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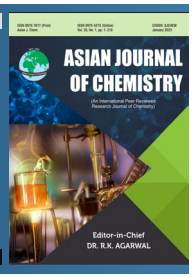

REVIEW

Flavonoids and their Role in the Remedy of Diabetes Mellitus: A Review

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The impact of diabetes mellitus on the health care system is significant due to its global prevalence affecting millions of individuals. This condition is commonly related with factors such as obesity, urbanization, and genetic alterations. Those with diabetes mellitus have elevated blood glucose levels because an inability to produce, secrete or bind to insulin causes a lowering of insulin levels. Flavonoids are phenolic compounds found in fruits, vegetables and fungi. Carbon atoms are comprised of 15 chains of three carbon atoms in a skeleton. The anthocyanidin family includes flavonoids, flavones, flavanones, isoflavones, flavanols and flavonoids. In addition to their antidiabetic properties, flavonoids also have antioxidant properties. Molecular mechanisms underlying the antidiabetic properties of dietary flavonoids are summarized in this review. Other natural compounds with antidiabetic properties include cosmosiin, didymin, diosmin, naringin, isosiennsetin, nobiletin, poncirin, quercetin, rhoifolin, sinensetin, naringenin, sudachitin, rutin, hesperidin and tangeretin, which also improve lipid and phospholipid metabolism. The progression of diabetes is influenced by diabetes biomarkers. Citrus flavonoids are therefore promising candidates for antidiabetic action, even though further research is necessary to prove their effectiveness.

Keywords: Diabetes mellitus, Flavonoids, hyperglycaemia, Antidiabetic, Glycaemic control.

INTRODUCTION

Diabetic mellitus is caused by inadequate or inefficient insulin action or secretion, causing high blood sugar [1]. There are many different types of phytochemicals in this family, including flavonoids, phenolic acids, stilbenes and lignans. A number of studies have found that polyphenols contribute to weight loss, antioxidant activity and anti-inflammatory activity [2,3]. Type-2 diabetes mellitus may be prevented with flavonoids because of their antioxidative and anti-inflammatory effects [4]. In both molecular and clinical studies, flavonoids have been shown to influence insulin resistance [5]. There are numerous polyphenolic compounds present in plants that contain a benzopyrone structure and also known as flavonoids. Secondary metabolites of a phenolic type, such as flavonoids, have been associated with a wide range of pharmacological actions [6,7]. Among the leading causes of death and diseases by 2030, diabetes will rank seventh according to the World Health Organization [8]. Inflammation and atherosclerosis are associated with excessive glucose in diabetes, but there is some evidence that excessive glucose may result in oxidative stress [9,10]. Citrus flavonoids have been shown to have beneficial effects on a number of different physiological processes, including those related to oxidative stress, glucose tolerance, insulin sensitivity, lipid metabolism, adipocyte differentiation, inflammation and endothelial dysfunction [11-14].

In this review article, the metabolic illnesses such as abdominal obesity, hypertension, insulin resistance and dyslipidemia are discussed in relation to flavonoids and their primary dietary sources [15]. The diagnosis of diabetes mellitus type 2 has been associated with the occurrence of cardiovascular illnesses [16,17].

Flavonoids: The compounds flavonoids are naturally occurring compounds with the phenolic structures. It was

discovered in 1930 that oranges contained a new substance. As per literature data, at least of 6000 phenolic compounds have been identified in flavonoids. These compounds can be found in fruit, vegetables, nuts, tea, soy, red wine, berries, herbs, coffee, herbs, chocolate, grains and cocoa [18]. When aromatic rings (A and B rings) are oxygenated, heterocyclic flavonoids (C rings) become heterocyclic (Fig. 1). Flavonoids are classified based on their oxidation levels and substitution levels of the C ring, whereas compounds within a class differ by the substitution pattern of the A and B rings (Fig. 2). Some of these compounds include flavones such as flavones, apigenin and luteolin. The hesperetin and naringenin, the aglycones of flavanone, are present along with citrus flavonols, such as quercetin, kaempferol, myricetin and fisetin. These compounds are capable of chelating metals and scavenging free radicals [19].

