ROS

REVIEW ARTICLES

Role of Plant-Derived Polyphenols in Reducing Oxidative Stress-Mediated Diabetic Complications

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ABSTRACT | Diabetes is a prevalent systemic disease affecting a significant proportion of the population worldwide. There is growing scientific evidence in connecting oxidative stress with the pathogenesis and development of diabetes and its secondary complications. Therefore, it seems reasonable that molecules with antioxidant activities can play an important role in the improvement of diabetes. In recent years, research showed that plant-derived polyphenols, due to their various biological properties, could be effective for the treatment of diabetes and its associated complications. In this review, we discuss the role of oxidative stress in diabetes and examine the impact of some plant-derived polyphenols with antioxidant properties, in relation to the development and progression of the disease. Several in vitro and animal studies showed that dietary plant polyphenols could modulate carbohydrate and lipid metabolism, attenuate hyperglycemia, dyslipidemia, and insulin resistance, improve adipose tissue metabolism, and alleviate oxidative stress and stress-sensitive signaling pathways and inflammatory processes. Polyphenolic compounds can also prevent the development of long-term diabetes complications including cardiovascular disease, neuropathy, nephropathy, and retinopathy. However, further investigations via human clinical studies are needed before these polyphenolic compounds can be used as therapeutic agents for reducing oxidative stress-associated diabetic complications.

KEYWORDS | Diabetes; Oxidative stress; Plant-derived polyphenols; Reactive oxygen species; Secondary diabetic complications

ABBREVIATIONS | AGEs, advanced glycation end products; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, adenosine monophosphate-activated protein kinase; AP-1, activator protein 1; AR, aldose reductase; AST, aspartate aminotransferase; CAMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CAT, catalase; CCR6, chemokine receptor 6; Cdk-4, cyclin dependent kinase 4; CRP, C reactive protein; DAG, diacylglycerol; FFA, free fatty acid; FGF-2, fibroblast growth factor 2; FOXO-1, forkhead box protein O1; GCK, glucokinase; GLUT, glucose transporter; GPx, glutathione peroxidase; GST, glutathione S-transferase; Hb, hemoglobin; HbA1C, glycosylated hemoglobin; HSPGs, heparan sulfate proteoglycans; ICAM, intracellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MMP, metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; Ngn 3, neurogenin 3; NLRP-3, NOD-like receptor 3; NO, nitric oxide; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PARP, poly ADP-

ribose polymerase; PDX-1, pancreatic and duodenal homeobox 1; PKC, protein kinase C; PPAR-γ, peroxisome proliferator-activated receptor gamma; RAGE, receptor for advanced glycation end products; RNS, reactive nitrogen species; ROS, reactive oxygen species; SIRT 1, silent information regulator 1; SOD, superoxide dismutase; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor

CONTENTS

1. INTRODUCTION

The relationship between man and plant is as old as the history of mankind itself. Since antiquity, man has studied plants, particularly as a source of food and to ward off ailments. Plants have been used for medical treatments since the beginning of civilization. A lot of research work has been carried out on medicinal plants, and they have been found to have definite action on the nervous, circulatory, respiratory, digestive, and urinary systems, as well as the sexual organs, the skin, vision, hearing, and taste [1]. Thus, they have always been a very good source of drugs, and many of the currently available drugs have been derived directly or indirectly from them.

Diabetes mellitus (diabetes in short) is one of the common metabolic disorders afflicting around 2.8% of the world's population and has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and peripheral vascular disease) complications [2]. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides, and glinides. Many of them have a number of serious adverse effects; therefore, the search for more effective and safer hypoglycemic agents is one of the important areas of investigation [3]. Plant products provide the best option for this. The ethnobotanical information suggests that approximately 800 plant species have been reported to possess antidiabetic properties [4].

In this review article, an attempt has been made to discuss the current knowledge of the role of oxidative stress in the pathogenesis of diabetes and its complications. It also focuses on the effects of some of the plant-derived polyphenols in reducing oxidative stress-related complications in diabetes.

2. FREE RADICALS, OXIDATIVE STRESS, AND DIABETES

A free radical is any chemical species that contains one or more unpaired electrons in its outer shell [5]. These are formed from molecules via the breakage of a chemical bond such that each fragment keeps one electron, by cleavage of a radical to give another radical, and also via redox reactions [6]. When cells use oxygen to generate energy, free radicals are created as a consequence of adenosine triphosphate (ATP) production by the mitochondria. These are also produced from external sources like pollution, cigarette smoke, radiation, and medications, among others. [7]. Apart from these free radicals, some oxidants are also produced as by-products that can easily lead to free radical reactions in living organisms [8]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are more inclusive terms that describe both radical and non-radical oxidants. These ROS

and RNS play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. At low or moderate levels, ROS and RNS exert beneficial effects on cellular responses and immune functions. At high concentrations and when the cells cannot adequately destroy the excess of free radicals formed, they can damage normal tissue, generating a phenomenon called oxidative stress [7, 9].

Oxidative stress is defined as an imbalance between the formation and neutralization of ROS/RNS. It occurs when the production of reactive species in a biological system exceeds the system's ability to detoxify and eliminate them. The accumulation of free radicals leads to oxidative damage of the structural components (such as lipids, proteins, and DNA) of cells [7]. For example, hydroxyl radical and peroxynitrite in excess can damage cell membranes and lipoproteins by a process called lipid peroxidation. This reaction leads to the formation of malondialdehyde (MDA) and conjugated diene compounds, which are cytotoxic and mutagenic. Lipid peroxidation occurs by a radical chain reaction, i.e., once started, it spreads rapidly and affects a great number of lipid molecules [10]. Proteins may also be damaged by ROS/RNS, leading to structural changes and loss of enzyme activity [9]. Oxidative damage to DNA leads to the formation of different oxidative DNA lesions, which can cause mutations. Thus, if not regulated properly, oxidative stress can induce a variety of chronic and degenerative diseases as well as the aging process [7].

