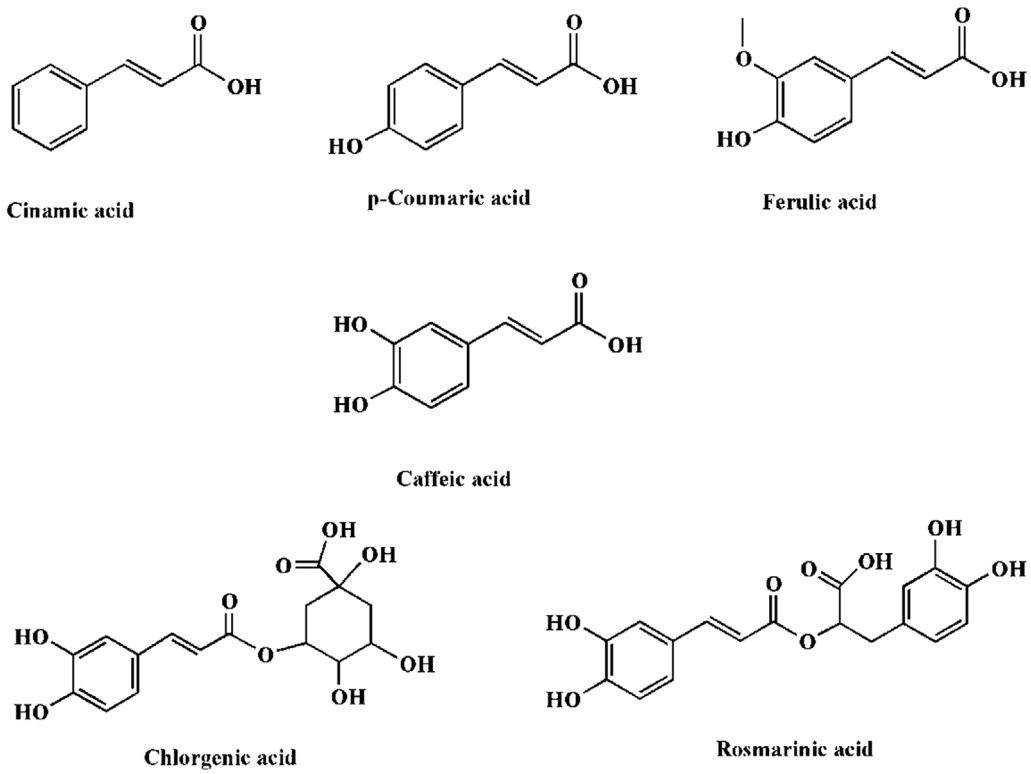


FIGURE 6 Chemical structure of important hydroxycinnamic acids

acid (Figure 6), have shown considerable hypoglycemic activity via in vivo experiments, such as streptozotocin, alloxan, and dietary (high fructose and fat diets) inducing T2D in animal models.

Cinnamic acid improved glucose intolerance and insulin resistance in streptozotocin (STZ)-induced diabetic rats (Kasetti, Nabi, Swapna, & Apparao, 2012). Ferulic acid reduced blood glucose level and increased blood insulin level in several diabetic animal models (Jung, Kim, Hwang, & Ha, 2007; Ohnishi et al., 2004). Ferulic acid also increased glucokinase activity (Jung et al., 2007) and decreased glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities in liver (Son, Rico, Nam, & Kang, 2011). Caffeic acid has been studied extensively in experimental diabetes and related complications. Caffeic acid shows hypoglycemic effects (Celik, Erdogan, & Tuzcu, 2009; Jung, Lee, Park, Jeon, & Choi, 2006), improves insulin level (Cy, Mc, Kc, & Mc, 2010), and enhances glucose intolerance (Bezerra et al., 2012) in diabetic animals.

p-Coumaric acid shows antidiabetic activity by reducing the intestinal absorption of carbohydrate, modulating glucose metabolism enzymes, improving β-cell function, stimulating insulin secretion, increasing insulin sensitivity, activating AMP-activated protein kinase, inhibiting adipogenesis and gluconeogenesis, and enhancing antioxidant potential and anti-inflammation effects (Pei, Ou, Huang, & Ou, 2016). The supplementation of *p*-coumaric acid can prevent bone loss (Yamaguchi, Uchiyama, & Lai, 2007), inhibit diabetes-associated spontaneous destruction of periodontal tissue by (Bhattarai et al., 2019), and alleviate diabetic nephropathy in diabetic animals (Zabad, Samra, & Eissa, 2019).

Chlorogenic acid is the major phenolic components in coffee, which evidently reduces the risk of type 2 diabetes. Chronic dietary chlorogenic acid consumption attenuated cardiovascular, liver, and metabolic changes (Bhandarkar, Brown, & Panchal, 2019). Chlorogenic acid was found to attenuate diabetic complications in animals such as retinopathy via inhibiting retinal neoangiogenesis (Mei et al., 2018) and sensorineural auditory function (Hong, Nam, Woo, & Kang, 2017). However, chlorogenic acid could lower the fasting plasma glucose and HbA1c levels during late diabetes in db/db mice (Jin et al., 2015), and there is no sufficient evidence that decaffeinated coffee-enriched chlorogenic acid can control blood glucose in animals (Faraji, 2018). Chlorogenic acid poorly inhibits carbohydrate-digesting enzymes (Nyambe-Silavwe & Williamson, 2018) and weakly impacted the fasting blood glucose level and blood glucose levels in the oral glucose tolerance tests in kk-[a.sup.y] mice (Igarashi, Takahashi, & Sato, 2017). Chlorogenic acid supplementation in a high-fat diet does not protect against features of the metabolic syndrome in diet-induced obese mice (Mubarak, Hodgson, Considine, Croft, & Matthews, 2013).

Rosmarinic acid could protect pancreatic β-cell dysfunction and glucolipotoxicity-mediated oxidative stress (Govindaraj & Sorimuthu, 2015), ameliorate scopolamine-induced memory impairment (Hasanein & Mahtaj, 2015) and diabetic neuropathy (Hasanein & Mohammad, 2014), attenuate vascular dysfunction (Sotnikova et al., 2013), and prevent diabetes-induced sexual disorders (Khaki, Imani, & Golzar, 2012).

4.5 | Caffeoylquinic acids

It has been demonstrated that 5-caffeoylquinic acids inhibit both human salivary and pancreatic α-amylase, suggesting that these compounds could contribute to reduce intestinal glucose absorption after meal in obese or diabetic subjects (Narita & Inouye, 2009; Nurul Islam et al., 2013). Despite studies of pharmacokinetic highlighted that caffeoylquinic acids are poorly absorbed from digestive tracts (Lafay, Morand, Manach, Besson, & Scalbert, 2006), numerous studies have been addressed to assess whether caffeoylquinic acids could influence the metabolism of peripheral tissues. It has been reported that in vitro dicaffeoylquinic acids inhibit hepatic glucose-6-phosphatase, the enzyme that catalyzes the last reaction of gluconeogenesis, in a competitive manner. This evidence raised the question whether caffeoylquinic acids could exert their hypoglycemic activity by inhibiting hepatic glucose production (Arion et al., 1997; Hemmerle et al., 1997; Henry-Vitrac, Ibarra, Roller, Mérillon, & Vitrac, 2010). However, instant coffee, which contains large amount of 5-caffeoylquinic acid, did not change the glucose adsorption in rats (Bassoli et al., 2015). This result can be explained by hypothesizing that the concentration of caffeoylquinic acids in liver cells resulted too low to inhibit of the G-6-Pase (Bassoli et al., 2015).

PTP1B is one the most promising targets to improve insulin sensitivity, and overcome insulin resistance in peripheral tissues (liver, muscle, and adipocytes) (Eleftheriou, Geronikaki, & Petrou, 2019). Interestingly, recent studies demonstrated that chlorogenic acid and some caffeoylquinic acid derivatives behave as noncompetitive inhibitor of PTP1B: among all caffeoylquinic acids resulted the most potent inhibitor, showing a K_i value of about 15 micromolar (Chen et al., 2014; Zhang et al., 2018). These data suggest that caffeoylquinic acids could be used to improve insulin sensitivity in obese or T2D subjects. In keeping with this hypothesis, it has been reported that treatment with chlorogenic acid enhances glucose uptake in both insulin-sensitive and insulin-resistant adipocytes (Alonso-Castro, Miranda-Torres, González-Chávez, & Salazar-Olivo, 2008).