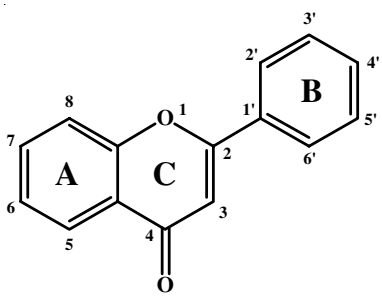

Fig. 1. General structure of flavonoid

Metabolism of flavonoids: Flavonoids derived from food are absorbed quickly into the gut when their physico-chemical properties are favourable, such as solubility, acid dissociation constants (pK_a), size and configuration. In order to absorb flavonoids, the small intestine or colon must be in contact with the flavonoids before they can be absorbed. Flavonoids can be glycosides or aglycones depending on their structure. Plants contain most flavonoids as β-glycosides bound to sugars, except for the catechin subclass. Flavonoid glycosides must be converted into aglycan form in order to enter the small intestine [20]. Flavonoid aglycones penetrate the lumen and reach the bloodstream easily due to their low molecular weight and high lipophilicity. It is likely that flavonoids with a high molecular weight and hydrophilicity will have a limited ability to absorb. The small intestine or colon is the site of absorption for flavonoids. As a result of their hydrophobic nature, epithelial cells can only absorb liberated aglycones passively [21]. Two phases of flavonoids' conjugation take place: the first occurs in the small intestine, followed by the second in the liver. A conjugated metabolite is further processed in the liver to form sulfate and glucuronide derivatives that are excreted through the bile and urine [22]. During the colonic fermentation process, unabsorbed flavonoids are hydrolyzed or fermented by colonic microbiota [23]. Microbiota hydrolyze flavonoids glucuronides in the liver to aglycones, which are then broken down further to macromolecules easy to absorb [24]. A relatively low concentration of glycosides is absorbed by the colon as compared to the small intestine. As soon as the flavonoids enter the small intestine, the liver processes them through processes like methylation, sulphuration, glucuronidation and sulfation to create smaller phenolic and hydrophilic compounds that are easier to absorb and distribute into the bloodstream [25]. The highest bioavailability of all flavonoids has been demonstrated for isoflavones [26]. Flavonoids are rapidly absorbed after ingestion of green tea, as evidenced by the high levels of flavonoid content in plasma and urine. As soon as the antioxidants enter the systemic circulation, their antioxidant status significantly increases [27].

Pancreatic regulation of glucose homeostasis: Following meals, glucose levels are controlled by two primary hormones, insulin and glucagon [28]. A monosaccharide is transported across plasma membranes as a first step in the carbohydrate metabolism. Hydrophilic monosaccharides such as glucose cannot pass through the lipid bilayer of the plasma membrane. As a result, membrane transport proteins known as glucose transporters (GLUT) play a role in the transport of monosaccharides across the plasma membrane [29]. By transporting the small compounds across the membrane, GLUT-family genes