Diabetes is a chronic metabolic disorder affecting millions of individuals worldwide. Based on the World Health Organization (WHO) report, the number of diabetic patients is expected to increase from 171 million in year 2000 to 366 million or more by the year 2030 [11]. It is characterized by hyperglycemia, i.e., an increase in blood glucose level due to abnormal insulin secretion and/or resistance to insulin action or both affecting metabolism involving carbohydrates, proteins, and lipids [12]. Insulin is a hormone secreted from the β-cells of pancreas that causes a reduction of the blood glucose level by increasing the import of glucose by the cells. Hyperglycemia, due to uncontrolled glucose regulation, is considered as the causal link between diabetes and diabetic complications. Moreover, oxidative stress is also known to play a pivotal role in the development of diabetes [12]. An imbalance of oxidants/antioxidants in favor of oxidants contributes to the pathogenesis of diabetes. Hyperglycemia-induced autoxidation of glucose and glycation of proteins result in the formation of ROS and RNS which potentiate diabetes-related complications [13].

Diabetes is divided into two main types, type 1 and type 2. Type 1 diabetes occurs when the body stops making or makes only a tiny amount of insulin, whereas type 2 diabetes occurs when the body does not make enough or has trouble using the insulin. Type 1 diabetes has been linked mostly to genetics and the production of auto-antibodies that destroy the pancreatic β-cells [14]. Type 2 diabetes results primarily from insulin resistance and has been linked to factors such as obesity and age. Type 2 diabetes accounts for more than 90% of individuals diagnosed with diabetes [15].

3. DIABETIC COMPLICATIONS: LINK TO OXIDATIVE STRESS

Persistent hyperglycemia is known to be responsible for serious damage to various organs and tissues in diabetic subjects (**Figure 1**). The chronic complications of diabetes include retinopathy, nephropathy, neuropathy, and cardiovascular complications. Diabetic retinopathy is a retinal disease and the leading cause of severe visual impairment in adults, disabling nearly 5000 patients per year [16]. Diabetic nephropathy is one of the most common microvascular complications of type 1 and type 2 diabetes and is the largest single cause of end-stage renal failure worldwide [17]. Diabetic neuropathy is a complication of diabetes causing damage to the nerves [18]. Furthermore, cardiovascular complications such as coronary heart disease, peripheral arterial disease, hypertension, stroke, and cardiomyopathy, though not specific to diabetes, are more prevalent and severe in diabetics compared with the non-diabetic population [19].

According to recent studies, the development of various diabetic complications is primarily related to the increase in oxidative stress during diabetes [20]. The etiology of oxidative stress in diabetes arises from a variety of mechanisms such as excessive ROS production from autoxidation of glucose, glycated proteins, and glycation of antioxidative enzymes, which limit their capacity to detoxify the free radicals [13]. Pancreatic β-cells are especially sensitive

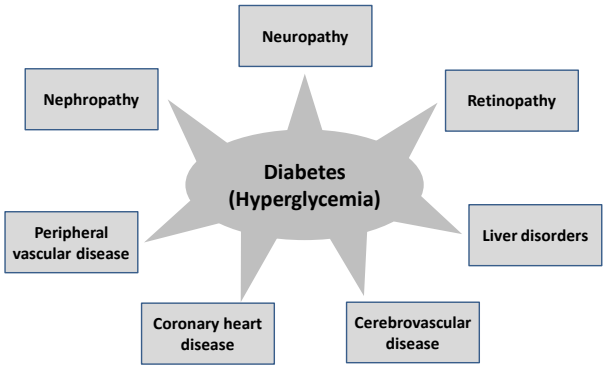

FIGURE 1. Secondary complications associated with diabetes. See text (Section 3) for more detailed description.

to ROS, because their natural enzymatic antioxidant defenses are lower compared to other tissues such as liver. Therefore, increase in ROS production leads to destruction of pancreatic β-cells and subsequent decrease in insulin secretion [21]. ROS also increase the stress signaling pathways in the β-cells, such as NF-κB activity, which potentially leads to β-cell apoptosis [22], and the JNK pathway which has been related to suppression of insulin gene expression. Development of diabetic complications is thought to occur via several other well studied mechanisms, including increased polyol pathway flux, increased intracellular formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), or overproduction of superoxide by the mitochondrial electron transport chain [23].

4. ANTIOXIDANTS AND PLANT POLYPHENOLS AGAINST DIABETES

The inhibition of intracellular free radical formation would provide a therapeutic strategy to prevent oxidative stress and the related diabetic complications. Antioxidants have been extensively investigated because of their ability to suppress oxidative stress by inhibiting the formation of ROS, scavenging free radicals, or increasing the antioxidants defense enzyme capabilities. Numerous studies have demonstrated that antioxidants like vitamin C, vitamin E, taurine, and supplements can help lower the markers indicative of oxidative stress and lipid peroxidation in diabetic subjects and animals [24–35]. Recently, there has been a considerable interest in finding natural antioxidants from plant materials to replace synthetic ones [36, 37]. Polyphenols are known as potent antioxidant phytochemicals due to their unique structures. Some experts believe that polyphenols, beyond the direct antioxidant capacities in scavenging of free radicals, also act by direct interactions with important cellular receptors or key signaling pathways, which may result in modification of the redox status of the cell and trigger a series of redox-dependent reactions [38]. In this section, we discuss some plant-derived polyphenols and their role in attenuating the oxidative stress-related diabetic complications.