Finally, studies conducted on human volunteers showed that the long-term assumption of coffee or extracts rich in caffeoylquinic acids reduces levels of blood glucose, increases the insulin response (Reis, Dórea, & da Costa, 2018), attenuates hepatic insulin resistance (Lecoultre et al., 2014), reduces serum lipids, and favors a reduction of body weight (Martínez-López, Sarriá, Mateos, & Bravo-Clemente, 2019). Together, these evidences support the hypothesis that caffeoylquinic acids have a deep impact on energetic metabolism of humans and can explain why the extracts rich in these compounds are recommended by traditional medicine for treatment of diabetes and obesity (Spínola & Castilho, 2017; Xie et al., 2019).

4.6 | Anthocyanins/anthocyanidins

The biological activities of anthocyanidins have been extensively studied, including health promotion effects such as antioxidant, anti-inflammatory, and blood glucose regulation (Zhu, Jia, Wang, Zhang, & Xia, 2012). Anthocyanidins showed antidiabetic activity mainly via inhibition of oxidative stress, improvement of insulin resistance, and promotion of insulin secretion.

Anthocyanidins have a phenolic hydroxyl structure and are a class of hydroxyl donors with strong free radical scavenging ability. Anthocyanidins could reduce blood glucose by enhancing the antioxidant ability of bio-organisms through upregulating superoxide dismutase (SOD), lowering serum malonic dialdehyde, and inhibiting increasing thiobarbituric acid reactive substances (Roy, Sen, & Chakraborti, 2008; Tsuda, Horio, & Osawa, 1999). In vitro experiments indicated that cyanidin-3-glucoside protected cells from high glucose-induced oxidative stress by activating of glutathione synthesis (Zhu et al., 2012). Islet β cells are very sensitive to oxidative stress due to low expression of antioxidant enzymes such as CAT, SOD, and GPx in islets (Evans, Goldfine, Maddux, & Grodsky, 2003). Anthocyanin-rich mulberry extract exerted oxidative stress on islet cells against hyperglycemia through AMPK/ACC/mTOR pathway (Yan & Zheng, 2017).

Anthocyanidins could improve insulin resistance by regulating blood lipid through reducing the levels of cholesterol, triglycerides, and low-density cholesterol and increasing the level of apolipoprotein and high-density cholesterol (Shi, Loftus, McAinch, & Su, 2017). Anthocyanidin-enriched bilberry extracts improved insulin resistance in KK-A^y mice, and reduced total cholesterol and triglycerides in liver and serum (Takikawa, Inoue, Horio, & Tsuda, 2010). Pro-inflammatory factors such as TNF-α and IL-6 were found associated with insulin resistance (Guo et al., 2012). Studies also shown that Cyanidin-3-glucoside inhibited 3T3-L1 cell adipocytes, activated insulin pathway via FoxO1, and inhibited TNF-α-mediated insulin resistance (Guo et al., 2012).

Anthocyanins promoted insulin secretion in many ways (Rosanska & Regulska-llow, 2011). Cyanidin-enriched purple potato extract promoted insulin secretion by upregulating the expression of intracellular Ca^{2+} signaling pathway and glucose transport-related gene (*Glut2*) in mouse islet beta cells (INS1) (Sun, Du, Navarre, & Zhu, 2018). Anthocyanidins (delphinidin 3-arabinoside) in fermented berry beverages regulated DPPIV and its substrate GLP-1, increased insulin secretion, and upregulated mRNA expression of insulin receptor-related genes (Johnson & Mejia, 2016). Delphinidin 3-rutinoside could induce GLP-1 release via a calcium-dependent kinase pathway (Kato, Tani, Terahara, & Tsuda, 2015).

4.7 | Stilbenoids

Dietary stilbenoids have shown antidiabetic activity in animal models and human studies. However, most data focused on resveratrol, pterostilbene, and polydatin. Other stilbenoids are rarely reported as antidiabetic agents. Resveratrol supplement improves metabolic control (Rašković et al., 2019), increases DNA integrity and sperm parameters (Bahmanzadeh, Goodarzi, Rezaei, Fathi, & Alizadeh, 2019), enhances insulin sensitivity (Sadi et al., 2015) and cardiovascular function (Yan, Sun, & Xu, 2018), prevents cognitive deficits by attenuating oxidative damage and inflammation (Gocmez et al., 2019), contributes hepatoprotective effects (Pektaş et al., 2016), alleviates testicular dys-

function (Faid, Al-Hussaini, & Kilarkaje, 2015), reduces oxidative stress (Bagul, Deepthi, Sultana, & Banerjee, 2015) and inflammatory response (Sadi et al., 2015), and protects pancreatic β-cell (Ku et al., 2012) in diabetic animals.

The antidiabetic action of resveratrol has several tissue targets: liver, skeletal muscle, and pancreas. In the liver, resveratrol modifies the activity of enzymes controlling glucose homeostasis. Indeed, it restores normal activity of enzymes that are altered in diabetic individuals. Thus, it reduces the activity of phosphoenolpyruvate carboxykinase, lactate dehydrogenase, and glucose-6-phosphatase (Palsamy & Subramanian, 2009) and increases the activity of hexokinase and pyruvate kinase. Moreover, resveratrol increases hepatic glycogen content by activating glycogen synthase and inhibiting glycogen phosphorylase (Palsamy & Subramanian, 2009). These changes lead to a reduction in hepatic glucose output.

Another important target of resveratrol is skeletal muscle, the main tissue responsible for glucose uptake in the body. In muscles, this compound increases the number of glucose transporter GLUT4 (Burges et al., 2011; Do et al., 2012), as well as their translocation to plasma membrane of myocyte (Deng, Hsieh, Huang, Lu, & Hung, 2008; Tan et al., 2012), via PI3K-Akt pathway (Chi et al., 2007), which leads to enhanced intracellular glucose transport. Moreover, it increases fatty acid oxidation, thus avoiding lipotoxicity that leads to insulin resistance (Chen et al., 2011).

As far as pancreas is concerned, resveratrol improves antioxidant defense in pancreatic tissue, because it enhances the activity of antioxidant enzymes (CAT, SOD, GPx, and glutathione-S-transferase) (Palsamy & Subramanian, 2010). Furthermore, this polyphenol is able to reverse degeneration in beta cells in diabetic rats and also to prevent beta cell apoptosis due to the inhibition of caspase-3. As a consequence, plasma insulin level increases.

Inflammation is also closely related to the onset and development of diabetes (Xu et al., 2003) and thus the anti-inflammatory effect of resveratrol is involved in glucose homeostasis improvement induced by this compound in diabetic subjects. In this context, it has been reported that resveratrol decreases the expression of transcription factor NF-κB, as well as pro-inflammatory cytokines (IL-1β and IL-6) in liver (Andrade et al., 2014).

Pterostilbene (*trans*-3,5-dimethoxy-4-hydroxystilbene) is a dimethoxyl derivative of resveratrol, which increases bioavailability because the presence of just one hydroxyl group (instead of three as in the case of resveratrol) in its chemical structure makes it to exhibit increased absorption and decreased phase II metabolism in intestine and liver. Pterostilbene showed antidiabetic activity via regulating glucose metabolism enzymes (Pari & Satheesh, 2006), inhibiting digestive enzymes (Zhao et al., 2019), protecting pancreatic β-cell (Bhakkiyalakshmi et al., 2014), contributing hepatoprotective activity (El-Sayed, Mansour, & Nady, 2015), enhancing antioxidant signaling pathways (Elango, Dornadula, Paulmurugan, & Ramkumar, 2016), ameliorating insulin sensitivity (Kosuru & Singh, 2017), and reducing oxidative stress (Kosuru & Singh, 2017; Kosuru et al., 2018). Piceatannol was found to promote glucose uptake and reduce the blood glucose levels in db/db mice (Minakawa, Miura, & Yagasaki, 2012; Uchida-Maruki et al., 2015). Polydatin ameliorates diabetic fibronectin (Xie et al., 2012) and cardiomyopathy (Zhang et al., 2017), improves glucose and lipid metabolism (Hao et al., 2014), and protects diabetic heart against ischemia-reperfusion injury (Yu et al., 2018). The structure–antidiabetic activity relationship of stilbenoids is not clear due to limited data.

