MODULATING THE COURSE OF DIABETES BY FLAVONOIDS: FLAVONOIDS AND THEIR EFFECT AS AN ANTIDIABETIC AGENT

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Abstract
"Flavonoids are compounds with diverse biological activities and active roles in the prevention of various diseases. Their protective actions are largely due to their anti-oxidant property of scavenging harmful free radicals or because of their ability to bind and interact with various key enzymes and proteins involved in inflammation by modulating their activities. Thus, they help to reduce oxidative stress and inflammatory response and mitigate the damage inflicted during the process to alleviate various pathological conditions including chronic diseases like diabetes mellitus (DM) and cardiovascular diseases (CVDs). Their varied activities like anti-inflammatory, anti-lipidemic and anti-glycemic, vasodilatory, and antihypertensive properties are outcomes of their protective antioxidant nature. Recently, flavonoids have received significant attention from researchers and clinicians. Numerous studies have demonstrated through several lines of evidence to show that flavonoids can control and treat diabetes and diabetes-related complications including CVDs. There is a direct relationship between hyperglycemia and cardiovascular disorders in terms of morbidity and mortality. This review focuses on the signaling mechanisms that contribute to diabetes and its associated disorders and discusses the potential role of flavonoids as a complementary therapy in alleviating disease producing conditions.

Keywords: Flavonoids, diabetes mellitus, atherosclerosis, cardiovascular diseases, phytoconstituents

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1. Introduction

Polyphenols are subdivided into various subclasses such as stilbenes, lignans, phenolic acids & flavonoids. Flavonoids are among the most diverse group of polyphenols and are ubiquitously occurring bioactive secondary metabolites found in plant. Though flavonoids are not essential for survival, they possess biological activities that are beneficial to cope with biotic and abiotic stress. Besides plants, flavonoids are found in bacteria, fungi, and algae also. Flavonoids are structurally identified by the presence of flavan nucleus and are present in different types of fruits and fruit parts, flowers, vegetables, plant-derived beverages tea, beer, coffee, red wine, and mostly all parts of the plants [1]. They are low molecular weight compounds that are easily recognizable by their colorful appearance in different plant parts occurring as pigments [2]. Flavonoids defend plants from biotic and abiotic stress conditions like infections, drought, extreme cold, therefore, play an important role in adapting to the heat and freeze tolerance. Thus, they can alter metabolic activities. Flavonoids exhibit anti-oxidant, anti-inflammatory, anti-mutagenic and anti-carcinogenic, enzyme modulating, and immunomodulatory activities while protecting against various oxidative stress-related diseases like diabetes mellitus, asthma, atherosclerosis, osteoporosis, neurogenerative disease, like Alzheimer's disease (AD), Parkinson's disease, motor neuron disease, amyotrophic lateral sclerosis (ALS)[3]. Flavonoids can protect humans against diseases using their diverse wide-ranging activities. Flavonoids exert and manifest their beneficial and protective actions through their radical scavenging activity, ability to interact with enzymes and other proteins to modulate their function and activity. Thus, they can upregulate and downregulate enzymes responsible for lowering or promoting oxidative stress. Flavonoids because of their structural specificity can bind and interact with their cognate partners regulate gene expression and thus can determine cell fate, cell survival, progression of the cell cycle, and development [4], [5], [6].

Phenylalanine is the starting point for the synthesis of flavonoids from plants and via phenyl propanol, 4-coumarate coenzyme-A. This transformation leads to the generation of a compound known as chalcone and is the precursor for all flavonoids. 2-phenylchromen or 3-phenylchromen are two large groups of flavonoids, which are produced when the enzyme acts on chalcone which is derived from a plant [7]. Structurally flavonoids comprise of two A and B benzene rings which are connected by heterocyclic oxygen containing pyran ring (C) and its skeleton can be expressed as C6-C3-C6 as shown in figure 1[8]. More than10, 000 structurally different flavonoids have been identified which are further subdivided into six different groups such as flavanol, flavones, flavonol, flavanone, isoflavone, and anthocyanidins [9]. Sub-classification of flavonoids also depends on the position of attachment, unsaturation, and oxidation of C ring [2]. The difference in the structures brings about changes in the metabolism, bioactivity that results in distinct actions on the health [10]. In each subcategory, a single component known by a particular pattern of hydroxylation and conjugation [11] makes it different from others.

2. Diabetes and its associated complications

Diabetes Mellitus (DM) is a chronic pancreatic metabolic disease that is characterized by hyperglycemia caused by either inadequate insulin production by pancreatic ß cells or by resistance towards insulin hormone due to disturbances in the carbohydrate, lipid, and protein metabolism leading to long-lasting complications [12]. Insulin is involved in carbohydrate metabolism in all tissues of the body and is also an important regulator in brain metabolism. The brain is insulin sensitive but insulin-independent and helps to regulate entire body metabolism [13]. Insulin regulates the absorption and distribution of glucose in cells and maintains normal blood glucose levels [14]. As per the latest information available from the International Diabetes Federation, 537 million adults of20-79 years were inflicted by diabetes in 2017 with the expected number of cases going up to 783 million by the year 2045[15].

