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Review Article

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Role of dietary flavonoids having antidiabetic properties and their protective mechanism

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Abstract

Worldwide diabetes is the most prevailing health concerns and their incidence is increasing at a high rate. Diabetes mellitus (DM) is a metabolic disorder characterized by the destruction of pancreatic β cells or diminished insulin secretion. Flavonoids are the secondary metabolites of plants and have 15-carbon skeleton structures containing two phenyl rings and a heterocyclic ring. More than 10000 naturally occurring flavonoids have been reported from various plants and have been found to possess many beneficial effects with advantages over chemical treatments. A number of studies have demonstrated the potential health benefits of natural flavonoids in treating DM and show increased bioavailability and action on multiple molecular targets. This review summarizes the current progress in our understanding of the anti-diabetic potential of natural flavonoids and their molecular mechanisms for preventing and diabetes.

Keywords: Diabetes, flavonoids, anti-diabetic, molecular mechanism.

Introduction

For a long time, herbal medicines or their extracts have been used to cure various diseases [1–2], because plant products are frequently considered to be less toxic and free from side effects than synthetic ones [3-4]. Nowadays, so herbal medicine is an interestingly growing field. After cancer and cardiovascular diseases (two main killer of mankind),diabetes mellitus ranks third. Group of naturally occurring polyphenolic compounds ubiquitously found in plants are flavonoids. Flavonoids are well known for their multi-directional biological activities including anti- diabetic efficacy. About 500 million years ago, flavonoids were first appeared in green algae from the fusion of two biogenetic pathways i.e., cinnamate and ancient polyketide route. With plant evolution they have become more and more complex. Flavonoids are found in fruits, vegetables, and plant-derived products like red wine and tea [5]. The treatment of diabetes using the naturally derived agents has more beneficial effects, and does not cause any toxic symptoms. These herbal drugs protect the β-cells during the diabetic condition and reduce the amount of glucose level in the blood [6].

For a very long time diabetes has been treated with several medicinal plants, whereby the medicinal plant extracts was found to improve the diabetic control. Therefore, the search for more effective and safer anti-diabetic agents has become an area of active research.

Classification of Diabetes mellitus

Diabetes have been identified and mainly classified into 3 types:

Type I Diabetes

This type of diabetes is also known as insulin dependent diabetes mellitus (IDDM) juvenile. Pancreas which is a large gland behind the stomach, when it fails to produce insulin then diabetes occurs. In the absence of insulin, the body's cells are unable to use glucose (sugar) that is required by the body for production of energy. As a substitute it begins to burn its own fats. To control the glucose level in blood of the subject, suffering from diabetes insulin injection is required every day.

Type II Diabetes

This type of diabetes is also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes. This kind of diabetes results from insulin resistance. A condition in which, cells are unable to use insulin properly. This results in the accumulation of glucose (sugar) in the blood stream.

Gestational Diabetes

Gestational Diabetes is a kind of diabetes consisting of high blood glucose levels during pregnancy and it goes away after the baby is born. As a result of the changes in the mother's hormones it develops towards the middle of the pregnancy.

Around all over the world there are more than 1200 plants which are used in the treatment diabetes. It is a challenging problem in front of medical community to treat the diabetes without any complication or any side effects [7]. Traditional medicines are used for very long time to treat diabetes. About 30% of the traditionally used plants serve as a major source of therapeutic agents for the treatment of diabetes as well as the human disease [8].

More than 4000, million people suffer from diabetes all over the world. The number will grow due to rapid increase in the incidence of the disease caused by population growth, aging, urbanization and increasing prevalence of obesity and physical inactivity. Diabetes mellitus is now a major global public health problem; currently available drugs for the management of diabetes are costly and produce adverse effects. For the development of new antidiabetic drugs flavonoids have recently attracted attention as source materials. From various epidemiological, animal and *invitro* studies, emerging evidence confirmed the beneficial effects of many dietary flavonoids in the treatment and management of type 2 diabetes and complications related to it.