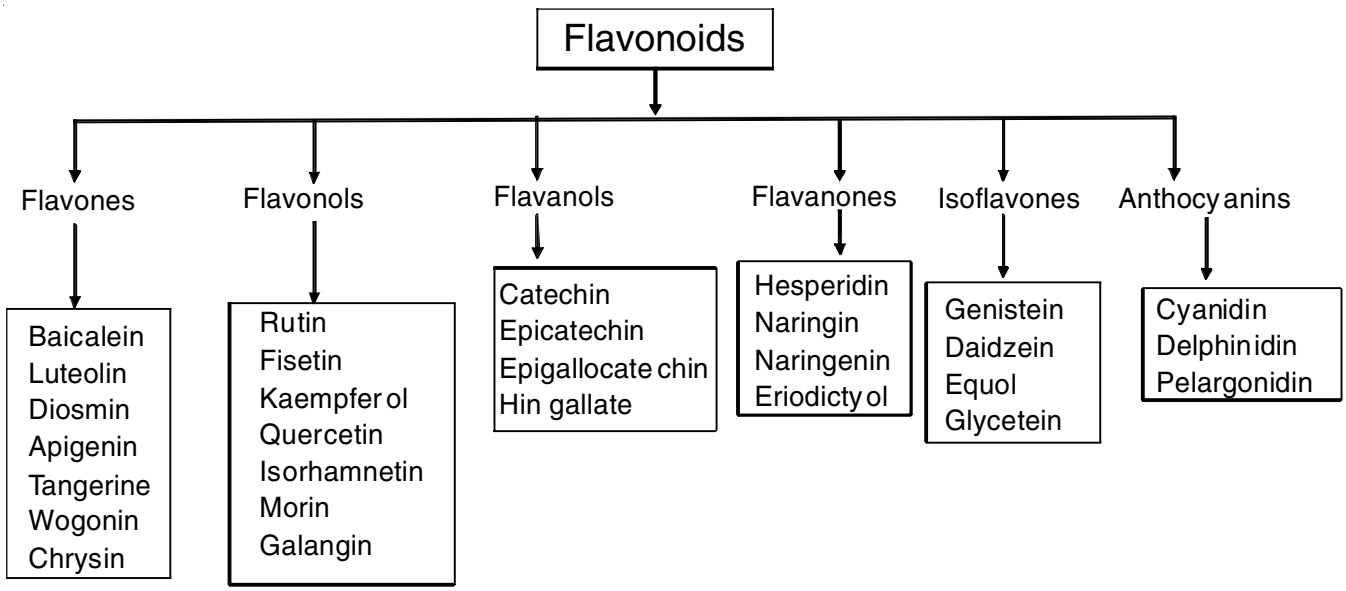

Fig. 2. Different classes of flavonoids

transport monosaccharides, polysaccharides and other compounds [30]. Fourteen GLUT isoforms are defined as part of the GLUT family: GLUT1, GLUT2, GLUT5 and HMIT (GLUT13). Proton-driven myoinositol transit is carried out by HMIT [31]. Pancreatic β-cells produce insulin by oxidizing glucose transported from the circulation to the cells. As a result of translocating GLUT 4, blood glucose levels are reduced in three main ways: (i) glucose uptake by peripheral tissues is increased; (ii) lipolysis and lipogenesis are inhibited; and (iii) the liver utilizes glucose more efficiently and stores it more efficiently [28]. A low blood glucose level causes the level of glucagon to rise because two mechanisms are involved: (i) increased glucose production and release in the liver and (ii) increased lipolysis and fatty acid release from adipose tissue [32,33].

Mechanisms of insulin resistance: The primary cause of the diabetic insulin resistance is insulin receptor mutations. Other causes include abnormal insulin production and impeded post-receptor signaling [33]. The lack of sensitivity to insulin is not only caused by metabolic abnormalities, but also obese people who have impaired pancreatic function. A functional glucose transporter-4 (GLUT-4) protein regulation is observed in type 2 diabetes associated with insulin resistance [34]. The GLUT-4 protein translocation is defective when insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation is inhibited. PI3K is activated by serine phosphorylation of IRS-1 after phosphatidylinositol 3-kinase (PI3K) is activated [35]. Inhibition of insulin signaling and action by free fatty acids (FFAs) and tumour necrosis factor alpha (TNF-α) can be attributed to the phosphorylation of IRS-1 by both of these substances [36]. Metabolic stress activates intracellular and extracellular signals that activate inflammatory signaling pathways. It is believed that obesity is mediated *via* the inflammatory signaling pathway both in the endoplasmic reticulum and in its stress response. Consequently, insulin resistance occurs more frequently when the inflammation signaling pathway changes [37-39].

Defects in insulin release: Hyperglycaemia and relatively constant insulin resistance characterize the pathogenesis of T2DM. Maintain euglycemia by increasing insulin production when insulin resistance occurs. An increase in the insulin production is accompanied by an increase in insulin-producing cells in all organ systems, including the pancreas [40]. Several factors have been demonstrated to induce β-cell death in chronic hyperglycaemia, including the endoplasmic reticulum stress (ER), the intracellular calcium level, reactive oxygen species (ROS) and oxidative stress [41]. β-Cells could also be diminished by exposure to high levels of FFAs due to pro-apoptotic effects [42].

Lipogenesis regulation in adipocytes: As adipocytes differentiate, progress through adipogenesis and accumulate lipid droplets in the cytoplasm, several transcription factors contribute to differentiation, adipogenesis and resistance to the oxidative stress. PPARγ, a nuclear hormone receptor, is predominantly expressed in adipose tissue, however it is also expressed in colon, immune cells and retina [43]. *In vivo*, it modulates insulin sensitivity and adipogenesis as well as peripheral glucose homeostasis. Through either direct or indirect stimulation of genes encoding proteins like fatty acid binding proteins (aP2), GLUT4-fatty acid transporters and acyl-CoA synthases [44].