Diabetes mellitus is broadly categorized as type-1 (T1DM) and type-2 (T2DM) diabetes. The type-1 (T1DM) is an immune-dependent type, which is described by the damage of pancreatic ß cells, whileT2DM is idiopathic which is characterized by the deficiency of insulin or resistance of insulin occurs but ß cells are not damaged. Another type of diabetes that is associated with pregnancy is termed as gestational diabetes, indicated by intolerance to glucose at the timeof first of pregnancy [16]. The complications associated with diabetes mellitus of both types are further categorized as minor and major problems. Acute metabolic complications include diverse conditions leading to coma like lactic acidosis coma, ketoacidosis coma, hyperosmolar non-ketosis coma, and hyperglycemia coma besides diabetic ketoacidosis [17]. Chronic diabetic complications that include distinct tissues and

organs are nephropathy, neuropathy, cataract, retinopathy, and cardiovascular aberrations and disorders such as atherosclerosis, paresis, myocardial infarction (MI), and gangrene [18]. There are large number complications in diabetes which makes its treatment more complex and challenging due to damage and dysfunction of different organs. The prime target organs are the eyes, kidneys, nerves, heart, and blood vessels, and leads to uncontrolled hyperglycemia complications [19].

3. Flavonoids and their relation with diabetes

Flavonoids are obtained through diet from plants and various plant based products. Flavonoids are constituents of many medicinal plants and used in controlling inflammatory disorders [9].80% of the world's population relies on plant derived drugs, and many herbal medicines have been approved for clinical use in modern times [20]. But flavonoids like other phenolic compounds have yet to gain approval of drug regulating agencies for their therapeutic use. Thus, they can serve as complementary drugs or medicines.

Mammalian cells in a manner similar to plant cells also activate their defense system after injury to cells by chemicals that are products of the lipoxygenase activity. The presence of large amounts of antioxidant compounds like flavonoids in plant tissues prevents them from oxidative damage [21]. Recently, flavonoids have received significant focus in pharmaceutical and clinical research in the control and treatment of diabetes and diabetes-related complications [22], [17]. Flavonoids reduce inflammation and oxidative stress by different mechanisms in the treatment of high blood glucose and other diabetes-associated complications. Flavonoids help in the regeneration of pancreatic β-cells by ameliorating conditions that lead to cellular degeneration and cell death [23]. Diabetes is an outcome of complex reactions resulting from oxidative-stress triggered pancreatic beta-cell dysfunction and subsequent hyperglycemia (figure 2).

The insulin secretion by beta-cells facilitates the utilization of glucose by converting them into fats and muscle and simultaneously it reduces the absorption and conversion of glucose by inhibiting hepatic glucose metabolizing enzymes [24]. *In vitro* study involving treatment of flavonoid-rich fractions on the pancreatic islets showed that flavonoids caused increased insulin release and diminished LDL, triglycerides concentrations, and enhanced HDL concentrations. The mode of action of these two activities may be due to the dual action of increased levels of peroxisome proliferator-activated receptor alpha (PPAR-alpha) and peroxisome proliferator-activated receptor gamma (PPAR-gamma). The study also demonstrated that the symptoms of diabetes could be managed by using flavonoids to maintain low blood glucose and lipid levels [25]. Diabetes related complications such as neuropathy, retinopathy, and cataracts are found to be due to intracellular accumulation of sorbitol. Some important flavonoids are found effective in inhibition of NO production and thus effective in the management of high blood glucose levels in diabetic animals [26]. Flavonoids have demonstrated their potential as insulin secretagogues, insulin-mimetic compounds, cytoprotective agents, and promoters of pancreatic beta-cell regeneration [27]. Most flavonoids lead to the restoration of GSH by decreasing oxidative stress.

4. Mechanism of prevention of diabetes and associated cardiovascular disorders by flavonoids:

The relationship between hyperglycemia and cardiovascular disorders is directly related to the observed morbidity and mortality in the patients suffering from diabetes. Patients with diabetes and CVDs exhibit the disorders like peripheral vascular disease, coronary artery disease, diabetic cardiomyopathy, cerebrovascular diseases, pulmonary hypertension, and hypertensive cardiomyopathy [28],[29],[30]. The global incidence of these disorders is on the rise among the patients affected by diabetes. Atherosclerotic patients are predisposed to MI and stroke is the major reason for the increased mortality rate among diabetics. Metabolic alterations mainly promote the rise and progress of vascular inflammation leading to a variety of pathological conditions associated with CVDs. The events of initiation and progression of inflammation leading to CVDs are linked to various factors that include age, diet, life style, genetic makeup, obesity, hypertension, hyperlipidemia, diabetes mellitus, tobacco consumption, etc. This is considered a chronic inflammatory disease of fibro-proliferative nature that predominantly affects the medium and large-sized arteries. The vascular production of NOX derived ROS like superoxide ($O2^-$) is a clear indication of endothelial dysfunction [31].

Natural products like flavonoids that have recently attracted the attention and interest of researchers have significantly demonstrated potential in treating different metabolism-related disorders like hyperglycemia. Foods rich in flavonoids have been shown to be beneficial in the prevention of CVDs and act as hypoglycemic agents derived from plant

sources. Several studies revealed that flavonoids play a key role in treating diabetes and exhibited hypoglycemic activity in experimental models [32], [33].

Flavones also act differently depending upon the route of administration like flavones such as tangeritin, kaempferol, luteolin, apigenin, myricetin, rutin, and its metabolite quercetin exhibit anti-hyperglycemic activity but the oral administration of the rutin results in the reduction of plasma glucose levels. Number of studies has demonstrated the involvement of flavonoids in competitive inhibition of glucose absorption and result in the reduction of intestinal absorption of glucose demonstrating their hypoglycemic potential [34], [35]. The anti-diabetic action of flavonoids can be understood through various mechanisms of action that are shown in figure 3 and table 1.