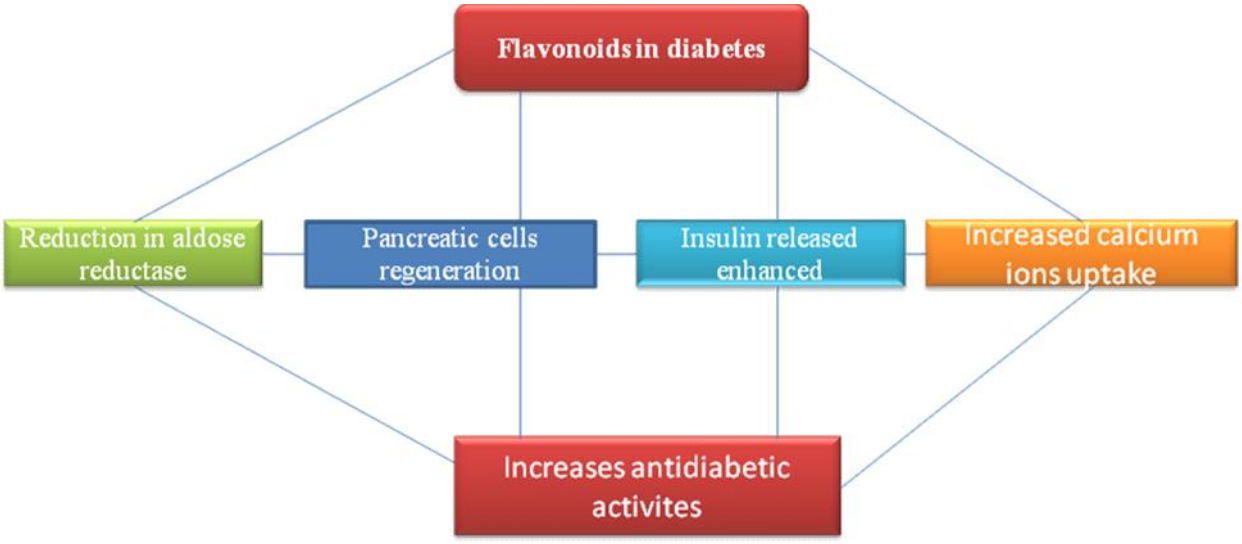

Fig.1 Function of flavonoids in diabetes mellitus

Mechanism of action of dietary flavonoids:

1. Inhibition of PARP by flavonoids:

Both in *vivo* and *in vitro* dietary flavonoids inhibit poly (ADP-ribose)-polymerase. In all living cells in an oxidized (NAD^+) and reduced (NADH) form nicotinamide adenine dinucleotide is found. By carrying electrons from one reaction to another the main function of NAD^+ in cells is to modulating cellular redox status. Moreover, it is involved in the other cellular processes (e.g., acting as a substrate for enzyme involved in post translational modification) [9].