Different flavonoids and their antidiabetic activity

Quercetin: Human nutritional supplementation has widely used a flavonoid known as quercetin [45]. There are many foods containing it, including fruit, fennel, lovage, apples, pepper, tea, coriander, dill, berries, onions, radish and wine [46]. The effects of quercetin on insulin-dependent PI3K activation and intestinal glucose absorption are thought to be mediated by GLUT2 inhibition [47,48], resulting in decreased lipid peroxidation, an increase in antioxidant enzymes (such as SOD, CAT and GPX) and a reduction in intestinal glucose absorption. In an evaluation of quercetin's effect on Caco-2E intestinal cells, the study found quercetin inhibited the transport of fructose and glucose by GLUT2. Adenosine diphosphate consumption of mitochondria is decreased by quercetin by activating the AMPK pathway through 5′-adenosine-activated protein kinase and increasing mitochondrial GLUT 4 translocation. The mechanism works similarly to that of metformin, which is used in treating type 2 diabetes [49]. By inhibiting insulin-dependent phosphoinositide 3-kinase activity (PI3K), quercetin regulates blood sugar levels by reducing lipid peroxidation and GLUT2 glucose absorption [50]. Furthermore, quercetin activates AMPK in muscle cells, while also stimulating glucose uptake [51]. Streptozotocin induced diabetic rats were found to have reduced glucose blood levels when quercetin was given [52].

Rutin: Citrus fruits, grapes, peaches, limes, oranges, lemons and grape juice all contain rutin [53]. Sophorin, quercetin-3-O-rutinosie and sophorin-1-O-rutinosie are also names for glycosylated quercetin other than rutin [54]. Rutin has antidiabetic effects in the small intestine, reducing carbohydrate absorption from the small intestine, improving the glucose uptake by tissues, suppressing tissue gluconeogenesis, activating β-cells to secrete insulin and protecting the islets of Langerhans from degeneration. Additionally, rutin reduces the oxidative stress and sorbitol levels as well as proinflammatory cytokines [55]. A number of experimental studies have found that rutin is antihyperglycemic and hypolipemic [56]. Rat soleus muscle glucose uptake is stimulated by the PI3K pathway when this enzyme is activated by protein kinase C [57]. The rubin-treated rats showed improved body weight, plasma glucose levels, HbA1c, inflammatory cytokines (IL-6 and TNF-α) and liver antioxidant function compared to the rats, which were untreated after the HFD/STZ induction [58]. As well, the heart of diabetic rats were shown to be protected from the inflammatory response, oxidative stress, apoptosis and myocardial dysfunction by rutin [59]. The practice of supplementing rutin with vitamin C resulted in an increase in brain-derived neurotrophic factor, nerve growth factor and GSH levels, while a reduction in those interacting with thiobarbituric acid. Moreover, rutin also decreased caspase-3 activity and increased the Bcl-2 activity in diabetic retinas under rutin treatment; these effects partially reversed apoptosis in diabetic retinas [60].

Fisetin: A flavonoid, fisetin is also a dietary component found in strawberries, apples, grapes, cucumbers, persimmons, onions and *Cotinus coggygria* Scop [61]. In addition to its anti-

cancer, antiinflammatory, antiproliferative and antihyperglycaemic properties, fisetin plays an important role in pharmacological properties. Additionally, fisetin can reduce protein glycation caused by methylglyoxal and exhibits antidiabetic effects. By limiting complications associated with diabetic mellitus, it serves as a preventative measure [62]. The NF-B p65, hemoglobin A1C, serum nitric oxide and blood glucose levels were significantly reduced by fisetin in an *in vitro* study. A study published in the journal Diabetes Prevention Institute found that fisetin inhibited monocyte cytokine production induced by high glucose levels [63]. A number of hepatic enzymes are affected by fisetin's antidiabetic effects, including hexokinase, glucose 6-phosphate dehydrogenase and glucose 6-phosphatase. The blood glucose homeostasis of streptozotocin diabetic rats is also improved by fisetin by reducing enzymes that are involved in carbohydrate metabolism [64]. Fisetin downregulates glycogenolysis and gluconeogenesis *in vitro*, according to one study. The fermentation of endogenous glycogen can be inhibited by fisetin. It was possible to inhibit glycogenolysis and glycolysis by increasing the concentration of fisetin to 200 mM, which was 69% effective. Fisetin, when present in 300 mg, inhibits the gluconeogenesis of lactate, fructose or pyruvate [65].

Kaempferol: It is also called kaempferol flavanol or kaempferide and may be found in several plants. In addition to *Ginkgo biloba*, grapefruits, tea bags, cruciferous vegetables and some edible fruits, kaempferol is present in high concentration [66-69]. Additionally, *Bauhinia forficata* leaves contain kaempferol, which has reduced serum glucose levels and increased glucose uptake in soleus muscles as effectively as insulin in rats [70]. Moreover, kaempferol has been found to promote cell viability and inhibit apoptosis, as well as to reduce the production of caspase-3 protein in human pancreas frequently exposed to hyperglycaemia. These protective effects may be caused by the activation of *c*AMP signalling, Akt and Bcl-2 protein expression and insulin secretion and the synthesis in β-cells [71]. In NRK-52E and RPTEC cells, kaempferol suppressed the pro-inflammatory signalling through RhoA/Rho-kinase (TNF-α, TGF-β1 and IL-1β) [72]. Similar to kaempferol, it may prevent diabetes by fighting the inflammation and antioxidants [73,74].