The figure 4 clearly shows how diabetes is linked to causing of CVDs. As the diabetic heart has decreased mitochondrial antioxidant capacity, therefore, it results in the alteration of mitochondrial structure and function induced by ROS and RNS [36]**.**An increase in the ROS concentrations leads to mitochondrial depolarization and subsequent diastolic dysfunction. This is noticed in patients with metabolic disturbances [37]. Flavonoids have been observed to be very helpful in mitigating such oxidative stress related disorders. In CVDs flavonoids have been noticed to inhibit high glucose induced vascular inflammation that leads to atherosclerosis, cardiac remodeling, and ischemia-reperfusion injury [38]. They elevate the expression of GLUT-4 and lower the expression level of CD36. They inhibit NFκB phosphorylation by blocking HMGB1 expression. Flavonoids are known to reverse advanced glycation end products (AGE) and thus reduce protein and insulin degradation. All of these events decrease overall inflammatory response and oxidative stress-reducing the risk of developing CVDs.

4.1. Apigenin

Apigenin is a trihydroxyflavone isolated from leaves of *M. alba* was used for the evaluation of diabetic wound healing activity. The diabetic wound healing effect was found to be higher with strong antioxidant activity and the levels of SOD & catalase were increased in apigenin treated groups [39]. Apigenin has the ability to attenuate the oxidative damage caused in β cells via destruction of ROS & improved antioxidant enzyme activities [40]. Apigenin plays a significant role in reducing diabetic nephropathy and promoting antioxidant, anti-inflammatory, and anti-apoptotic activities. It diminishes fibrosis by altering transforming growth factor β1 (TGF-β1), fibronectin, and type IV collagen expression. It reduces TNF-α, IL-6 & NF-κb expression which leads to the inhibition of inflammation. Apoptosis is inhibited by apigenin by increasing the status of Bcl-2 and reducing the Bax and Caspase-3[41].

4.2. Eriodictyol

The flavonoid eriodictyol [(S)-2-(3,4-dihydroxy phenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one] is a flavanone, subtype of flavonoid. It is isolated from a North American plant *Eriodictyoncalifornicum.* The compound is widely found in citrus fruits. Eriodictyol treated human glomerular mesangial cells demonstrated attenuated oxidative stress, which was marked by an increased level of superoxide dismutase (SOD) enzyme and a decrease in the generation of ROS and malondialdehyde (MDA), a marker for oxidative stress. The levels of NADPH oxidase (NOX) isoforms such as Nox2 and Nox4 were also found to be decreased which cause the production of ROS. The expression of proteins like fibronectin and Collagen IV, and the inflammatory cytokines like TNF-α, IL-1β, and IL-6 were also suppressed. The activation of the Akt/NF-κB pathway induced by high concentrations of glucose was also blocked by Eriodictyol[42].

In vitro and *in vivo* studies suggested that eriodictyol is a potent insulin inducer. In mice, pancreatic islets and MIN6 cells were studied for stimulation of insulin by eriodictyol. Eriodictyol increased secretion of insulin from mice islets and MIN6 cells. Adenylate cyclase inhibitor (SQ22536) partially inhibited the insulin secretion induced by eriodictyol and the same study demonstrated that insulin secretion was fully inhibited by PKA inhibitor (H-89). This conclusively demonstrates that the eriodictyol is more effective on PKA than adenylate cyclase. In eriodictyol treated diabetic rats glucose tolerance and plasma insulin were found to be increased [43]. The high glucose-induced rat RGC-5 cells were evaluated by eriodictyol for improved cell viability. Eriodictyol lowered the ROS generation and rise in the action of SOD, GPx, and catalase. Eriodictyol also inhibits the generation of tumor necrosis factor-alpha and IL. Eriodictyol can also block cell apoptosis and improves the nuclear translocation of nuclear factor erythroid-2 (E2)-related factor 2(Nrf2)[44] resulting in cell survival and strengthening of antioxidant response. Eriodictyol significantly alleviated the condition of hepatic steatosis and diminished the generation of

pro-inflammatory cytokines while decreasing the expression of hepatic enzymes. It plays a role in enhancement of hepatic fatty acid oxidation-related enzymes and genes. Eriodictyol also mitigates insulin resistance, glucose utilization, and shows a positive impact on 2 incretin hormones, GIP and GLP-1in experimental diet-induced obese mice [45].

4.3. Naringin

Naringin is the potent component that possesses the hypolipidemic effect of diabetic rats in which cholesterol and triglycerides were diminished. It improved all lipids profiles except HDL-C in serum of rats [46]. A study conducted to elucidate the impact of naringin on serum glucose, glycosylated hemoglobin, and insulin in T2DM diabetic rats where 50 mg/kg dose of naringin was orally administered daily for 30 days. Naringin was found to significantly decrease the high concentrations of glucose, glycosylated hemoglobin, aspartate aminotransferase, and the cardiovascular markers of MI lactate dehydrogenase, and creatine kinase-MB, and the lower the concentrations of serum and hepatic insulin as well as glycogen concentration in muscles in insulin-resistant rats[47].

The two flavonoids naringin and naringenin have been reported to be normoglycemic, anti-lipidemic and anti-oxidative in the rat models diabetes. When both the compounds were orally administered for 1 month, it resulted in the improved diabetic status of the diabetic rats and decreased serum insulin and C-peptide concentrations, while lowering glycogen concentration, andenhancingthe activities of liver glucose-6-phosphatase and glycogen phosphorylase.Further, it alsoreduced decreased serum lipid profile, and antioxidant status of liver. The expression of insulin receptor b-subunit, adiponectin, and GLUT4 was found to improve via their insulinotropic effects [48]. Naringin treatment significantly improved hyperglycemia, polydipsia, polyuria, weight loss, glucose intolerance, low fasting plasma insulin, and reduced hepatic glycogen content [49].