4.1. Curcumin

Curcumin, chemically recognized as diferuloylmethane ($C_{21}H_{20}O_6$) (**Figure 2**), is the most active component of turmeric. The spice turmeric, which is derived from the root of the plant *Curcuma longa*, has been described as a treatment for diabetes in Ayurvedic and traditional Chinese medicine for thousands of years [39]. Recently, it has caught scientific attention as a potential antidiabetic agent for the treatment of diabetic complications. Srinivasan in 1972 first reported the blood glucose lowering effect of curcumin in one diabetic individual [40]. Since then many papers have been published to discuss the ability of this plant polyphenol in controlling blood glucose in various diabetic rat models. In alloxan-induced diabetic rats, streptozotocin (STZ)-induced rat models, and STZ-nicotinamide-induced rat models, oral administration of various dosages of curcumin were able to prevent body weight loss, reduce the levels of glucose, hemoglobin (Hb), and glycosylated hemoglobin (HbA1C) in blood, and improve insulin sensitivity [41–43]. It also offered a protective effect on pancreatic cells. Curcumin increased the islet viability and delayed islet ROS production, which is mediated through inhibiting poly ADP-ribose polymerase-1 (PARP-1) activation [44] and normalizing cytokine (TNFα, IL-1β, and interferon-γ)-induced NF-κB translocation. It also normalized glucose clearance by regulating pancreatic GLUT2 levels in STZ-treated mice [45]. Curcumin also enhanced recovery of pancreatic islets from cellular stress-induced inflammation and apoptosis in diabetic rats [46]. A very recent study showed the use of

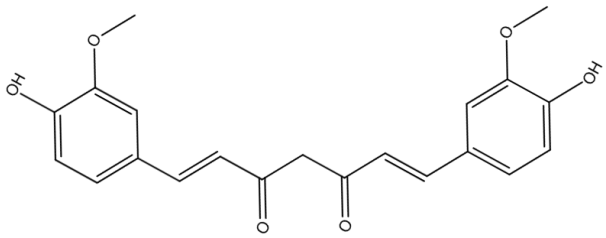

FIGURE 2. Structure of curcumin. Curcumin is chemically recognized as diferuloylme-thane.

nano-curcumin to prevent STZ-induced inflammation and apoptosis in pancreatic β-cells for effective management of type 1 diabetes [47].

Apart from lowering the blood glucose level, curcumin could also ameliorate the secondary complications that occur in diabetes. In diabetic nephropathy, curcumin has been found to attenuate both renal dysfunction and oxidative stress. It decreases the blood urea nitrogen and albuminuria and promotes clearance of creatinine and urea [48, 49]. A recent study demonstrated that curcumin exerts a renoprotective effect by inhibiting renal lipid accumulation and oxidative stress through adenosine monophosphate-activated protein kinase (AMPK) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathways [50]. Another study showed that it protects renal damage during diabetes by its antifibrotic property and by inhibiting NOD-like receptor 3 (NLRP3) inflammasome activity [51]. Curcumin, by virtue of its antioxidant and anti-inflammatory properties, also exhibited a neuroprotective effect as evidenced by alterations in MDA, total oxidant status, total antioxidant status, oxidative stress index, and NO levels in the brain and sciatic tissues of diabetic rats [52–54]. It has shown neurogenic and cognition-enhancing effects in aged diabetic rats through its antioxidant, antiapoptotic, and anti-inflammatory efficacies [55]. It regulates insulin pathways and glucose metabolism in the brains of APPswe/PS1dE9 double transgenic mice, a model for Alzheimer's disease. The study showed that curcumin ameliorated the defective insulin signaling pathway by upregulating insulin-like growth factor (IGF)-1R, IRS-2, PI3K, p-PI3K, Akt, and p-Akt protein expression while downregulating IR and IRS-1 and thus partly improved spatial learning and memory by increasing glucose metabolism in the brain [56]. Li et al. [57] demonstrated that curcumin attenuated diabetes-induced apoptosis in retinal neurons by reducing the glutamate level and downregulating the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). It also significantly inhibited the activation of NF-κB signaling induced by diabetes, and subsequently decreased the expression of VEGF, iNOS, and ICAM-1. These changes were associated with a decrease of diabetes-induced retinal vascular leakage [58]. In addition, curcumin administration suppresses collagen synthesis in the hearts of rats with experimental diabetes by inhibiting TGF-β1 production and canonical Smad signaling as well as by blocking the non-canonical AMPK/p38 MAPK pathway [59]. Another study reported that it suppressed accelerated accumulation of AGE collagen and cross-linking of collagen in the tail tendon and skin of diabetic rats. These effects were mediated by inhibition of VEGF, NF-κB, and AP-1 [60]. It has been also found that curcumin attenuates high glucose-induced neonatal rat cardiomyocyte apoptosis by inhibiting NADPH oxidase-mediated oxidative stress and this protective effect is most likely mediated by PI3K/Akt-related signaling pathway [61]. A recent study showed that curcumin inhibits angiogenesis in a STZ-induced diabetic rat model with an aortic ring assay [62]. Curcumin also offers a protective effect against various organs and tissue damage that could occur either directly or indirectly as a result of the persistence of hyperglycemia. It alleviates lung injury in diabetic rats by reducing oxidative stress level and inflammatory responses through inhibition of NF-κB activation [63]. It is also found to attenuate oxidative stress-induced NF-κB-mediated inflammation and endoplasmic reticulum-dependent apoptosis of splenocytes in diabetes [64]. Curcumin inhibits apoptosis and alleviates oxidative stress in testes of STZ-induced diabetic rats [65, 66]. It protects rat liver from STZ-induced diabetic pathophysiology by counteracting ROS and inhibiting the activation of p53 and MAPK-mediated stress response pathways [67].