Isorhamnetin: It is present in several medicinal plants, including *Hippophae rhamnoides* L., *Ginkgo biloba* L. and *Oenanthe javanica* (Blume) DC. Assays in streptozotocin-induced diabetes demonstrated the effect of isorhamnetin in reducing hyperglycemia and oxidative stress [75]. O-methylated is found in medicinal plants including *Hippophae rhamnoides* and *Oenanthe javanica* (also known as Chinese celery, blueme, or ginkgo) [76]. The effects of flavonoids on obesity and diabetes have also been documented [77]. A treatment of isorhamnetin at 10 mg/kg or 20 mg/kg for 10 days significantly reduced hyperglycemia and oxidative stress in streptozotocin-induced diabetic mice. Isorhamnetin has many antidiabetic properties, including increasing sorbitol concentrations in rat lenses, red blood cells and in the sciatic nerve [78].

Morin: *Prunus dulcis*, figs and guavas are examples of traditional medicine herbs that contain morin [79]. In animal models, morin oral administration significantly improved glucose tolerance, insulin resistance and hyperglycaemia [80]. Hyperglycaemia, glucose intolerance and insulin resistance in animal models were significantly improved by morin oral administration for 30 days. An improvement in antioxidant capacity and a decrease in lipid peroxide levels were observed in rats with diabetes treated with morin. Following treatment, serum lipoprotein and lipid profiles were normalized. As a result of treating the rats with morin, α-TNF levels were decreased [81]. It has been demonstrated that morin has a differential effect on the enzyme activities of the liver, with G6Pase activity being significantly decreased and fructose-1,6-diphosphatase activity being enhanced [82].

Baicalein: *Scutellaria baicalensis* Georgi roots and fruits contain a flavonoid called baicalein, which is anti-free radical. 5,6,7-Dihydroxyflavone aglycone is produced by the roots of *Scutellaria baicalensis* and the fruits of *Oroxylum indicum* [83]. Inflammation, neurodegeneration and cardiovascular effects are all beneficial to the compound [84]. Baicalein significantly reduced hyperglycemia, glucose tolerance and insulin levels in mice fed a high fat diet [85]. The blood glucose levels and the hemoglobin A1c levels in diabetic rats treated with baicalein were significantly reduced, as were food intake and weight [86]. The α-TNF levels, AGE levels and NF-κB activation were decreased by baicalein treatment [87]. The ability of baicalein to activate AMPK signaling pathways inhibits insulin resistance and inflammation [88].

Luteolin: Among the foods containing luteolin are celery, parsley, onion leaves, carrots, peppers, broccoli cabbage and chrysanthemum flowers [89,90]. Adiponectin, leptin and GLUT 4 are genes that luteolin is shown to activate and enrich in 3T3-L1 adipocytes, as well as in primary mouse adipose cells and this induction is inhibited by PPARγ antagonists [91]. A combination of luteolin and luteolin-7-O-glucoside has been shown to have antioxidant properties, which may be useful for treating diabetes, improving insulin levels, blood glucose levels, reducing HbA1c values, decreasing HOMA-IR values and inhibiting lipid synthesis [92]. The antioxidant luteolin causes macrophage polarization to be altered in adipose tissue, thereby reducing insulin resistance and inflammation [93].

Diosmin: *Scrophularia nodosa* L. was discovered as a source of flavonoid glycosides in 1925. Several plant sources of hesperidin can be found or it can be dehydrogenated from hesperidin [94]. The effect of diosmin on diabetic complications has been demonstrated. Diabetic patients who were treated with a diosmin before and after intervention were measured for glycation and oxidative stress. Glutathione peroxidase increased along with haemoglobin glycation (HbA1c) [95]. Sodium diosmin significantly reduced blood glucose levels and increased key liver enzymes like hexokinase and glucose-6-phosphate dehydrogenase in rats given 45 days of the drug. After streptozotocin + nicotinamide treatment, glucose-6-phosphatase and fructose-1,6-bisphosphatase levels decreased [96]. Diaosmin inhibited the oxidative stress caused by STZ-nicotinamide in diabetic rats, which resulted in a decrease in plasma glucose levels and an increase in plasma insulin levels. Diabetic rats treated with diosmin had increased levels of glutathione, superoxide dismutase (SOD) and catalase (CAT). There was an

increase in vitamin C and E levels, as well as reduced glutathione levels [97].