4.4. Naringenin (4, 5, 7-trihydroxy-flavanone)

It is a flavanone that contains an oxygen atom at carbon 4. Naringenin is generally found in citrus fruits, with significantly high amounts present in grapefruit and lower concentrations in orange juice (2.13 mg/100 mL), and in far lesser amounts in lemon juice (0.38 mg/10 mL). It causes attenuation of ROS generation while it increased glutathione production, along with the upregulation of superoxide dismutase and nuclear factor erythroid 2–related factor 2 (Nrf2) in the nucleus was found to be improved in spinal cord neuroblastoma hybrid (NSC34) cells. Naringenin improved neurite length, enhanced IGF-1R and p-Akt in NSC34 cells. It also down-regulates the cleaved PARP and up-regulated the β-cell lymphoma-2 (Bcl-2) expression [50]. *In vitro* and *in vivo* animal studies indicated that naringenin has the ability to reduce the absorption of glucose through the intestine, decrease re-absorption of renal glucose, and elevated the uptake of glucose by muscle and adipose tissues. The hepatocytes indicated the decrease in triglyceride generation and gluconeogenesis gives in the downregulation of hyperglycemia and hyperlipidemia [51].

Naringenin has the potential to activate the activator of Nrf2 and prevent pancreatic b-cells from STZ-induced damage in MIN6 cells and its targeted genes GST and NQO1. The blood glucose level was reduced with balanced, the lipid profile was balanced, and the levels of antioxidants in pancreatic tissues were increased. Overall, Naringenin collectively helps in the restoration of insulin and causes glycolysis while inhibiting Gluconeogenesis [52]. Naringenin was found significantly important in the reduction of blood glucose level, restoration of body weight, and balancing lipid concentrations in the serum and the markers of oxidative stress when administered with 100mg/kg for 15 days. The virtual docking studies and data revealed a strong binding affinity towards the two proteins namely, peroxisome proliferator-activated receptor gamma (PPARγ) and glucose transporter type 4 (GLUT4). The study also validated that the compound exhibited anti-diabetic action via dual generation of PPARγ/GLUT4 signaling pathways [53].

4.5. Myricetin

Myricetin investigated for significantly the decrease in the enhanced productivity of free radicals cell abnormalities and ischemic injury. Myricetin is a strong candidate to remove a distinguish ROS and shows the anti-oxidative status because of the presence of a huge figure of active hydroxyl groups. It also restores the capability of mitochondrial trans-membrane, enhances the Bcl-2/Bax ratio, and suppresses the caspase-3 activation in 1-methyl-4-phenyl-pyridinium treated MES23.5 cells[54]. Myricetin derivatives(F2) isolated from *Syzygiummalaccense*, predominantly consisted of myricitrin (77%). It showed action against α-glucosidase and α-amylase. Myricetin also showed an ‘insulin-like’ effect. It also influenced Akt1 (protein kinase B), PPARγ (peroxisome proliferator-activated

receptor gamma), and Slc2a4 (glucose transporter) genes with PRKAG2 and adiponectin to stimulate glucose uptake[55]. Myricetin has been proven to stimulate D-glucose and D-3-O-methyl glucose uptake in rat adipocytes. Myricetin also caused 50% reduction in hyperglycemia and a rise in the hepatic glycogen and glucose-6-phosphate level. Another interesting reported fact is that myricetin blocked the aggregation of islet amyloid polypeptide (IAPP) which leads to the death of pancreatic beta islet cells in type II diabetes. In vivo study suggested that myricetin can be used for treating diabetic associated nephropathy by decreasing glomerulosclerosis, blood urea nitrogen (BUN), urinary volume, and protein excretion. It also restores the activity of the glutathione peroxidase enzyme and improves the action of xanthine oxidase in diabetic rats. Myricetin's normoglycemic effect in insulin-deficient rats is manifested by means of opioid receptors'excitation in peripheral tissues which stimulate endorphin secretion[56]. Myricetin acts by promoting insulin action by inducing the secretion of β-endorphin, which further stimulates the activation of peripheral μ-opioid receptors (MOR)[57].

4.6. Cyanidin-3-O-glucoside

Cyanidin-3-O-glucoside (C3G) and proanth-ocyanidins(PCs) improve insulin sensitivity by activation of AMPK in the skeletal muscles and liver. AMPK activation stimulates glucose transporter 4 (GLUT4) and causes the inhibition of gluconeogenesis. C3G-rich extracts show the preventive effect on pancreatic β-cell damage, increased insulin level, reduced gluconeogenesis by AMPK activation, and expression of PEPCK. AMPK expression in the liver was induced by C3G and showed a reduction in hyperglycemia [58].C3G which is an anthocyanin pigment decreases hyperglycemia and improves insulin sensitivity. C3G significantly reduced blood glucose levels and unregulated the GLUT4[59]. Black mulberry extract composed of cyanidin-3-glucoside, cyanidin-3-rutinoside, and cyanidin-3-xyloside, was able to inhibit the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals more effectively. The extract was found to be effective in inhibition of α-amylase and α-glucosidase [60]. Another study in which diabetic nephropathy was induced and C3G treatment was given. The study suggested that C3G from black rice reduces glucose, lowers insulin resistance, and improves kidney function in experimentally induced diabetic rats. It also prevented renal interstitial fibrosis, glomerular sclerosis (all symptomatic of glomerular nephropathy), and alleviated ROS production in diabetic rats. The renal Nrf2 mRNA, renal TNF-α mRNA, and NF-κB mRNA expression were downregulated in C3G treated experimental animals [61].