The antidiabetic action of pterostilbene is due in part to the effects on enzymes involved in glucose and glycogen metabolism. This phenolic compound decreased the expression of hepatic glucose 6-phosphatase and fructose 1,6-biphosphatase, two gluconeogenic enzymes, and increased the expression of the glycolytic enzyme hexokinase in rats showing type 2 diabetes induced by streptozotocin and nicotinamide administration (Pari & Satheesh, 2006; Satheesh & Pari, 2006). In line with these results, Gómez-Zorita et al. (2015) showed that pterostilbene decreased insulin resistance index and decreased the activity of glucokinase in skeletal muscle from rats showing insulin resistance induced by high-fat high-fructose feeding. In addition, in this study rats treated with pterostilbene showed increased ratio phosphorylated-Akt/total Akt in skeletal muscle, indicating that GLUT4 could be more efficiently translocated to the surface membrane, and also increases in parameters related to fatty acid oxidation, showing thus a protection against lipotoxicity. Upregulation of GLUT4 by AMPK phosphorylation in skeletal muscle has also been observed in a clinical trial carried out in a cohort of diabetic subjects (Goh et al., 2014).

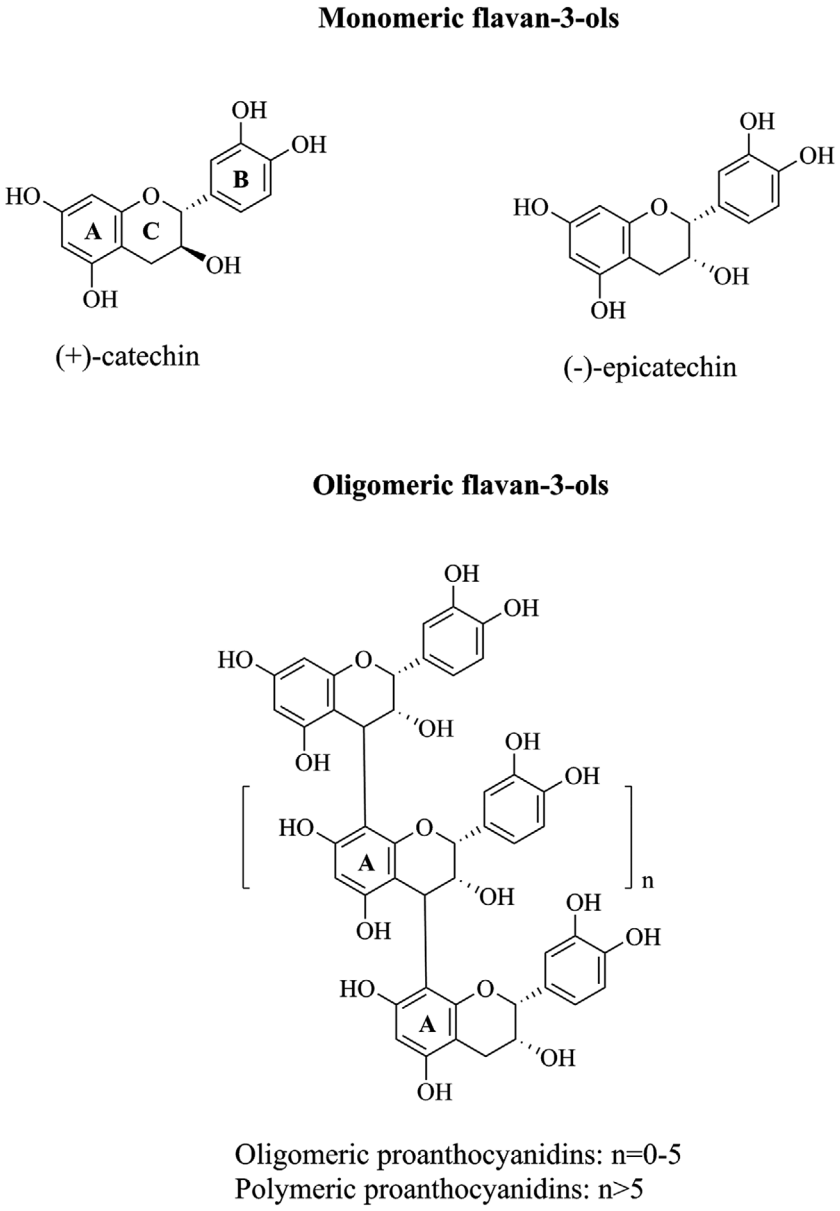
Another proposed mechanism for the antidiabetic effect of pterostilbene is it antioxidant activity. In fact, several studies have shown decreases in CAT, SOD, and GPx (Sun et al., 2019). Moreover, Bhakkiyalakshmi et al. (2014) showed a clear reduction in oxidative stress via the NF-E2-related factor 2 (Nrf2) downstream target genes, heme oxygenas-1, CAT, SOD, and GPx, and increased expression of anti-apoptotic protein, Bcl-2 as well as the downregulated of the pro-apoptotic proteins Bax and caspase-3, in pancreatic INS-1E cells. With regard to the inflammation, pterostilbene has shown interesting anti-inflammatory effects by inducing reductions in plasma pro-inflammatory cytokines, such as TNF-α, IL-6, and CRP (Sun et al., 2019).

Little information has been reported concerning piceatannol, a hydroxylated analog of resveratrol. The administration of piceatannol lowers blood glucose levels in *db/db* mice (Uchida-Maruki et al., 2015). Unfortunately, the authors did not analyze the mechanisms underlying the glucose-lowering effect of piceatannol. Skeletal muscle can be involve in the beneficial effects because Minakawa et al. (2012) observed that piceatannol increased the glucose uptake in L6 myotubes through promotion of GLUT4 translocation to plasma membrane via AMPK activation.

4.8 | Procyanidins

Procyanidins (PCs) are polyphenolic compounds that belong to the class of flavonoids and are oligomers of monomeric flavan-3-ols (+)-catechin and (-)-epicatechin (Gonzalez-Abuin et al., 2015) (Figure 7). The B-type PCs are formed by monomeric units linked to each other

FIGURE 7 Structure of procyanidins



by a single linkage (C4-C8 or C4-C6). Besides these single linkages, an additional ether bond can be present (C2-O-C7 or C2-O-C5), which is referred to as A-type. PCs are widespread in the plant kingdom. Well-known PC food sources are cocoa, cinnamon, apple, grape seeds, wine, and nuts, which possess anti-inflammatory and antioxidative effects related with the pathophysiology of insulin resistance and type 2 diabetes mellitus.

Animal studies provide a great opportunity to assess the contribution of physiological effects regarding PC consumption in different models of diabetes. In studies performed on rats fed a diet rich in fructose, procyanidins had a clear hypoglycemic effect (Cremonini, Bettaieb, Haj, Fraga, & Oteiza, 2016). Pinent, Cedo, Montagut, Blay, and Ardevol (2012) analyzed the effects of procyanidins based on the specific origin of each type of disruption in glucose homeostasis, and found that the mode of administration is important for efficacy, suggesting that PCs are more effective when administered in a single acute dose than when mixed with food, and that antihyperglycemic effects were more controversial in insulin resistance induced by high fat diets, compared to diets rich in fructose. In a study conducted on rats fed with a high-fat diet, Baiges, Palmfeldt, Bladé, Gregersen, and Arola (2010) assumed that the improvement in hyperglycemia was related to the effects of procyanidins that suppressed liver lipogenesis, which is a major player in the progress to insulin resistance, dependent on liver proteomics.

In a study aimed to clarify the effects of specific types of procyanidin oligomers in different cinnamon species, the results showed that two of the three samples of *Cinnamomum cassia* were rich in procyanidin type B and the other sample rich in procyanidin type A. Cinnamon extracts were given to mice with fat-rich diet and low-dose STZ induced diabetes for 14 days. Blood glucose concentrations decreased significantly in all cinnamon extract groups compared to the control group. These results suggest that both procyanidinic type A and type

B oligomers have hypoglycemic activity and can improve insulin sensitivity in type 2 diabetes. (Lu et al., 2011).

In another study investigating the effects of oral administration of PCs from apples on glucose metabolism using db/db diabetic mice, an improvement in glucose tolerance, insulin resistance, and hepatic gluconeogenesis was observed, by suppressing pro-inflammatory cytokine expression. It has been suggested that suppression of hepatic inflammation may be a mechanism with possible beneficial health effects in diseases with disrupted glucose metabolism. When *C. cassia* extract (CC-E) and *Cinnamomum tamala* extract (CT-E) rich in B- and A-type procyanidin oligomers were administered by gavage to diabetic db/db mice in a study conducted by Chen et al. (2012), it was observed that both CC-E and CT-E exhibited antidiabetic effects and that lipid accumulation in the adipose tissue and liver was inhibited by CC-E, whereas CT-E mainly improved seric and pancreatic insulin concentration.