In summary, the possible mechanisms of the antidiabetic effect of curcumin are multifactorial (**Figure 3**). It can decrease the levels of thiobarbituric acid reactive substances (TBARS) and inhibit lipid peroxidation and protein carbonyl formation, thereby decreasing the oxidative stress [68, 69]. Curcumin can also regulate insulin signaling and DAG-PKC-MAPK pathways. Moreover, it activates the enzymes

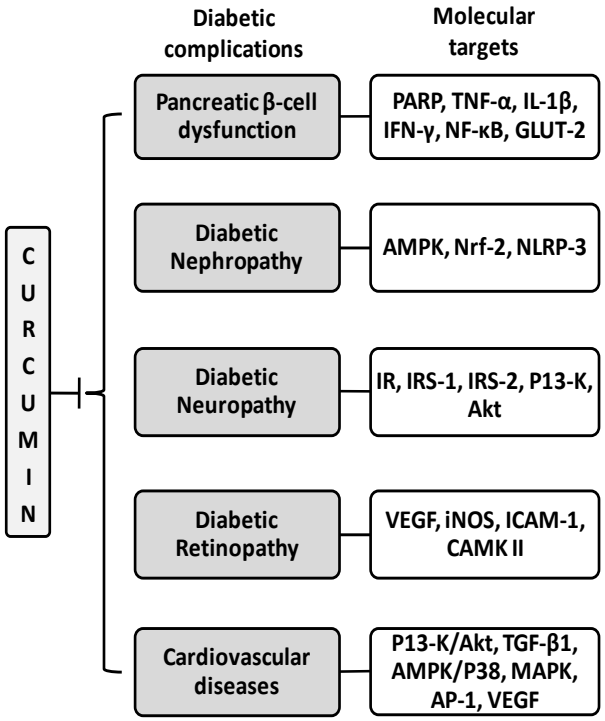

FIGURE 3. Schematic representation of the different molecular targets in diabetic complications modulated by curcumin. Curcumin is actively involved in treating diabetes and its complications, which include pancreatic β-cell dysfunction, nephropathy, neuropathy, retinopathy, and cardiovascular diseases. A number of mediators and factors have been involved in the modulation process. The figure represents the relevant molecular targets modulated by curcumin in the respective organ pathophysiology in diabetes.

of the liver, which are associated with glycolysis, gluconeogenic, and lipid metabolic process and thus help in glucose absorption and metabolism [70]. It has been found to inhibit the release of inflammatory cytokines like TNFα, IL-6, and IL-1β levels and decrease plasma free fatty acids (FFA) [71]. It also inhibits NF-κB activation and induces peroxisome proliferator-activated receptor gamma (PPAR-γ) and Nrf2 activation [72]. All these studies suggested the role of this plant polyphenol for the treatment of not only hyperglycemia but also the associated complications during diabetes.

4.2. Arjunolic Acid

Arjunolic acid (2,3,23-trihydroxyolean-12-en-28-oic acid; structure shown in **Figure 4**) is a naturally occurring chiral triterpenoid saponin which is used as a cardiac tonic in Ayurvedic medicine for centuries. It was first isolated from the bark of *Terminalia arjuna* (Roxb. ex DC.) [73], but later, it has been isolated from other plants also [74, 75]. Arjunolic acid is well known for its multifunctional therapeutic applications including its antidiabetic effect.

Manna et al. [76] have investigated the protective role of arjunolic acid against STZ-induced type 1 diabetes in the pancreatic tissue of Swiss-albino rats. STZ exposure caused the production of both ROS and RNS in the pancreatic tissue leading to pancreatic β-cell damage, reduced secretion of insulin, and development of type 1 diabetic pathophysiology. Formation of the above reactive intermediates also increased lipid peroxidation and protein carbonylation, with an accompanying decrease in intracellular antioxidant levels. The level of TNF-α was also found to be increased in STZ-induced diabetic rats. Treatment of animals with arjunolic acid (at a dose of 20 mg/kg body weight, orally) both prior to and after STZ administration effectively reduced these adverse effects by inhibiting excessive ROS and RNS formation [76]. Upon investigating the mode of action of this molecule, it has been observed that it downregulates the activation of phospho-ERK1/2, phospho-p38, NF-κB and mitochondrial dependent apoptotic cell death pathways [76]. It has also been found to be effective against STZ-induced diabetic nephropathy in rats [77]. It effectively ameliorates diabetic renal dysfunctions as evidenced by reduced kidney weight to body weight ratio, glomerular area, glomerular volume, blood urea nitrogen, and creatinine levels. It also inhibits the elevated ROS production in the glomeruli of diabetic animals along with reducing the lipid peroxidation, protein carbonylation, and altering the other antioxidant indices [77]. Polyol pathway is an alternative route of glucose metabolism in addition to the insulin-stimulated glucose metabolism pathway. Aldose reductase (AR) is an important enzyme of this signaling pathway and it catalyzes the NADPH-dependent reduction of glucose to sorbitol. Increased cellular sorbitol accumulation decreases the Na^+/K^+-ATPase activity leading to dysfunction of renal tubular re-absorption in diabetic nephropathy [78]. Arjunolic acid can deactivate the

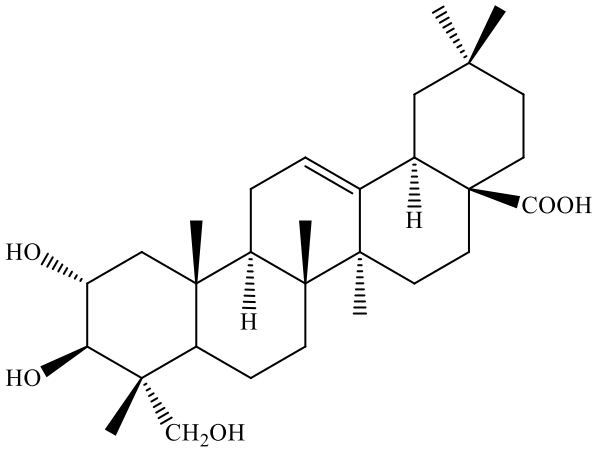

FIGURE 4. Structure of arjunolic acid. Arjunolic acid is chemically recognized as 2,3,23-trihydroxy-olean-12-en-28-oic acid.