4.7. Catechin

The effect of catechin-rich green tea consumption was studied on postprandial glucose metabolism. The study included the level of insulin and incretin in human beings. The study revealed that catechin enriched green tea ingestion during the evening hours lowered postprandial plasma glucose concentrations [62]. Catechin reduces glycemia and improves glucose tolerance. This effect can be due to multiple mechanisms such as stimulation of peripheral glucose utilization, intestinal glucose absorption or improved glycolytic and glycogenic process. Catechins also reduce serum triglycerides and total cholesterol [63]. Streptozotocin induced diabetic rats were administered with catechin for 4 weeks. Catechin caused an increase in the body weight, glucose, malondialdehyde, triglycerides, total cholesterol, low-density lipoprotein-C, and apoB and inhibited HDL-C, apo A-I, SOD, CAT, and GST [64]. *In vivo* studies revealed that quercetin and catechin have the potential to regulate blood glucose levels in both normal fasting mice and high-fat diet taking diabetic mice. Furthermore, the estimated action of the quercetin and catechin determined that quercetin could not be effective in stimulating insulin secretion, but catechin was specifically and in a dose-dependent manner induced insulin secretion. Catechin in particular was able to alleviate glucose intolerance and its associated symptoms [65].

4.8. Tangeretin

Tangeretin (5, 6, 7, 8, 4′-Penta-methoxy flavone), a compound found naturally in the extracts of citrus fruit peels and shows several pharmacological properties. Tangeritin has significant potential to reduce the levels of plasma glucose, glycosylated hemoglobin (HbA1c) and modulate the status of insulin and hemoglobin. It reverses the action of glycolytic enzymes and stimulates glycogen conversion in the liver by modulation liver function in diabetic animals by normalizing liver glycogen phosphorylase concentration [66]. Tangeretin is a potential target molecule in the treatment of diabetes and its associated complications like nephropathy. As it can significantly inhibit high glucose-induced proliferation of glomerular mesangial cells (MCs) as well as down-regulated the level of fibronectin and collagen IV expression. Tangeretin lowered

the ROS content and MDA, andactivate SOD in MCs induced by the high level of glucose. Tangeretin also significantly inhibits ERK signaling pathway. Another study demonstrated that tangeretin blocks high glucose-induced cell proliferation, extracellular matrix expression, oxidative stress in glomerular MCs through the inhibition of the extracellular signal-regulated kinase (ERK) signaling pathway [67]. The lipid profile modulation shows the involvement of animportant pathway for reducing obesity and cholesterol. Tangeretin significantly exhibited anti-lipogenic, anti-diabetic and lipid lowering activities. It significantly lowered body weight, serum total cholesterol and low density lipoprotein (LDL) cholesterol levels, and also mitigated the fatty liver condition.

The combined effect of downregulation of lipogenesis-related genes and upregulation of lipid oxidation- and bile acid biosynthesis-related genes contributed to mitigation of lipogenesis and anti-obesity activity of tangeretin.

4.9. Daidzein

Daidzein was found to be functional only when it was present in its aglycone form and is not active till the glycosidic bonds of diadzin are cleaved. Daidzein is hydrolysed by intestinal bacterial enzymes and causes improvement in the glycemic index, insulin resistance, lipidemia, obesity, inflammation, and other problems related with T2D. It alsointeracts with a number of signaling molecules and receptors to demonstrate its activity [68]. In Type 2 diabetic cell model, L6 myotubes, daidzein promoted glucose uptake through AMPK phosphorylation to increase glucose transporter-4 (GLUT-4) translocation which brings about insulin-independent glucose homeostasis. It has been shown that daidzein has normoglycemic potential [69]. In another reported study in diabetic mouse strain C57BL/KsJ-db/db anti-diabetic, anti-lipidemic effects of daidzein were demonstrated by modulation of enzyme activity. Genistein and daidzein treatment significantly lowered the ratio of glucose-6-phosphatase and phosphoe-nolpyruvate carboxykinase (PEPCK) in the liver and ameliorate the ratio of insulin/glucagon. Moreover, it enhanced the metabolism of lipids in the liver, and it regulates the blood glucose level [70]. Daidzein promotes pancreatic β-cell survival and insulin stimulation but does not affect glucagon. The hepatic glucose and lipid metabolism was found to be regulated by lowering of enzyme activities of G6Pase, PEPCK, fatty acid beta-oxidation, and CPT and promoting the activities of malic enzyme and G6PD [71]. It also helps in regulating glucose and lipid metabolism mediated through PPAR-α and PPAR-γ[72].

4.10. Morin

It is a flavonoid isolated from *Morus alba***.** The cellular action of morin was studied in HepG2 cells. It non-competitively inhibited the PTP1B, stimulated the phosphorylation of the substrate receptor and Akt, downregulated gluconeogenesis, and increased glycogen synthesis. Morin has demonstrated the potential to stimulate metabolic pathways [73].

Endoplasmic reticulum stress is found to be associated with hyperglycemia and significantly lowers the expression of glucose transporter proteins hindering glucose metabolism during diabetes. Morin inhibits the PERK-eIF2α-ATF4 pathway as demonstrated by its interaction with PERK protein. Morin also suppresses the expression of PERK, a pro-apoptotic-autophagy protein that acts through ATF4 and CHOP, and prevents cell death [74]. Activities of morin (MO) and quercetin (QU) were compared for their role protective and modulatory role in endothelial function in isolated aorta from control and streptozotocin (STZ)-induced diabetic mice. Both polyphenols showed increased phosphorylation of Akt and endothelial NO synthase (e-NOS) and come up as potent vasodilators. Plant polyphenols MO and QU both enhanced e-NOS mediated NO production and vasodilation in the diabetic aorta. MO acted via activation of the Akt pathway and QU acted via activation of PI3K/Akt and AMPK pathways [75]. Morin caused a significant decline in serum glucose levels. Morin also demonstrated low status of LPO and activity of endogenous antioxidants (glutathione peroxidase, catalase, and superoxide dismutase) and was found to be unregulated. It also lowers the concentration of inflammatory cytokines like TNF-α, IL-1β, and caused upregulation of VEGF leading to an increase in retinal thickness [76].