A study on male mice explored the protective effects of procyanidin A2 against glucose homeostasis disturbance and gene expression of pancreatic and duodenal homebox 1 (Pdx1) as well as glucose transporter 2 (Glut2) induced by bisphenol A (BPA). The results showed that procyanidin A2 strongly prevents islet cells apoptosis and that co-administration of procyanidin A2 and BPA modified hyperglycemia. BPA reduced Pdx1, Glut2 mRNA expression, and antioxidant levels in pancreatic tissue, whereas procyanidin A2 prevented these effects. These findings suggest that use of plants rich in procyanidin A2 has preventive effects on T2D (Ahangarpour, Afshari, Mard, Khodadadi, & Hashemitabar, 2016). Another study, using dimeric and tetrameric PCs from black soybean seed coat extracts, focused on translocation of glucose transporter 4 (GLUT4), hypoglycemic effects, and underlying molecular mechanisms in skeletal muscle of mice. The hypoglycemic effects of procyanidins were compared with those of (-)-epicatechin and major the anthocyanin cyaniding 3-*O*-β-glucoside (C3G) monomer. The obtained results showed that the trimeric and tetrameric procyanidins activated both insulin and AMPK signaling pathways to induce the translocation of GLUT4 in mice skeletal muscle. It has been confirmed that procyanidins suppressed acute hyperglycemia induced by an oral glucose tolerance test in a dose-dependent manner. Among these beneficial effects, cinnamatin A2, one of tetramers, was most effective (Yamashita et al., 2016).

In diabetes, decreased levels of beta cell sirtuin SIRT1 could be a key step in the onset of beta cell dysfunction, occurring via abnormal elevation of ROS levels and amplification of beta cell IL1β synthesis. Aragones et al. (2016) demonstrated that proanthocyanidin (PAC) administration increased dose dependently the hepatic NAD^+ content and mRNA levels of genes involved in the pathway of NAD^+ biosynthesis in the livers of healthy rats. The concomitant activation of SIRT1 by PACs was the result of increasing both the cellular NAD^+ and SIRT1 concentrations. This represents an attractive strategy to increase beta cell activity in the future. The results of these animal studies show that the hypoglycemic effect of PCs and their benefits as antidiabetic agents are mediated by various mechanisms and by structure–activity relationship. Some mechanisms include insulin-mimetic effects on liver and peripheral tissues, as well as on beta cell function and/or mass. Procyanidins may also have complementary effects in collateral aspects related to diabetes (e.g., lipid accumulation and inflammatory profile).

Inhibition of is also an accepted strategy to prevent diabetes. PACs bind, precipitate, and inhibit enzymes in the digestive process, being potential bioDrugs. PAC degree of polymerization is responsible for differential inhibitory potency. Vazquez-Flores et al. (2018) used four semipurified fractions from *Carya illinoinensis* kernels rich in oligomeric and polymeric PACs, which showed different inhibitory activity against intestinal proteases, lipases, and amylases, as predicted by in silico methods. The authors conclude that small oligomeric PACs could be inhibitors of digestive enzymes due to their capacity to enter and bind to the enzymes' specific cavities and suggest that experimental testing of this hypothesis may have a major role in understanding health-related biological actions of PACs.

4.9 | Proanthocyanidins

In this scenario, numerous in vitro and in vivo studies have been performed to elucidate the antidiabetic mechanisms of proanthocyanidins, including reduction of carbohydrate digestion, modulation of hepatic glucose metabolism, protection of pancreatic β-cell function, and impact of skeletal muscle on glucose uptake. Proanthocyanidins have been reported to inhibit α-glycosidase, an enzyme that breaks down starch and disaccharides to glucose (Johnson, de Mejia, Fan, & Lila, 2013; Lee, Cho, Tanaka, & Yokozawa, 2007; Schafer & Hogger, 2007), thus reducing carbohydrate digestion and consequently, the availability of glucose for absorption in intestine. It has been suggested that this activity increases as the molecular weight of the polyphenol increases (Ma, Sato, Li, Nakamura, & Hattori, 2010). Some authors have also observed the inhibition of α-amylase, the enzyme that hydrolyzes the 1,4-glycosidic bonds in both amylose and amylopectin, but this result is controversial (Johnson et al., 2013).

As far as the modulation of hepatic glucose metabolism is concerned, proanthocyanidins increase glucose uptake and limit glucose output. It has been reported that these compounds increase hepatic glucokinase activity. This enzyme phosphorylates glucose to glucose-6-phosphate, thus facilitating the storage of glucose as glycogen and the disposal of glucose by glycolysis (Zhang et al., 2007). These polyphenols also decrease phosphoenolpyruvate carboxykinase, an enzyme that catalyzes an irreversible step of gluconeogenesis (Bang & Choung, 2014). Moreover, proanthocyanidins decrease glucose-6-phosphatase via activation of AMPK and PI3K/Akt pathways (Cordero-Herrera, Martin, Bravo, Goya, & Ramos, 2013; Kurimoto et al., 2013).

With regard to the effects on pancreatic β-cell function, proanthocyanidins are considered insulin secretagogues. Proanthocyanidins modulate pancreatic β-cell functions, such as prevention of oxidative stress, enhancement of insulin secretion, and promotion of β-cell survival (Yang & Chan, 2017). This ability to stimulate insulin secretion depends on several factors. One of them is the number of hydroxyl groups on their chemical structure; those compounds with higher number of hydroxyl groups are more effective (Chen et al., 2016). Another

important factor is the dose. Thus, in prolonged treatments, doses in the range of 25 mg/kg body weight are less effective than doses in the range of 15 mg/kg body weight. Ho, Kase, Wangensteen, and Barsett (2017) have demonstrated that proanthocyanidins stimulate glucose uptake in human myotubes in a range of concentrations of (0.1–10 μM). Unfortunately, in this study the exact mechanism explaining this effect (for instance the effect on GLUT1 and GLUT4 glucose transporters) was not addressed.

Specially, grape seed proanthocyanidins are benefits for diabetic complications through attenuating diabetic nephropathy (Gao et al., 2018), preventing early functional and morphological abnormalities in the peripheral nerves (Ding, Dai, Jiang, Zhang, & Li, 2014), ameliorating pancreatic β-cell dysfunction and death (Hu, Shi, Chen, Zou, & Li, 2018) and glycation-associated cardiac damage (Cheng et al., 2007), protecting against early diabetic peripheral neuropathy by modulating endoplasmic reticulum stress (Ding, Dai, Zhang, et al., 2014), and inhibiting oxidative stress-induced vascular impairment in pulmonary arteries in diabetic animals (Pinna, Morazzoni, & Sala, 2017).

4.10 | Tannins

Tannins are a heterogeneous group of water-soluble polyphenolic compounds of high molecular weight (500–3,000 Daltons) with 20 hydroxyl groups, present in plants, foods, and beverages. Tannins can delay intestinal glucose absorption and the onset of insulin-dependent diabetes mellitus by producing an insulin-like effect on insulin-sensitive tissues, which lowers glucose levels by regulating the antioxidant environment of pancreatic β-cells (Serrano, Puupponen-Pimiä, Dauer, Aura, & Saura-Calixto, 2009). Field bean, sweet potato, and amaranth leaves exhibit effective α-amylase inhibition activity. Amaranth leaves and sweet potatoes having the highest activity. Similarly, the tannin and ellagic acid derivatives from Banaba (*Lagerstroemia speciosa* L.) leaves have been reported to be potent inhibitors of α-amylase (Hosoyama, Sugimoto, Suzuki, Sakane, & Kakuda, 2003). Zhang and Kashket (1998) also identified tannins as the bioactive constituents in green and black teas responsible for inhibition of α-amylase.

Condensed tannins present in acetonic extract of food ingredients can significantly inhibit α-glucosidase. Finger millet, field bean, sweet potato, and drumstick leaves, which have the highest tannin content, are most effective inhibitors of α-glucosidase. Tannins have been reported to effectively inhibit intestinal α-glucosidase activity similar to synthetic inhibitors such as acarbose and voglibose, which are already being used therapeutically to control noninsulin-dependent diabetes mellitus (Matsui et al., 2007). A study of patients with noninsulin-dependent diabetes mellitus revealed that tannic acid and tannin-rich nonalcoholic compounds of red wine can reduce the serum glucose levels after starch-rich meals (Gin, Rigalleau, Caubet, Masquelier, & Aubertin, 1999).