polyol pathway by decreasing the activity of AR and increasing the activity of Na^+/K^+-ATPase. Arjunolic acid supplementation has been found to be effective in reducing the activation of PKCs (PKC δ and PKC ε) and MAPK family proteins (p38, ERK1/2, and JNK) as well as NF- κB (p65) which lead to the over production of the cytokine TNF-α, causing pathological changes related to diabetic nephropathy [77]. It also exhibits a protective effect against diabetes associated liver disorders by regulating the oxidative stress and its associated signaling pathways [79]. The association of hyperglycemia with an alteration of lipid profile presents a major risk for cardiovascular disease in diabetes [80]. Various inflammatory biomarkers such as C-reactive protein (CRP), sICAM, sE-selectin, sP-selectin, sCD40L, MCP-1, and VEGF [81, 82] are elevated in diabetic patients leading to vascular inflammation and cardiac dysfunction. Arjunolic acid has an antilipidemic effect preventing the alteration in plasma lipid profile in diabetes. It also reduces the elevated level of the vascular inflammation markers and prevents cardiac dysfunction associated with diabetes [83]. Arjunolic acid also exhibits a protective effect on STZ-induced activation of oxidative stress responsive splenic cell signaling pathways [84]. α-Glucosidase and α-amylase inhibitors are widely used in the treatment of patients with type 2 diabetes. Arjunolic acid isolated from the leaves of *Lagerstroemia speciosa* inhibits α-glucosidase and α-amylase to some extent [85, 86]. All these studies suggested that treatment with antioxidant supplements like arjunolic acid could prevent the development of diabetes and its associated pathophysiology (**Figure 5**).

4.3. Mangiferin

Mangiferin is a naturally occurring polyphenol of C-glycosylxanthone structure (**Figure 6**) with diverse pharmacological actions. While it is widely present in higher plants, mangiferin is found in higher concentrations in *Mangifera indica*, *Cyclopia*, and *Salacia* species. The presence of catechol moiety containing four hydroxyl groups makes mangiferin an efficient antioxidant and anti-free radical molecule [87]. Thus, it helps in combating many oxidative stress-related pathophysiological conditions including diabetes.

Oral administration of mangiferin in STZ-induced diabetic rats decreased blood glucose and increased plasma insulin levels [88]. It has been observed that mangiferin administration significantly increased the levels of SOD, CAT, and GPx and prevented cellular membrane damage by reducing lipid peroxidation in the hepatic and renal tissues of diabetic rats [88]. Several other parameters including urea, uric acid, creatinine, and enzymes like AST, ALT, and ALP were also significantly reduced after treatment with mangiferin [89]. Sellamuthu et al. [90] demonstrated that mangiferin from *Salacia chinensis* prevented oxidative stress and protected pancreatic β-cells in STZ-induced diabetic rats. The electron microscopic study revealed damaged nuclear envelope and mitochondria and fewer secretory granules in pancreas of diabetic rats and mangiferin treatment nearly normalized pancreatic architecture [90]. Another study showed the therapeutic effect of this molecule by the regeneration of β-cells in adult C57BL/6J mice following 70% partial pancreatectomy [91]. Mangiferin-treated mice exhibited an improved glycemia and glucose tolerance, increased serum insulin levels, enhanced β-cell hyperplasia, elevated β-cell proliferation, and reduced β-cell apoptosis. Further dissection at the molecular level showed several key regulators of cell cycle, such as cyclins D1 and D2 and cyclin-dependent kinase 4 (Cdk4) were significantly upregulated in mangiferin-treated mice. In addition, critical genes related to β-cell regeneration, such as pancreatic and duodenal homeobox 1 (PDX-

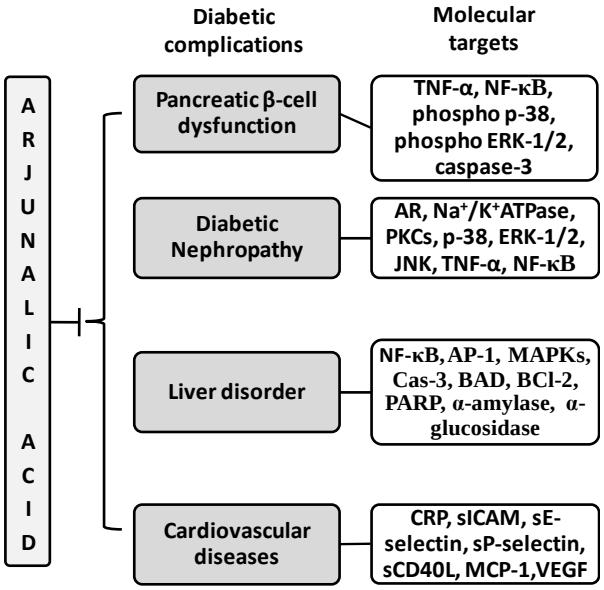

FIGURE 5. Schematic representation of the different molecular targets in diabetic complications modulated by arjunolic acid. Arjunolic acid is actively involved in treating diabetes and its complications, which include pancreatic β-cell dysfunction, nephropathy, liver disorders, and cardiovascular diseases. A number of mediators and factors have been involved in the modulation process. The figure represents the relevant molecular targets modulated by arjunolic acid in the respective organ pathophysiology in diabetes.