5. Conclusion

Today diabetes and atherosclerosis are among the most commonly occurring disorders that inflicta large number of people globally and are also responsible for increased morbidity and mortality rates. Atherosclerosis is closely linked to T2DM and implicated in numerous diabetes associated pathologies that involve multiple histological factors and associated regressive changes in the arterial walls which inhibit the blood flow to the tissues and organs caused by excessive lipid deposition in the arteries. The current review closely studied and analysed in the light of

available literature the properties and the role of flavonoids and their ability to affect multiple targets through their associated actions in influencing molecular networks and pathways in preventing and curing diabetes and its associated cardiovascular complications. There is a sufficient amount of evidence available that proves the role of flavonoids in the prevention and treatment of oxidative stress-related diseases by their diverse types of actions thereby ameliorating diabetes and hypercholesteremia. The growing research focused on flavonoids reflects upon their potential in the prevention and management of metabolism-related diseases resulting from oxidative stress. The review highlights the potential role of flavonoids in reversing diabetes and could be helpful to understand and probe the underlying molecular mechanisms involving the onset of diabetes that could help alter the course of the disease.

Numerous research papers and reports point towards the substantial progress made in this direction and confirm the crucial role of flavonoids in preventing diabetes and diabetes related CVDs. Thus, flavonoids can prove to be beneficial as complementary therapeutic alternatives in reversing the course of this globally burdensome and debilitating disease.

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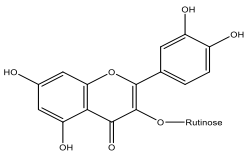
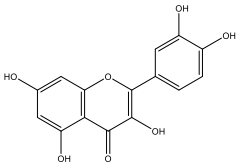
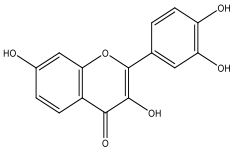
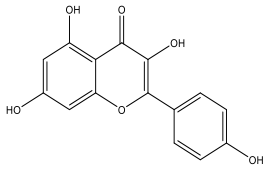
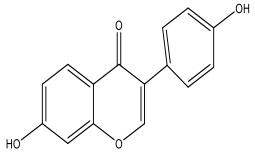
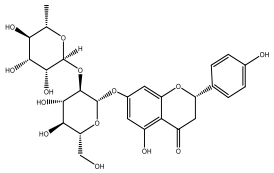
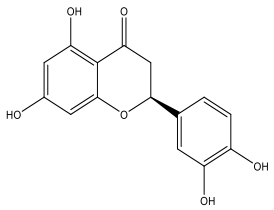
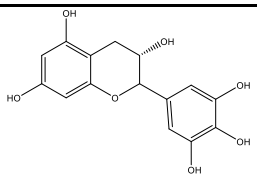
Table 1: Recent updates on flavonoids against diabetes and its complications

Flavonoid	Structure	Experimental models	Traditional uses	References
Rutin		Male Sprague-Dawley rats induced by streptozotocin	↓ levels of fasting blood glucose, ↓ oxidative stress and ↓ expression of AGEs, ↓ collagen IV and laminin, ↓ TGF-β(1)	[78]
		STZ-induced diabetic cataract	↓ AR, ↓MDA, ↓AGEs, ↑ glutathione	[79]
		Adult male Sprague–Dawley rats induced by STZ	↓ plasma glucose, ↓ oxidative stress, inhibited neuroinflammation, ↑ antioxidant system and H2S and Nrf2	[80]
Morin		HepG2 cells	↓miR-29a level, *IRS2* and *PI3K* expressio n	[81]
		Albino Wistar rats (male) induced by STZ	↓elevated serum glucose level, ↑ level of LPO, GPx, CAT, SOD and ↓ TNF-α, IL-1β, and VEGF	[77]
		Streptozotocin (STZ)-induced in rat insulinoma cell line (RINm5F pancreatic β cells)	↓ intracellular ROS production and apoptosis and ↑activation of the AMPK-FOXO3-catalase pathway	[82]
Fisetin		Male albino Waistar rats induced by STZ	↓ blood glucose level, ↑plasma insulin level and ↓ mRNA and protein levels of PEPCK and G6Pase	[83]
		STZ- induced DM rats	Improves diabetic cardiomyopathy, ↓hyperglycemia , ↓ oxidative stress	[84]
		Adult male Wistar rats induced by STZ	↓ oxidative stress, ↓ inflammation and ↓ apoptosis in diabetic cardiomyopathy	[85]

Kaempferol		NRK-52E (rat renal proximal tubular epithelial cell) and RPTEC (primary human renal proximal tubule epithelial cells) cells	inhibits hyperglycemia- and ↓oxidative stress, ↓TNF-α and IL-1β and TGF-β1 expression, ↓extracellular matrix protein expression	86
		Wistar rats induced with STZ	↑antioxidant property, ↓ lipid peroxidation markers	[87]
		male albino Wistar rats induced with STZ	↓hyperglycemia, ↓AGE-RAGE axis activation, ↓inflammatory markers (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and NF-κB.	[88]
Daidzein		C57BL/6 J mice	↓body weight gain, ↓fat content in adipose tissue, ↓ total cholesterol, ↓fasting glucose, ↓HbA1c, and ↓insulin leve	89
		Murine lung epithelial cells	↓PARP activity, ↓suppression of pro-inflammatory chemokine, ↓Cxcl2	[90]
		MaleC57BL/6 J-ob/ob mice	↓fasting blood glucose, ↓plasma cholesterol, ↓triglyceride levels, and ↑ glucose metabolism	[70]
Naringin		Male albino rats induced with STZ	↓ Glucose levels ↑ Lipid levels ↑ GLUT4 activity ↑ PPARγ in the pancreas	[54]
		Ldlr mice genetically induced diabetes	↓ Glucose levels ↓ Lipid levels ↓ Insulin levels ↑ β-hydroxybutyrate ↑ Energy expenditure ↑ Pgc1a mRNA ↑ Cpt1a mRNA ↑ Pnpla2 mRNA	[91]
		Sprague-Dawley rats induced with STZ	↑ Glucose tolerance ↓ Glucose levels ↓ Lipid levels ↓ ICAM-1 ↓ Malonaldehyde levels	[92]
Eriodictyol		RGC-5 cells	↓reactive oxygen species, ↓tumor necrosis factor alpha and interleukin-8, ↓cell apoptosis, ↑ Nrf2 and ↑the expression of antioxidant enzymes	44
		Human MCs line	↓oxidative stress, ↓NOX2 and NOX4, ↓production of fibronectin and Collagen IV, ↓inflammatory cytokines including TNF-α, IL- 1β, and IL-6	[42]
Epigallocatechin		Adult male Sprague Dawley rats induced with STZ	↓ Plasma level of glucose, ↓Lipid metabolites, ↓hypoglycemic effect, inhibits a-glucosidase	[54]