Acacia polyphenols extracted from the bark of the black wattle tree (*Acacia meansii*) are rich in unique catechin-like flavan-3-ols, such as robinetinidol and fisetinidol. Acacia polyphenols showed the antiobesity/antidiabetic effects on obese diabetic KKAy mice (Ikarashi et al., 2011). Acacia polyphenols increased mRNA expression of adiponectin and decreased mRNA expression of TNF-α and PPARγ in white adipose tissue. Furthermore, Acacia polyphenols significantly reduced the mRNA expression of GLUT4 in skeletal muscle (Ikarashi et al., 2011).

Tannic acid has an insulin-like glucose transport stimulatory activity in adipocytes, whereas it exhibits "anti-insulin" activity in preadipocytes. The banaba extract without tannic acid did have glucose transport-stimulatory or adipocyte differentiation-inhibitory activity. It is possible that tannic acid regulates both activities through different targets and signaling pathways. Tannic acid did not induce any Insulin resistance-independent glucose transport, strongly supporting that tannic acid applied the insulin-mediated pathway(s) exclusively for glucose transport. Tannic acid stimulated phosphorylation of protein factors in the insulin-mediated glucose transport pathway (Liu et al., 2005).

A study on 36 diabetic Wistar rats revealed that a combination of hydrolysable tannin from Chinese natural gallnuts and condensed tannin from the bark of the black wattle tree (*Acacia mearnsii*) rich in gallotannins and catechins decreased the glycemic levels, which delayed carbohydrate digestion (Kato et al., 2017). The bark of *Cinnamomum zeylanicum* (a species of cinnamon) rich in tannins and flavonoids inhibited α-glucosidase and decreased glycemic levels on streptozotocin-induced diabetic rats due to chronic malabsorption of carbohydrates (Choudhury et al., 2018).

4.11 | Curcumin

In animal models, curcumin and extracts rich in curcumin postpone diabetes development, protect beta-cell, decrease insulin resistance, regulate lipid metabolism, reduce diabetic cardiomyopathy, attenuate testicular injury and oxidative stress (Jin et al., 2018; Pivari, Mingione, Brasacchio, & Soldati, 2019; Rashid, Chowdhury, Ghosh, & Sil, 2017; Zha et al., 2018), as well as ameliorate diabetic complications, such as liver disorders, adipocyte dysfunction, neuropathy, nephropathy, vascular diseases, and pancreatic disorders (Zhang, Fu, Gao, & Liu, 2013). Curcumin analogs with shortened central seven-carbon chain hardly show hypoglycemic effects but potentially helpful for alleviating diabetes complications, whereas curcumin analogs preserving this chain reserve the hypoglycemic effects. For example, tetrahydrocurcumin (Figure 8) exhibited stronger antidiabetic activity than that of curcumin in hypoglycemic effect, improving carbohydrate metabolism, ameliorating liver and kidney injury, and restoring antioxidant enzymes activity (Rivera-Mancia et al., 2015).

5 | HUMAN STUDY AND CLINICAL TRIALS

5.1 | Clinical and human data of polyphenols as antidiabetic agents

Despite an abundance of in vitro and in vivo evidence, there are very few clinical reports that demonstrate the effectiveness of polyphenols

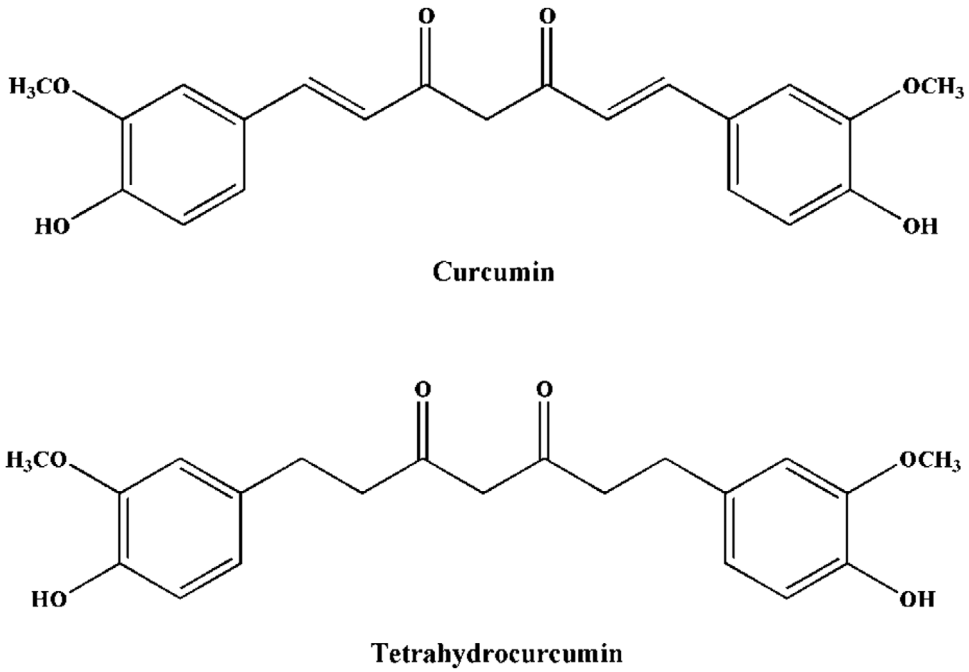


FIGURE 8 Chemical structure of curcumin and tetrahydrocurcumin

as a therapeutic agent against T2D. Here, we embark on randomized and concurrent clinical studies to evaluate the efficiency of polyphenols in management of diabetes to gain a better insight into its biological effects in humans.

Daily supplementation of 1,500 mg curcumin can decrease fasting blood glucose and weight and alleviate diabetic complications in type 2 diabetic patients in a randomized, double-blind clinical trial (Adibian et al., 2019; Hodaei, Adibian, Nikpayam, Hedayati, & Sohrab, 2019). A 9-month curcumin intervention prevents the prediabetes to develop T2D via improving overall function of β-cells (Chuengsamarn, Rattanamongkolgul, Luechapudiporn, Phisalaphong, & Jirawatnotai, 2012). Supplementation of both curcumin (1,000 mg/day) and piperine (10 mg/day) for 12-week period to 118 patients with T2D resulted in increased adiponectin and decreased leptin levels along with decreased inflammation.

Certain clinical studies have convincingly proved the antidiabetic effect of resveratrol; this could be resulting from improved glycemic control and insulin resistance. The first randomized clinical trial proved that resveratrol supplementation improves insulin sensitivity along with reduction of oxidative stress in T2D patients (Brasnyo et al., 2011). The effect of resveratrol administered at 1 g/day for a period of 45 days was beneficial for T2D patients, as they showed improved levels of fasting blood glucose, HbA1c, insulin, and systolic pressure (Movahed et al., 2013). Other clinical studies, however, reported contradicting results. Thazhath et al. (2016) conducted a randomized trial and supplemented resveratrol (500 mg) twice daily for 5 weeks to T2D patients, which revealed no significant improvement in glycemic control (Thazhath et al., 2016). In another placebo-controlled, double-blind, randomized trial, conducted in 2016, revealed that resveratrol treatment (500 mg/day) for 6 months did not improve metabolic parameters in T2D (Bo et al., 2016). Resveratrol may improve glycemic control (Bhatt, Thomas, & Nanjan, 2012) and neurovascular coupling and cognitive performance in T2D (Wong, Raederstorff, & Howe, 2016). Resveratrol supplementation does not improve hepatic or peripheral insulin sensitivity (Timmers et al., 2016), In patients with diet-controlled type 2 diabetes, 5 weeks of twice-daily 500-mg resveratrol supplementation had no effect on GLP-1 secretion, glycemic control, gastric emptying, body weight, or energy intake (Thazhath et al., 2016).

A randomized controlled trial conducted with 60 T2D patients administered green tea-extract powder daily for 2 months showed reduction in HbA1c level and diastolic blood pressure, whereas changes in body weight, systolic blood pressure, fasting blood glucose, HOMA index, and lipid levels were not observed (Fukino et al., 2008). In contrast, in clinical trial of T2D subjects administered with 1,500 mg of green tea, no significant changes in fasting HbA1C, blood glucose, and lipoproteins were observed (Hsu et al., 2011).