Apigenin: The flavone family includes apigenin, which is found in many fruits, vegetables, nuts, onions, oranges and tea [98]. There were elevated serum cholesterol levels, hepatic lipid peroxidation and a decrease in cellular antioxidant activity, including CAT, SOD and GSH, after alloxan administration. Apigenin was shown to ameliorate hyperglycaemia and improve antioxidant activity in diabetic mice [99]. In human pancreatic stellate cells, apigenin treatment inhibited the expression of proliferating cell nuclear antigen, TGF-I and IL-6 messenger RNA levels induced by parathyroid hormone-related proteins [100]. The phosphorylation of AMPK by apigenin is enhanced in HepG2 hepatocytes. There is a 200-fold increase in potency between apigenin and metformin because of this property. It was suggested that apigenin had a lowering effect on blood glucose by enhancing GLUT 4 translocation [101]. The STZ and apigenin treatment restored apoptosis for rats and apigenin administration significantly reduced DNA damage, ROS production, protein carboxylation and lipid peroxidation [102]. A peripheral *versus* central effect of apigenin treatment on diabetic nephropathy after STZ treatment has been shown to improve MAPK-NF-κB-TNF-α and TGF-β1-MAPK-fibronectin signalling [103].

Tangeretin: Tangeretin is abundant in citrus rinds, including the mandarin orange, *Poncirus trifoliate* Raf. (Rutaceae) and Yuja, found in Korea. Adiponectin, leptin, resistin, IL-6 and MCP-1 levels decreased and adverse adipocytokines such as adiponectin, leptin, resistin and IL-6 were decreased in animals given HFD plus 200 mg/kg body weight tangeretin [104]. Tangeretin administration for 30 days significantly reduced plasma glucose, HbA1c and insulin levels of diabetic rats and increased their haemoglobin and insulin levels. Diabetes rats were shown to produce higher insulin levels by using tangeretin's antioxidant potential, by stimulating the glycolytic enzymes in their liver hepatocytes [105]. The insulin sensitizing factor is increased when tangeretin is administered to 3T3-L1 preadipocytes, whereas the insulin resistance factor is decreased [106]. A second effect of tangeretin is that it decreases STZ-induced programmed cell death in INS-1 cells through modulating NF-κB signalling [107].

Wogonin: *Scutellaria baicalensis Gerogi* (Scutellariae radix) is the source of wogonin, a compound traditionally used as a traditional medicine in East Asian countries [108]. Furthermore, wogonin does not cause weight gain or fatty liver, despite its ability to raise blood glucose levels, increase insulin sensitivity and improve lipid metabolism [109]. The compounds in this compound have anti-inflammatory, neuroprotective, antiviral, antibacterial and antioxidant properties [110]. High glucose inducing vascular inflammation was reduced by pre-treatment with wogonin [111]. According to a preclinical study, wogonin exhibits antioxidative and anti-inflammatory properties [112].

Chrysin: Foods that contain chrysin include honey, fruits, beverages, vegetables, propolis and medicinal plants, such as *Passiflora caerulea* (L.), *Tilia tomentosa* Moench and *Pelargonium crispum* (Berg.) L'Her [112,113]. It is mainly composed of chrysin that *Oroxylum indicum* (L.) Benth produces. ex-Kurz is used as a common herbal medicine by Chinese and other East Asian countries [114]. A reduction in HDL-C, total protein, SOD, GST and CAT levels in streptozotocin-induced rats following chysin treatment was associated with lower glucose, TG, TC and LDL-C levels [115]. In renal tissue treated with chrysin, collagen-IV protein expressions decreased and renal pathology improved [114]. As a result, pro-inflammatory cytokines levels is reduced in the serum, chrysin significantly prevented diabetic neuropathy in streptozotocin treated diabetic rats [116]. The results of diabetic rats that were treated with chrysin show a reduction in lipid peroxidation, an increase in glucose levels and an increase in insulin levels [117]. In addition to its antihypertensive and hypoglycaemic properties, chysin also improves blood sugar levels [118].