	Male Swiss mice induced with STZ	↓fasting blood glucose levels, ↓triglycerides (TG), ↓Glucose intolerance and total cholesterol (TC)	[63]
	Docking study	Inhibits α-glucosidase, ↑ antioxidant activity	[93]
	Male Wistar rats induced with STZ	↓glycemia, ↓ insulin, ↓leptin, ↓cholesterol, and ↓triglycerides	[94]

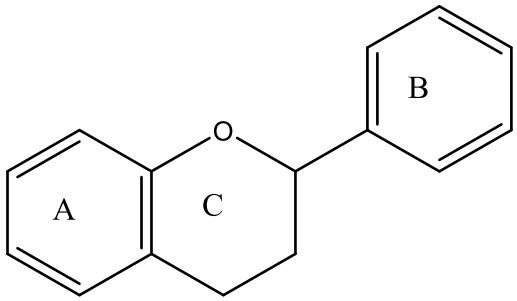


Fig. 1: Basic structure of a flavonoid

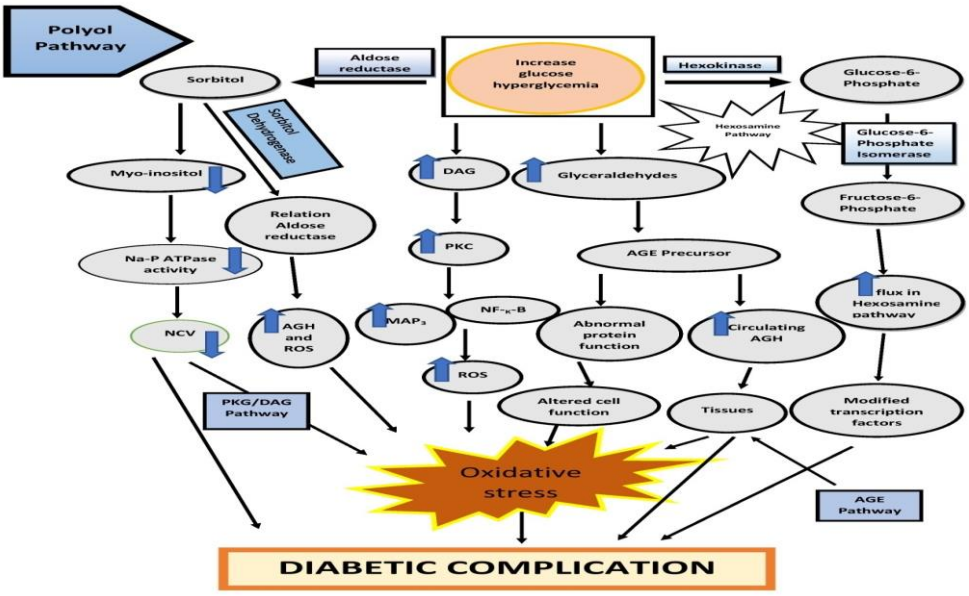


Fig. 2: Possible molecular mechanism for oxidative stress and diabetic complications