1), neurogenin 3 (Ngn3), GLUT-2, forkhead box protein O1 (FOXO-1), and glucokinase (GCK), were found to be promoted by mangiferin at both the mRNA and protein expression level [91]. Mangiferin also promotes glucose utilization by increasing its cellular uptake. It has been shown that *Salacia oblonga* extract, whose main active component is mangiferin, increased glucose uptake by 50% in rat myotubes [92] and 3T3-L1 adipocytes [93]. At 1 mM, mangiferin increased glucose utilization by two fold in 3T3-L1 cell lines compared to untreated controls [93]. The increased cellular uptake of glucose is attributed to the enhanced surface expression of GLUT4 transporters [92]. Periyar et al. have demonstrated that in STZ-induced diabetic mice mangiferin treatment increased the activity of glycolytic and glycogen synthesis pathways, while decreased gluconeogenesis [94]. Mangiferin has also been shown to reduce glucose absorption through its inhibitory effect on α-glucosidase enzymes in experimental rats [95]. Chronic treatment with mangiferin significantly ameliorated renal dysfunction in diabetic rats, as evidenced by decrease in kidney damage markers like albuminuria and blood urea nitrogen. Moreover, mangiferin treatment caused substantial increases in glyoxysylase-1 enzymatic activity and glutathione levels, and reduced the levels of AGEs, lowered lipid peroxidation, and reduced MDA in the kidney of diabetic rats [96]. Li et al. [97] demonstrated that mangiferin could significantly prevent progression of diabetic nephropathy and improve renal function. It was also observed that serum AGE level, MDA level, sorbitol concentration of red blood cells, and 24-h albuminuria excretion were significantly decreased, whereas the activity of serum SOD and GPx and creatinine clearance rate were increased by mangiferin. Mangiferin significantly inhibited glomerular extracellular matrix expansion and accumulation and TGF-β 1 overexpression in glomeruli of diabetic nephropathy rats. Moreover, it inhibited proliferation of mesangial cells induced by high glucose and the overexpression of collagen type IV of mesangial cells induced by advanced glycation end products [97]. It also inhibited oxidative stress mediated signaling cascades like PKCs (PKCα, PKCβ and PKCε) and MAPKs (p38, JNK, and ERK1/2) and mitochondria-dependent apoptotic pathways in STZ-induced diabetic rats, thereby attenuating diabetic nephropathy [98]. Zhu et al. showed that mangiferin prevented the renal glomerulus fibrosis of diabetic rats through the suppression of osteopontin overproduction and inflammation via inactivation of NF-κB [99]. Mangiferin was also found to be efficient in ameliorating diabetic cardiomyopathy. Very recently, Suchal et al. [100] showed that it attenuated myocardial ischemia-reperfusion injury in STZ-induced diabetic rats by modulation of AGE-RAGE/MAPK pathways which further prevented oxidative stress, inflammation, and apoptosis in the myocardium. Another study showed that mangiferin could significantly ameliorate diabetic cardiomyopathy by preventing the release of inflammatory cytokines, and inhibiting ROS accumulation, AGE/RAGE production, and NF-κB nuclear translocation in high fat diet-diabetic cardiomyopathy rats [101]. It can also mitigate diabetic cardiomyopathy by regulating matrix metalloproteinase-2 (MMP-2) and MMP-9 expression [102].

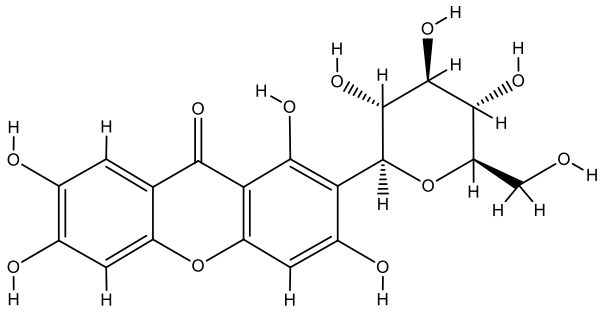

FIGURE 6. Structure of mangiferin. Mangiferin is chemically recognized as 1,3,6,7-tetrahydroxyxanthone C2-β-D-glucoside.

Mangiferin can also markedly ameliorate diabetes-associated cognitive decline in rats, which occurs likely through suppressing methylglyoxal hyperactivity that promotes protein glycation, oxidative stress, and inflammation [103]. Studies showed that it could attenuate diabetes-associated cognitive impairment of rats by enhancing the function of glyoxalase 1 (Glo-1) in the brain through activation of Nrf2/ARE signaling in central neurons cultured with high glucose [104]. Therefore, magniferin can be used as a potential therapeutic molecule for attenuating not only diabetes but also its associated complications (**Figure 7**).

4.4. Resveratrol

Resveratrol (3,4′,5- trihydroxy-trans-stilbene) (structure shown in **Figure 8**) is a naturally existing polyphenol phytoalexin originally isolated from the roots of white hellebore [105] and later found in *Polygonum cuspidatum*, grapes, peanuts, and berries as well as in their manufactured products, especially red wine [106]. However, the content of resveratrol in *P. cuspidatum* is much higher than that in grapes and other plants [107]. It exists in both cis- and trans-configurations, of which trans-resveratrol is the principal biologically active form [108]. Resveratrol is known for its extensive biological and pharmacological effects including antidiabetic activities.