Hesperidin: There is a large concentration of hesperidin in the Citrus genus, which is an abundant and inexpensive by product of citrus cultivation [119,120]. By lowering hyperglycaemia, hyperlipidaemia and release of pro-inflammatory cytokines, hesperidin not only attenuates diabetic condition and reverses neuropathic pain [121]. Researchers also observed a decrease in the oxidative stress with hesperidin [122,123]. Hesperidin also increases the translocation of GLUT 4 and PPARs, leading to a significant reduction in blood glucose levels [124]. Having increased the activity of glucose-6-phosphatase (G6Pase), hesperidin supplementation decreased glucose excretion from cells in streptozotocin-induced diabetic rats [125]. The effects of hesperidin treatment on glucose levels are reversed when it is administered in 10 g/kg of diet [126]. Combined administration of hesperetin and hesperidin lowers cholesterol and glucose levels and affects lipid metabolism differently. A study of STZ-induced diabetic mellitus rats demonstrated that hesperidin positively regulates the Ros-Klotho pathways, which is related to insulin toxicity, thereby countering diabetic toxicity to the liver and kidneys [127].

Naringenin: The antioxidant properties of grapefruits, oranges and tomatoes are attributed to their high levels of naringenin [128]. *In vitro* studies have demonstrated that naringenin suppresses poliprotein-B secretion by acting as an insulin-*mimic* [129]. When naringenin was administered *in vivo* in healthy male Wistar rats, blood glucose level decreased [130]. Oral naringenin were administered to diabetes rats at a dose of 25 mg/kg bw, which resulted in lower postprandial blood glucose levels. Acarbose, a commercial glucosidase inhibitor, was compared with experimental results [131]. Various diabetic rat models showed a variety of effects when naringenin was administered to them: (i) the flavonoid lowered plasma glucose in streptozotocin induced diabetes rats; (ii) insulin-resistant rats fed fructose showed improvement in insulin sensitivity, whereas high-fat diet (HFD) mice showed decreased insulin resistance [132,133]. Diabetes-related issues improved in the treated animals, including insulin resistance, glucose levels, liver indicators, and antioxidant capacity. In diabetic rats, naringenin has been found to protect against retinal degeneration and apoptosis [134-137].

Eriodictyol: In addition to preventing obesity and diabetes, eriodictyol is found in lemon fruits [138]. Insulin secretion is modulated solely by cAMP/PKA pathway activity *in vitro* and

in vivo by eriodictyol [139]. Further, eriodictyol supplementation in diabetic rats suppresses oxidative stress effectively [140]. According to the findings, eriodictyol treatment causes enhanced activity of both PPARγ2 and the adipocyte-specific fatty acid binding protein [141]. Further, it induces insulin resistance in HepG2 cells by stimulating Akt activity [138]. A number of studies have shown that eriodictyol reduces intercellular adhesion molecule-1 (ICAM-1), retinal TNF+, endothelial NOS (eNOS) and vascular endothelial growth factor (VEGF). A diabetes related lipid peroxidation was also significantly suppressed by eriodyctiol treatment [141].

Genistein: There are several plants that contain genistein, which is a natural isoflavone found in soy, including *Genista tinctoria* Linn. and *Sophora subprostrala* [142]. The molecular mechanisms underlying the modulatory effect of genistein on diabetes must be examined in order to understand how estrogens and enzyme inhibitors (tyrosine kinase inhibition) contribute to diabetes dysregulation [143]. In addition to improve hyperglycemia-induced inflammation *ex vivo*, genistein promotes the *c*AMP/PKA signaling pathway, which is partially mediated by its effects on vascular endothelial cells [144]. Palanisamy *et al.* [145] reported that genistein reduced insulin resistance-induced pathology in rats fed fructose rich diets. In addition to decrease the urinary TBAR excretions and levels of renal $gp91^{phox}$ in diabetic mice, genistein injections (10 mg/kg) reduced inflammation markers such as p-ERK, ICAM-1 and MCP-1 [146]. Obese diabetic mice were significantly better at regulating their hyperglycemic, glucose tolerance and insulin levels with the addition of genistein (250 mg/kg body weight). Obese diabetic mice were significantly better at regulating their hyperglycaemic, glucose tolerance and insulin levels with the addition of genistein (250 mg/kg body weight) [147]. The anti-dysregulation effects of genistein on tyrosine kinase have been demonstrated [148]. Mice feeded genistein showed that it decreased their body weight, improved glucose and lipid metabolism and reduced their body fat [149]. Genistein could modulate hypothalamic circadian rhythm regulation through transcriptome analysis, providing a novel target for diabetes and obesity therapy. Aside from its anti-inflammatory properties, genistein also protects against neuropathy and oxidative stress [150,151].