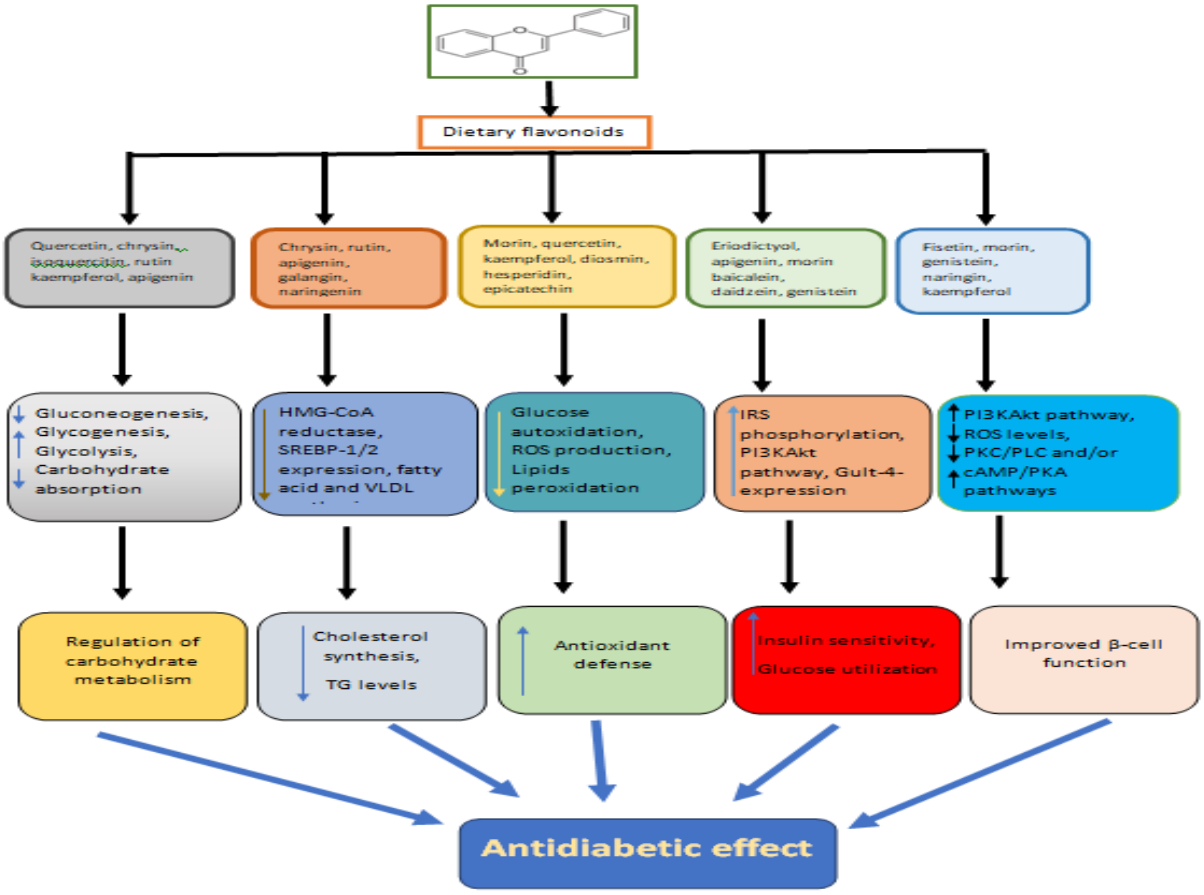
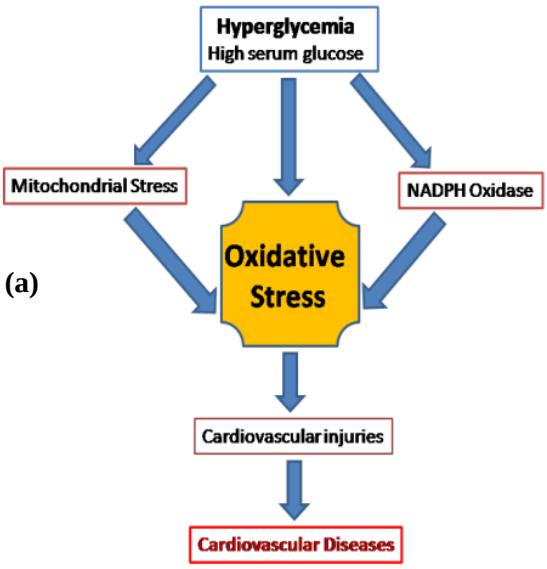


Fig. 3: Schematic presentation of molecular functions of different flavonoids



(a)

(b)

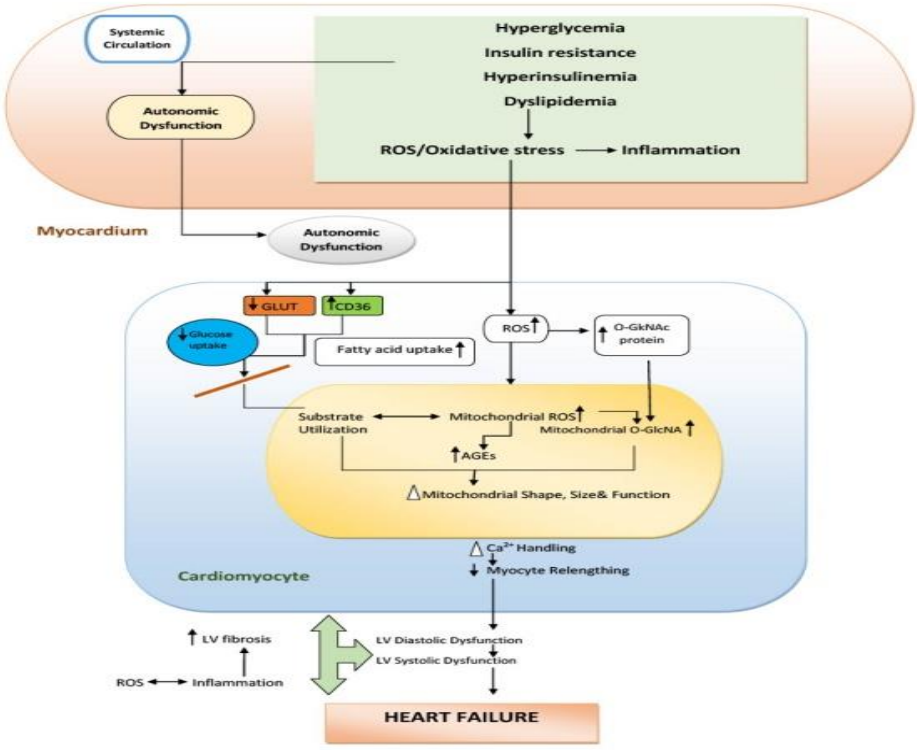


Fig. 4: Hyperglycemia generated oxidative stress is the outcome of reactive oxygen species production from mitochondrial stress and the activities of proinflammatory enzymes like NADPH oxidase (NOX), lipoxygenase (LOX1), cycloxygenase (COX1) leading to cardiovascular injuries and subsequent progression to full-blown cardiovascular diseases and other associated disorders. (a) Provides a general scheme of progression of diabetes related hyperglycemia to CVDs and (b) gives a detailed picture showing involvement od different pathways leading to CVDs and heart failure