The anti-diabetic properties of resveratrol have been extensively studied in various animal models. It can lower the blood glucose level in rats with diabetes induced by STZ alone [109–115] and STZ with nicotinamide [116–119]. Some studies also revealed that administration of resveratrol to diabetic rats resulted in diminished levels of HbA1C, which reflects the prolonged reduction of glycemia [116, 118]. The blood glucose-lowering effect of resveratrol is associated with the rise in blood insulin levels. Since pancreatic β-cells are the only source of insulin, this strongly suggests that resveratrol is capable of protecting these cells. The protective action of resveratrol on pancreatic tissue of type 1 diabetic animals has been demonstrated to be partially related to the antioxidant activity of this compound. It improves antioxidant defense in pancreatic tissue, i.e., increases activities of antioxidant enzymes (SOD, CAT, GPx, and GST) and protects cells from free radical damage [118]. Resveratrol was also found to reverse the degenerative changes in the β-cells of STZ-nicotinamide-induced diabetic rats [118] and to prevent STZ-induced β-cell apoptosis. The decrease in apoptosis is accompanied by blocking the activity of caspase-3 and inhibition of PARP cleavage [113]. It also attenuates autoimmune destruction of these cells as demonstrated in non-obese diabetic mice [120]. It has been observed that it increased total islet number, number of insulitis free islets, and improved general islet condition by downregulating chemokine receptor 6 (CCR6) expressions on multiple inflammatory cell types and blocking the migration of pathogenic cells to the pancreas [120]. Another important aspect of resveratrol action is its influence on skeletal muscle. It was demonstrated that skeletal muscle dysfunction in animals with type 1 diabetes is mitigated by resveratrol [109, 121, 122] via different mechanisms. It is known that this compound stimulates mitochondrial biogenesis and improves fatty acid metabolism in muscles of diabetic animals. Moreover, resveratrol decreases expression of NF-κB and pro-inflammatory cytokines (IL-1β and IL-6) in muscle cells [122] and thereby exerts anti-inflammatory effects. Recent research also indicates that resveratrol decreases oxidative stress in skeletal muscle of animals with insulin-deficient diabetes [121]. In addition, beneficial effects of resveratrol in skeletal muscle of diabetic animals are associated with increased GLUT4 expression [109] and with increased intracellular glucose transport [123]. It is also known that effects of resveratrol in muscle cells of diabetic animals are mediated via PI3K-Akt pathway [109, 121]. In the muscular tissue of diabetic rats, resveratrol was demonstrated to increase Akt

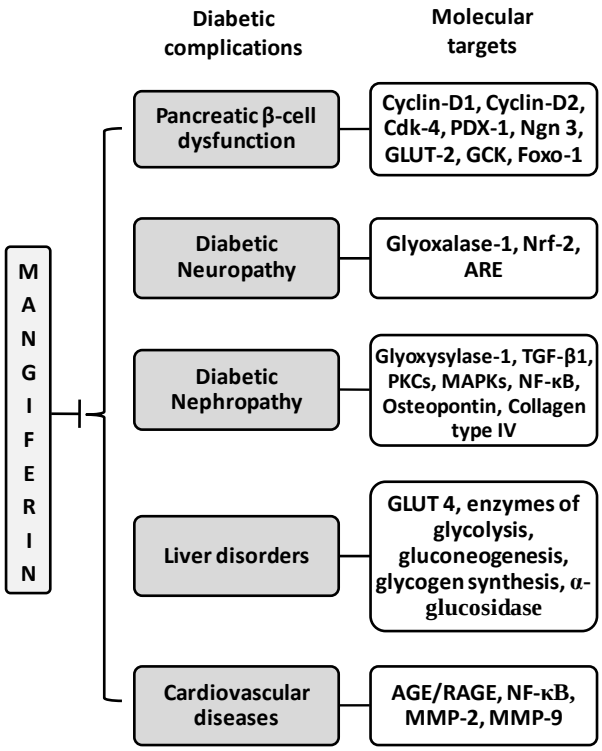

FIGURE 7. Schematic representation of the different molecular targets in diabetic complications modulated by mangiferin. Mangiferin is actively involved in treating diabetes and its complications, which include pancreatic β-cell dysfunction, nephropathy, neuropathy, liver disorders, and cardiovascular diseases. A number of mediators and factors have been involved in the modulation process. The figure represents the relevant molecular targets modulated by mangiferin in the respective organ pathophysiology in diabetes.

phosphorylation and this effect was dependent on PI3K [109, 121]. Apart from changes in skeletal muscle, resveratrol was also found to beneficially affect the liver of diabetic animals. It decreases the activities of key enzymes of gluconeogenesis, lactate dehydrogenase, and glucose-6-phosphatase and increases the activities of hexokinase and pyruvate kinase [117]. Moreover, resveratrol increases glycogen synthase, decreases glycogen phosphorylase, and increases liver glycogen content [117]. These changes lead to the shifting of the metabolic pathways toward reduced hepatic glucose output. Resveratrol-induced hepatoprotection also results from improvement in the antioxidant defense mechanisms and anti-inflammatory effects. It increases the activity of antioxidant enzymes [114, 124] and decreases NF-κB and IL-1β contents in the liver of diabetic rats [114]. Numerous studies have demonstrated that resveratrol improves insulin action in animals with experimentally induced insulin resistance, a characteristic for type 2 diabetic patients. This effect was noticed in mice on a high-fat diet [125–128], in rats on a high cholesterol-fructose diet [123], and in obese Zucker rats [129]. Resveratrol-induced increase in intracellular glucose transport in insulin-resistant animals results from two events related to GLUT4. It is known that resveratrol enhances GLUT4 translocation to the plasma membrane of muscle cells [123, 130], and also increases GLUT4 expression in skeletal muscle of animals with diet-induced insulin resistance [131] and in db/db mice [132]. It ameliorates insulin resistance in skeletal muscle via various mechanisms, including changes in metabolism and lipid accumulation. Beneficial effects of resveratrol in muscle tissue of insulin-resistant rodents are strongly related to changes in the activities and/or expression of two intracellular regulators, silent information regulator 1(SIRT1) and AMPK. SIRT1 is an NAD^+-dependent histone deacetylase involved in the regulation of many processes, such as mitochondrial biogenesis, inflammation, intracellular metabolism, stress resistance, apoptosis, glucose homeostasis, and others. It is thought that SIRT1 activity/expression is reduced in type 2 diabetic patients, and this enzyme is being considered as a target for antidiabetic drugs [133, 134]. Resveratrol is known to activate SIRT1 in mammalian tissues [135]. Very recently, Yonamine et al. [136] showed that resveratrol improves glycemic control in type 2 diabetes which involves an increase in muscle Slc2a4/GLUT4 and a decrease in liver Slc2a2/GLUT2 expression by increasing SIRT1 nuclear content. Apart from SIRT1, AMPK is another enzyme involved in resveratrol action. Decreased AMPK activity occurs in animal models of diet-induced insulin resistance [137] and in insulin resistance determined genetically [129]. Resveratrol activates AMPK in insulin-resistant animals. Resveratrol can also ameliorate diabetic cardiomyopathy in rats through regulation of mitochondrial function, which is mediated partly through SIRT1 activation and increased PGC-1α deacetylation [138]. Resveratrol has been reported to have potent anti-