Berberine, an isoquinolien alkaloid of barberry, regulates carbohydrate and fat metabolism in vitro and in vivo. A meta-analysis of 14 clinical studies reported the effects of berberine to be like those of commercially available drugs such as glipizide, metformin, and rosiglitazone (Dong, Wang, Zhao, & Lu, 2012). Supplementation of berberine increased plasma antioxidant activity and lowered blood glucose and altered lipid profile in T2D patients. Yin, Xing, and Ye (2008) conducted a study in Chinese population with 36 newly diagnosed T2D with berberine supplementation (1.5 g/day) for a 3-month trial and proved its efficiency comparable to metformin. In the same study, berberine supplementation to 48 T2D patients at a dosage of 500 mg, thrice daily, for 3 months resulted in decrease in blood glucose levels within a week.

Clinical trials have investigated the impact of supplementation of quercetin, one of the most abundant flavanoids, on T2D subjects. Single oral dose (400 mg) of quercetin effectively suppressed postprandial blood glucose levels in patients with T2D loaded with maltose, which may be attributed to α-glucosidase inhibition (Hussain, Ahmed, Mahwi, & Aziz, 2012). Also, 100 mg of quercetin capsules each day for 49 patients for 10 weeks reduced cardiometabolic risks in male smokers and improved blood glucose, lipid profiles, and blood pressure in a clinical setup (Lee et al., 2011), whereas 47 T2D patients on diet supplemented with either quercetin (250 mg/d) or identical placebo (cellulose) capsules administered orally for 8 weeks showed no significant hypoglycemic and/or hypolipidemic effects (Zohreh, Seyedeh, Mohammad, & Abbas, 2014).

Anthocyanins exhibit antidiabetic property by reducing the levels of blood glucose and HbA1c, increasing the secretion of insulin, and improving insulin resistance. Liu et al. (2014) demonstrated that anthocyanins improved the endothelium-dependent vasodilation in diabetic individuals through the induction of adiponectin. Experimental studies have shown that cinnamon could be attributed to its beneficial effects on hyperlipidemia and glucose utilization. A clinical study with total of 60 T2D patients demonstrated that cinnamon supplementation (1–6 g/day) reduced the levels of blood glucose, serum triglyceride, and both Low density lipoprotein and total cholesterol in T2D patients (Khan, Safdar, Khan, Khattak, & Anderson, 2003).

Capsaicin is a polyphenol found in chili peppers reported for therapeutic uses in diseases such as diabetes, cardiovascular diseases, and cancer. In a clinical trial, supplementation of 5 g of *Capsicum frutescens* T2D patients resulted in a reduction in plasma glucose levels and maintenance of insulin levels (Chaiyasit et al., 2019).

5.2 | Clinical and human data of extracts or diet rich in polyphenols as antidiabetic agents

A randomized controlled trial found that a diet naturally rich in polyphenols improves glucose metabolism in individuals at high risk of diabetes (Bozzetto et al., 2015). A 4-week, double blind, randomized, placebo controlled trial involving 32 T2D patients showed that flavonoid-rich grape seed extracts significantly improved the biomarkers of inflammation, glycemia, and oxidative stress in the events of obese T2D subjects at high risk of cardiovascular (Kar, Laight, Rooprai, Shaw, & Cummings, 2009). A double-masked, randomized controlled trial found that the daily intake of flavanol-containing cocoa might improve the vascular function of medicated T2D patients (Balzer et al., 2008). A randomized, double-blind, placebo-controlled trial with 48 T2D patients revealed that a 12-week daily supplementation of Pycnogenol® (125 mg), a French maritime pine bark extract rich in procyanidins and bioflavonoids, could increase diabetes control, reduce cardiovascular disease risk factors, and lower antihypertensive medicine use vs controls (Zibadi, Rohdewald, Park, & Watson, 2008). In a double-blind, 8-week randomized controlled study involving in 80 T2D patients, Brazilian green propolis (226.8 mg/day) rich in polyphenols and flavonoids was found to prevent T2D patients from worsening developments in blood uric acid and estimated glomerular filtration rate (Fukuda et al., 2015). A randomized, double-blind, placebo-controlled trial (34 subjects) showed that the supplementation of acacia polyphenol (250 mg/day) might improve glucose homeostasis in nondiabetic subjects with impaired glucose tolerance (Ogawa, Matsumae, Kataoka, Yazaki, & Yamaguchi, 2013).

Coffee polyphenols can improve peripheral endothelial function following glucose loading in healthy male adults (Ochiai et al., 2014). Coffees with different contents of chlorogenic acids did not show different degrees of influence on glucose or insulin responses in healthy humans (Rakvaag & Dragsted, 2016). Red wine polyphenols were found to have a beneficial effect on insulin resistance and lipoprotein plasma concentrations in a randomized clinical trial involving 67 men with high cardiovascular risk (Chiva-Blanch et al., 2013). A whortleberry extracts rich in anthocyanins significantly lowered the levels of fasting blood glucose, 2-hr postprandial glucose, and HbA1c in a randomized, double-blind, placebo-controlled clinical trial, consisting of 37 T2D patients (Kianbakht, Abasi, & Dabaghian, 2013).

Supplements of high-polyphenol chocolate could protect against endothelial dysfunction and oxidative stress in T2D during acute transient hyperglycemia, as induced by a 75-g oral glucose challenge in a double-blinded randomized controlled crossover study (Mellor, Madden, Smith, Kilpatrick, & Atkin, 2013). Daily consumption of polyphenol-rich extra-virgin olive oil might improve metabolic control and the profile of circulating inflammatory adipokines in overweight T2D patients (Santangelo et al., 2016). The powdered dried leaves of *Eugenia punicifolia* (Kunth) DC. (Myrtaceae), rich in flavonol glycosides, are effective as an adjuvant to the treatment of T2D patients. In a pilot noncontrolled study, a 3-month treatment with powdered dried leaves of *E. punicifolia* was found to significantly reduce glycosylated hemoglobin and basal insulin levels (Sales et al., 2014). The aqueous extract (0.15% infusions) of *Bauhinia forficata* (L) subsp. pruinosa (Fabaceae), rich in rutin, could significantly reduce HbA1c concentration in diabetic and prediabetic volunteers ($n = 15$) (Toloza-Zambrano, Avello, & Fernandez, 2015). However, the onion extract did not show a hypoglycemic effect on healthy volunteers in an oral glucose tolerance test.

In summary, polyphenols from coffee, guava tea, whortleberry, olive oil, propolis, chocolate, red wine, grape seed, and cocoa have shown antidiabetic effects in T2D patients by increasing glucose metabolism, improving vascular function, and reducing insulin resistance and HbA1c.

6 | DIETARY POLYPHENOLS AND THE GUT MICROBIOME FOR DIABETES

The gut microbiota composition has been associated with several trademarks of chronic diseases (e.g., obesity, type 2 diabetes, cardiovascular diseases, and nonalcoholic steatohepatitis). Certain types of bacteria are linked with some diseases, whereas others are mainly important for our health (Everard & Cani, 2013). In recent years, gut microbiota has gained growing attention as a novel factor in the

management of diabetes. Several well-known researches indicated that the gut microbiota differed completely between type 2 diabetic patients and healthy people. Larsen et al. (2010), for instance, carried out studies on the differences between the composition of the intestinal microbiota in T2D patients and nondiabetic persons. They reported that the proportions of the phylum Firmicutes and the class Clostridia were significantly reduced, whereas *Betaproteo* bacteria, positively correlated with plasma glucose, was highly enriched in the feces of T2D patients compared with nondiabetic persons. Interestingly, food also affected the diversity of human gut microbiota. In accordance with the results, animal and clinical studies showed that dietary polyphenols and polyphenol-rich foods reduced the risk of T2D and/or its complications (Nie, Chen, Hu, Fan, & Nie, 2019). In addition, polyphenols and their microbial metabolites can effectively modulate the balance of gut microbiota, improving glucose metabolism (Cardona, Andrés-Lacueva, Tulipani, Tinahones, & Queipo-Ortuño, 2013).