Daidzein: Fruits, soybeans, nuts and products made from soy are high in isoflavones, such as daizzein [150]. According to earlier studies [151-153], daidzein enhances glucose and lipid metabolism, which could help treat diabetes. As demonstrated by Cederroth *et al.* [154], supplements of genistein in dietary soy increase glucose uptake by mice's skeletal muscles. In gastrocnemius muscle, treatment with daidzein resulted in a reduction in blood glucose, total cholesterol level, as well as an improvement in AMPK phosphorylation [155]. The potential therapeutic benefits of daidzein in Type 2 diabetes mellitus include improving glucose metabolism, lipid metabolism and the inflammation of the vascular system [156]. The control group had significantly higher glycated haemoglobin levels than the group that received daidzein pure synthetic [157].

Cyanidin: In addition to being anthocyanins, cyanidin and its glycosides are widely found in the diets of humans through crops, vegetables, fruits and red wine, which indicates significant consumption of these compounds every day. Intestinal glucose-sidase and pancreatic amylase can be inhibited by cyanidin, making it effective in treating diabetes mellitus [158]. Cyanidin inhibits intestinal glucosidase and pancreatic amylase, both of which contribute to diabetes [159]. Activation of insulin receptor phosphorylation and prevention of pancreatic apoptosis reversed degenerative changes in diabetic rats induced by streptozotocin [160]. In a study with high glucose induced liver damage, cyanidin-3-glucoside (C3G), a prominent anthocyanidin in the diet, was found to boost antioxidant levels and protect hepatocytes from oxidative stress [161]. Using cyanidin-3-glucoside (C3G) *in vivo*, Nasri *et al.* [160] reported that it inhibited the peroxidation of aortic lipids and prevented injury to the endothelium in diabetic rats. One of the most abundant anthocyanins we consume is cyanidin-3-glucoside, which can protect our hepatocytes from damage caused by high glucose by increasing antioxidant activity and inhibiting mitochondria-mediated apoptotic pathways by activating Akt and preventing the activation of *c*-Jun N-terminal kinase [161] and another author [162] claims anthocyanins are hepatoprotective in non-alcoholic fatty liver disease against hyperglycaemia-accelerated steatohepatitis.

Delphinidin: Pigmented fruits and vegetables such as berries, dark grapes, pomegranate and eggplant have a high antioxidant content known as delphinidin. Defining the mechanism by which delphinidin prevents diabetes and oxidative stress-induced endothelial dysfunction *in vivo*, is described in [163]. According to a study done *in vivo*, delphinidin protected endothelial cells from the damages that diabetes causes [163]. After 100 mg/kg delphinidin was administered to diabetic mice, glycation of HbA1c and albumin rates were reduced [164]. The redox signalling pathways of delphinidin and cyanidin were altered and inflammation was reduced in mice nourished with a high-fat diet, helping reduce insulin resistance [165]. Hidalgo *et al.* [166] discovered that delphinidin inhibits glucose uptake in mice jejunal tissue and human intestinal cell lines by inhibiting the free fatty acid receptor 1.

Pelargonidin: In blueberries, cranberries and raspberries, pelargonidin, a flavonoid, is abundant [167]. Hyperglycaemia and oxidative stress can be reduced with pelargonidin treatment [168]. A study involving diabetic rats showed that pelargonidin reduced the production of TBARS, reversed nitrite elevation and decreased superoxide dismutase production [169]. The aglycone and pelargonidin-3-galactoside increase secretion of insulin in rodent pancreatic β-cells under glucose conditions *in vitro* [170].

Conclusion

Phytochemicals, especially flavonoids, have been shown to be effective in treating and preventing diseases. The physicochemical, physiological and physical properties of flavonoids vary in nature. In addition to their medicinal efficacy as antibacterial, antidiabetic, hepatoprotective, anti-inflammatory and anticancer agents, flavonoids have been shown to be antiviral and anticancer agents as well. According to earlier studies common flavonoids in plants can prevent and treat diabetes mellitus and other chronic illnesses such as hypertension, obesity

and hypercholesterolemia. This may cause heart disease. The flavonoids discussed in this article act as effective antidiabetics in their own way. An actual mode of the antidiabetic agent is primarily determined by the modulation that flavonoids exert on the regulation of blood glucose levels by preventing glucose synthesis, increasing glucose uptake by muscle, improving insulin secretion, reducing insulin resistance, enhancing cell proliferation and reducing β-cell apoptosis. Researchers observed a considerable reduction in blood glucose levels in patients suffering from diabetes mellitus when quercetin, kaempferol, rutin and naringenin were tested. Various flavonoids based pharmaceutical agents can be developed in the future to successfully treat a wide range of degenerative diseases, including diabetes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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