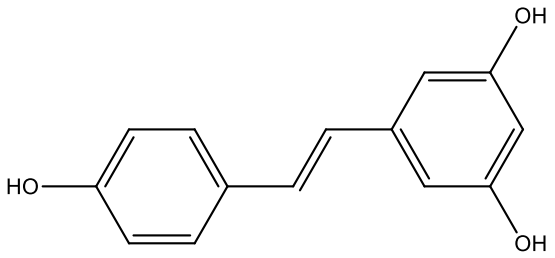

FIGURE 8. Structure of resveratrol. Resveratrol is chemically recognized as 3,4′,5-trihydroxy-trans-stilbene.

atherosclerotic effects as well [139]. Savi et al. [140] showed that resveratrol treatment inhibited pro-inflammatory cytokine production, leading to a recovery of cardiomyocyte contractile efficiency and reduced inflammatory cell recruitment. It can prevent endothelial dysfunction and reduce diabetic vascular complications and the risk of cardiovascular diseases via activating proteasome-dependent degradation of PTEN, which increases Akt phosphorylation, consequentially upregulating eNOS-derived NO production. [141]. Another study showed that resveratrol negatively modulated the expression of fibroblast growth factor 2 (FGF2) and its co-receptors, heparan sulfate proteoglycans (HSPGs: glypican-1 and syndecan-4) in cardiac muscle of type 2 diabetic rats, thus improving cardiac dysfunction in diabetes [142]. It has been found to have a therapeutic potential against diabetic cardiomyopathy by inhibiting apoptosis of neonatal rat ventricular myocytes via the PI3K/Akt/FOXO3a pathway [143]. Resveratrol has also been shown to have a renoprotective effect against diabetic nephropathy and this activity is via inhibition of the p38 MAPK/TGF-β1 signaling pathway [144]. It can modulate the SIRT1/FOXO3a pathway by increasing SIRT1 deacetylase activity as well, subsequently ameliorating hyperglycemia-induced renal tubular oxidative stress damage [145]. Resveratrol also significantly ameliorates cognitive decline in STZ-induced diabetic rats. The potential mechanism underlying the above protective effect could be attributed to the inhibition of hippocampal apoptosis through the Bcl-2, Bax and caspase-3 signaling pathways and improvement of synaptic dysfunction [146]. Very recently, Zhang et al. showed inhibition of intestinal α-glucosidase activity by

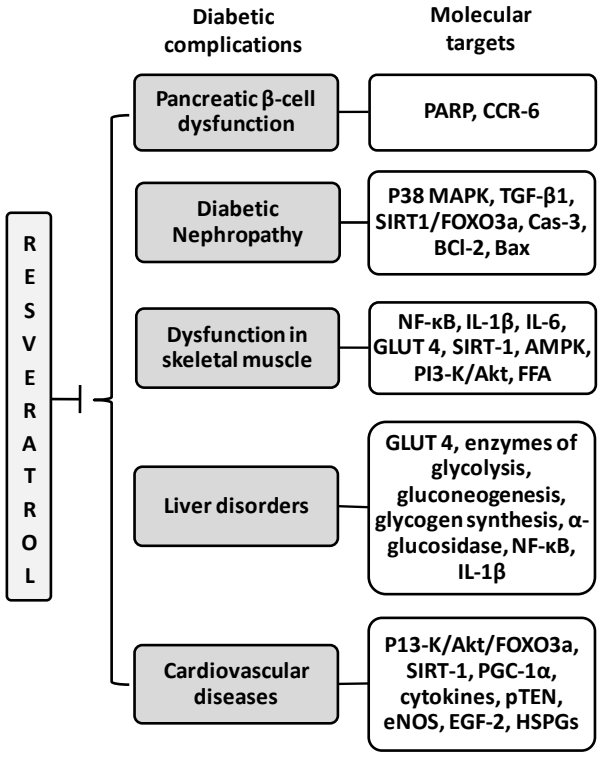

FIGURE 9. Schematic representation of the different molecular targets in diabetic complications modulated by resveratrol. Resveratrol is actively involved in treating diabetes and its complications, which include pancreatic β-cell dysfunction, nephropathy, skeletal muscle dysfunction, liver disorders, and cardiovascular diseases. A number of mediators and factors have been involved in the modulation process. The figure represents the relevant molecular targets modulated by resveratrol in the respective organ pathophysiology in diabetes.

resveratrol which may be a potential mechanism contributing to its antidiabetic property [147]. All these results indicate that resveratrol is not only capable of controlling the blood sugar level, but also attenuates the secondary complications associated with diabetes (**Figure 9**).

5. CONCLUSION

The rising trend in the prevalence of diabetic complications suggests that current medical treatments

for the management of diabetes are not sufficient and use of plant-based non-toxic supplementary treatments could increase the effectiveness of diabetes management. This review has discussed the role of different plant polyphenols in combating oxidative stress-related diabetic complications based on various in vitro and in vivo studies. The actual antidiabetic prospective associated with these molecules is usually large as a result of their modulatory effects on various signaling pathways, ultimately enhancing insulin secretion, reducing apoptosis and promoting proliferation of pancreatic β-cells, reducing insulin resistance, and attenuating inflammation and oxidative stress in different tissues. However, further investigations via human clinical studies are needed to confirm the beneficial effects of these polyphenolic compounds to treat diabetes and its complications.

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