Limited researches have examined the effect of dietary polyphenols on gut microbiota in diabetes. More recently, Lin et al. (2019) carried out studies on Green Macroalgae *Enteromorpha prolifera* (EPW) polyphenols in the modulation of intestinal microflora profiles in type 2 diabetic mice. They reported that EPW extract treatment significantly increased the relative abundance of *Akkermansia* and decreased the proportion of *Alistipes* and *Turicibacter*. Similarly, (Yan et al., 2019) investigated the antidiabetic activity of extract of green macroalgae EPW and its flavonoid-rich fraction less than 3 kDa (EPW3) in type 2 diabetic mice. They observed that EPW and EPW3 flavonoids significantly changed the gut microbiota flora with an increased proportion of *Bacteroidetes* and a reduced amount of the phylum *Firmicutes*. Furthermore, it also increased the abundances of *Lachnospiraceae NK4A136* group and *Alisties*, affecting the release of intestinal hormones for regulating insulin release. The antidiabetic activity of brown seaweed *Lessonia nigrescens* ethanolic extract (LNE), including phenolics and flavonoids, was investigated in type 2 diabetic mice fed with a high-sucrose/high-fat diet by (Zhao et al., 2018). They showed that the intake of LNE increased the growth of *Barnesiella*, *Helicobacter*, and *Turicibacter*, which were able to stimulate the host's antidiabetic effect, accompanied with the modification in the gene and protein expression of hepatic phosphatidylinositol 3-kinase and c-Jun N-terminal kinase.

It is worth noting that the difference apart from conventional treatments, a novel area of research for developing new strategies to tackle T2D using gut microbes is recognized. *Akkermansia* (reported to have effects on obesity, T2D, and gut inflammation) has recently been proposed as a new biomarker of intestinal health, indicating that the modulation of the *Akkermansia* may have beneficial effects on Type 2 diabetes (Blandino, Inturri, Lazzara, Di Rosa, & Malaguarnera, 2016; Delzenne, Cani, Everard, Neyrinck, & Bindels, 2015). Moreover, polyphenols were also found to positively regulate *Akkermansia* (Everard & Cani, 2013). For example, grape (Roopchand et al., 2015) and cranberry (Anhê et al., 2015) extracts rich in polyphenols were found to markedly increase the abundance of *Akkermansia*. Based on these findings, *Akkermansia* thwarts the deleterious increase in gluconeogenesis in diabetes, preventing the increase in glucose-6-phosphatase mRNA expression (Everard, Belzer, et al., 2013). Similarly, *Bifidobacteria* also potentially play protective role in preventing T2D. Some studies showed that polyphenols also promoted the growth of *Bifidobacteria* (Bialonska et al., 2010), for instance, it was also observed that the pomegranate extract enhanced the total growth of *Bifidobacterium* spp. and *Lactobacillus* spp. The authors suggested that pomegranate oligomers composed of gallic acid, ellagic acid, and glucose units may account for the enhanced growth of specific bacteria. Likewise, Vendrame et al. (2011) observed a significant increase in the amount of *Bifidobacterium* after the consumption of a wild blueberry drink, suggesting an important role of the polyphenol present in wild blueberries on the intestinal microbiota composition modulation. This association may be related to *Bifidobacteria*-restored gut barrier function and reduce gut epithelium permeability thus preventing the penetration of pathogenic organisms and inflammatory substances such as lipopolysaccharides. Hence, *Bifidobacteria* potentially plays a protective role in T2D (Klinder et al., 2016). In addition to *Akkermansia* and *Bifidobacteria*, *Faecalibacterium* might be beneficial in the treatment of diabetes (Blandino et al., 2016). For example, red wine polyphenols significantly changed the gut microbiota by increasing the number of fecal *Bifidobacteria* and *Lactobacillus* (intestinal barrier protectors) and butyrate-producing bacteria (*Faecalibacterium prausnitzii*) (Moreno-Indias et al., 2016). It could be related to the role of the short-chain fatty acids such as butyrate formed by this gut microbiota in the regulation of the levels of gut hormones such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1, which have important effects on carbohydrate metabolism (Moreno-Indias et al., 2016). Another study showed that the fecal samples of 174 healthy controls and 171 diabetic patients showed that diseased samples had lesser abundance of *F. prausnitzii*, butyrate-producing bacteria (Qin et al., 2012). In addition, the ratios of *Bacteroidetes* to *Firmicutes* significantly and positively correlated with reduced glucose tolerance (Larsen et al., 2010). Zhao, Chen, Yin, and Li (2017) showed that *L. nigrescens* ethanolic extract, rich in phenolics and flavonoids, had better glycemic control on type 2 diabetic mice, increasing the abundance of *Bacteroidetes* and reduced *Firmicutes* population in intestine.

Polyphenols and its degraded metabolites can also help ameliorate T2D. These components transformed by certain gut microbiota into secondary metabolites generally have greater absorption and bioactivity than their precursors (Nie et al., 2019). The microbial-derived flavonoid metabolites 3,4-dihydroxyphenylacetic acid and 3-hydroxyphenylpropionic acid may have antidiabetic potential by promoting survival and function of pancreatic β-cells (Fernández-Millán et al., 2014). Moreover, microbial metabolites of polyphenols might regulate the production of bile acids, which affect the host metabolism.

In short, studies have shown that there is a strong interaction between polyphenols and gut microbiota, which have the ability to protect against diabetes (Figure 9): first, polyphenols change the gut microbiota and promote growth of beneficial bacteria such as *Akkermansia*, *Bifidobacteria*, *Faecalibacterium prausnitzii*, and so on; second, not only polyphenols but also their microbial metabolites have greater bioactivity against diabetes; third, further studies are needed

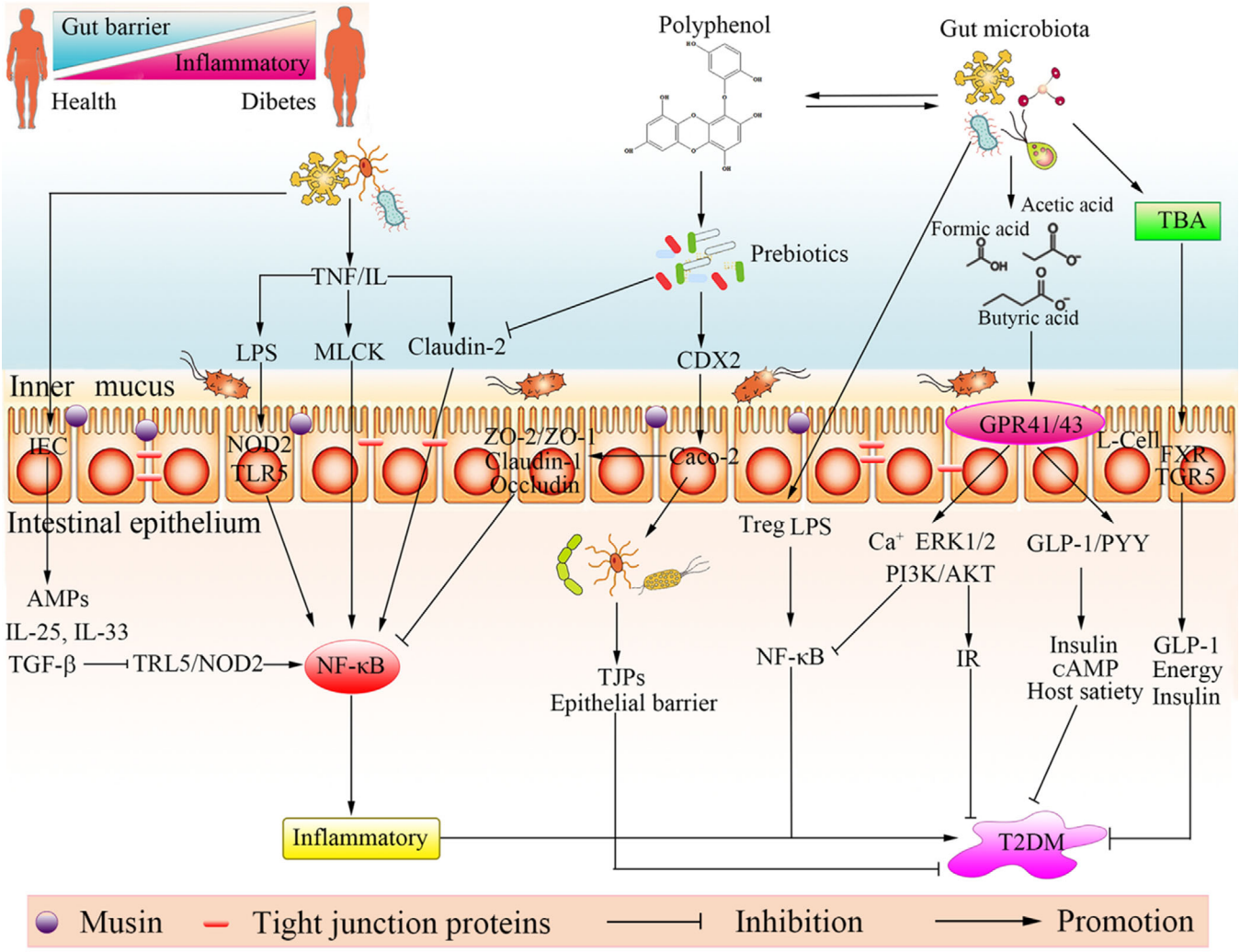


FIGURE 9 Effect of polyphenols and gut microbiota on diabetes

to clarify the role of polyphenols/their microbial metabolites in gut microbiota.

7 | DIABETIC STATUS INFLUENCES THE BIOAVAILABILITY OF DIETARY POLYPHENOLS

The hyperglycemic status could affect the bioavailability of small molecule drugs by regulating absorption, distribution, biotransformation, and excretion. The bioavailability between drugs and dietary polyphenols is different in dose per day, complexity of the components, and interaction with food. Dietary polyphenols are poorly absorbed, highly metabolized, or rapidly eliminated. Only about 5–10% of polyphenols can be absorbed, and over 90% of polyphenols digested pass to the colon. In contrast, clinical drugs are typically sufficiently absorbed and transported to their target tissues. The hyperglycemic status significantly affects the carbohydrate, protein, and lipid metabolism. The systems that regulate these biochemical pathways are also in many cases involved in phytochemicals biotransformation. Thus, the hyperglycemia obviously influences the bioavailability of dietary polyphenols. For example, compared with healthy animals, a significant increase of C_{max} and Area under curve of mangiferin, baicalin, wogonoside, and oroxyloside in diabetic animals was found (Xiao & Högger, 2015; Zhang et al., 2018). The bioavailability of phlorizin was significantly improved in type 2 diabetic rats (Wang et al., 2019). Absorption of cynaroside, quercetin, luteolin, isorhamnetin, rutin, and formononetin in the diabetic rats was significantly higher than those in the normal rat (Wei, Chen, Liu, & Wei, 2017). However, C_{max} values for catechin, epicatechin, quercetin, and resveratrol conjugated metabolites were diminished in Zucker diabetic fatty rat (Chen et al., 2017). The bioavailability of methylated flavan-3-ol, resveratrol, and quercetin metabolite was significantly lower in Zucker diabetic fatty rat (Chen et al., 2017). Moreover, very little progress for hyperglycemia-mediated changes in bioavailability of bioactive phytochemicals has been archived. An understanding of how hyperglycemia altering the bioavailability of dietary polyphenols will lead to improve the benefits and clinical outcomes of these phytochemicals.

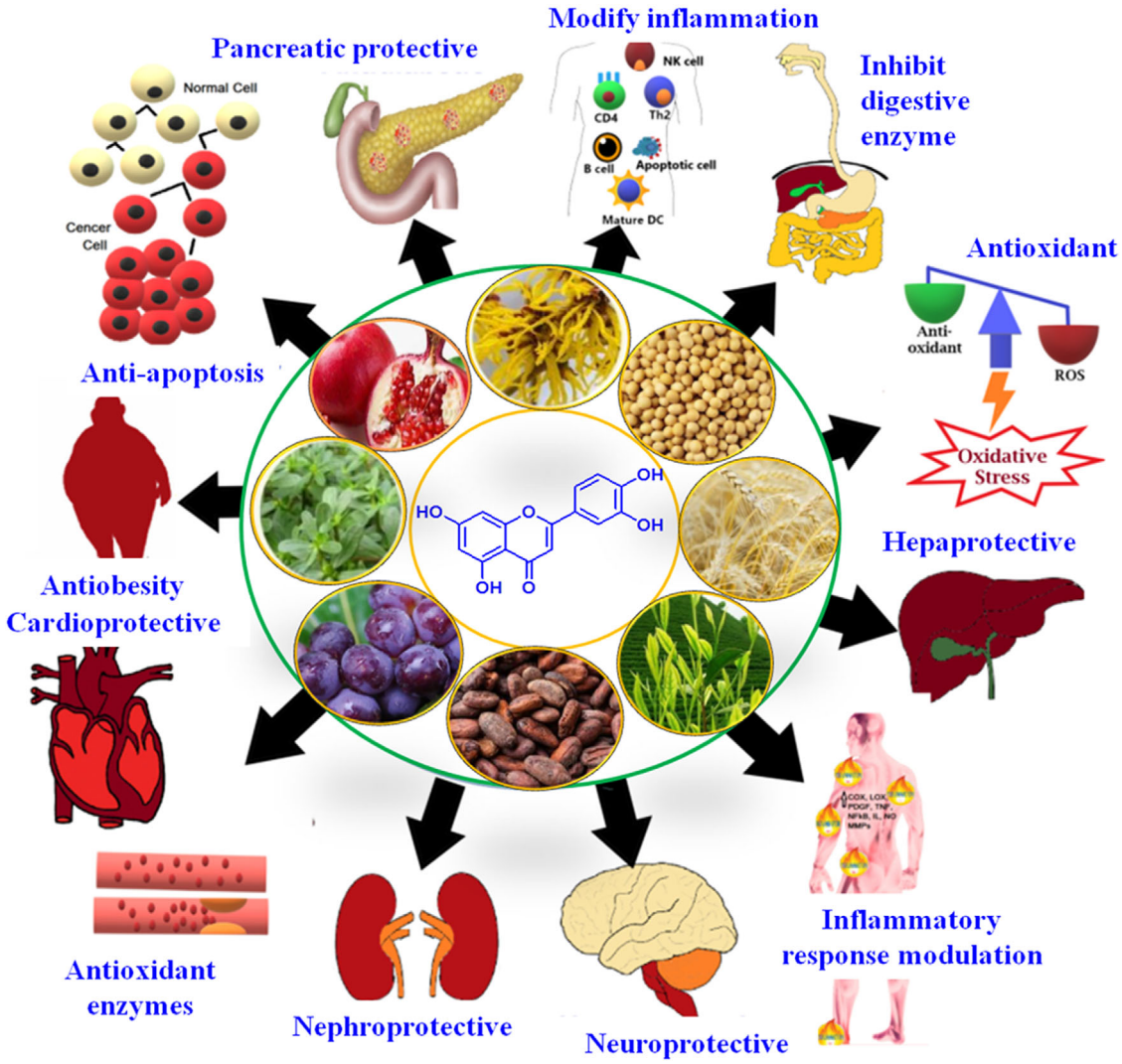


FIGURE 10 Antidiabetic effects of dietary polyphenols

8 | PERSPECTIVES

T2D is one of the most serious public health problems in the world. Nonpharmacological (reasonable diet and exercise) or pharmacological approaches (drugs or insulin) are known to control T2D. However, the pharmacotherapy for T2D is a considerable cost for patients and has serious side effects. The use of plants appears as an attractive alternative to the classical antidiabetic treatment. They contain complex substances with many natural bioactive principles that would have fewer side effects. Determining how these different plant-specialized metabolites and other dietary constituents interact in the human body is important. Are these effects additive, synergistic, or antagonistic with respect to antidiabetic treatment? Novel antidiabetic treatments must ensure products of consistent quality in enough quantities to improve the health of millions.

Dietary polyphenols are the most abundant phytochemicals in human diet and have attracted great interests since the 1990s due to growing evidence of their beneficial effects for humans. In animal level, dietary polyphenols prevent and manage T2D and ameliorates diabetic complications (Figure 10). The structure–activity relationship of polyphenols as antidiabetic agents is still not clear. Moreover, individual flavonoid or isoflavone has no therapeutic effect on diabetic patients, although the clinical data are very limited. Resveratrol, curcumin, and anthocyanins showed antidiabetic activity in humans. How T2D influences the bioavailability and bioactivity of dietary polyphenols is not well understood. An understanding of how diabetes alters the bioavailability and bioactivity of dietary polyphenols will lead to an improvement in their benefits and clinical outcomes.

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ORCID

Jesus Simal-Gandara https://orcid.org/0000-0001-9215-9737
Jianbo Xiao https://orcid.org/0000-0003-3311-770X

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