By an increased flux of glucose through the polyol pathway, hyperglycemia decreases NAD^+ levels. When intercellular glucose levels are elevated [10], this pathway becomes activated. Only ~ 3% of all glucose will enter in the polyol pathway during normal glycemia. Maximum glucose will be phosphorylaated to glucose - 6 - phosphate and hexokinase. Due to saturation of hexokinase [11] under hyperglycemic conditions ten times more glucose enters into the polyol pathway [12]. In the pathway aldose reductase, the first and rate-limiting enzyme reduces glucose to sorbitol using NADPH as a cofactor. By sorbitol dehydrogenase then sorbitol is reduced to fructose uses NAD^+ as a cofactor. The osmotic stress that accompanies sorbitol accumulation and the redox imbalance following the depletion of NADPH and NAD^+ contributes to cell damage and organ injury, ultimately leading to cataract genesis, neuropathy and other diabetic complications [13-15]. Poly (ADP-ribose) - polymerase activation can also lead to NAD^+ depletion. In the regulation of many important cellular functions like DNA repair, gene transcription, cell cycle, progression cell death, chromatin function and genomic stability[16], the nuclear enzyme poly (ADP-ribose) - polymerase has been implicated. Poly (ADP-ribose) - polymerase detects and signals single- strand DNA breaks, which can be induced by hyperglycemica. Upon detection of a single-strand DNA breaks, poly (ADP-ribose)-polymerase binds to DNA and synthesizes a poly (ADP- ribose) chain as a signal for DNA repair enzymes. For the synthesis of these poly (ADP-ribose) monomers NAD^+ is required as a substrate. Over activation of poly (ADP-ribose) - polymerase therefore deplets cellular NAD^+ stores [17]. Several studies have suggested an important role of PARP activation in the pathogensis of diabetic complications in neuropathy and retinopathy [18-20]. Thus, this mechanism shows role of dietary flavonoid having antidiabetic property. Flavonoids can protect cells under hyperglycemic stress in several ways. First, flavonoids are able to inhibit over activation of PARP-1, preventing a decrease in NAD^+ levels. Furthermore, flavonoids are able to inhibit aldose reductase activity, preventing an additional decrease in NAD^+ and NADH levels. Also, because of their antioxidant properties, flavonoids are able to prevent damaging effects of oxidative stress. By a combination of all these effects flavonoids are able to protect cells against high glucose induced damage.

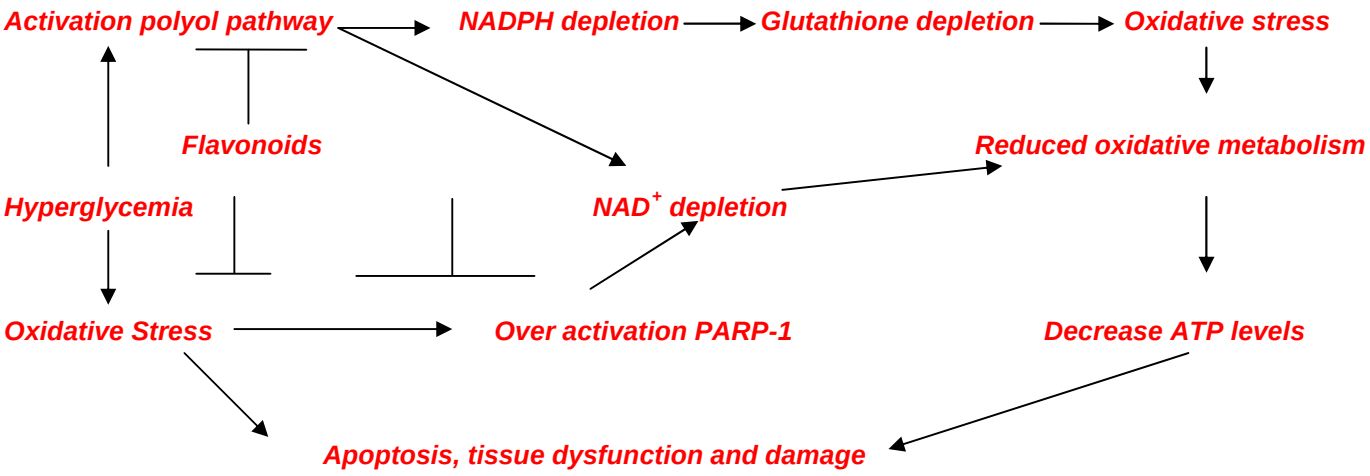

Fig. 2 Mechanism of inhibition of PARP-1 by flavonoids

2. Mechanism of action of dietary flavonoids on glucose transported proteins:

In eukaryotic cells, one of the most vital cellular nutrient transports is the transport of glucose across plasma membrane. This is catalyzed by a glucose transport proteins. Glucose transporter protein is encoded by the solute carrier 2 (SLC2) genes and are members of the major facilitate or super family of membrane transporters. Fourteen glucose transporter proteins are expressed in humans. Based on sequence similarity they are categorized into three classes:

Class I : Glucose transporter proteins 1 to 4 and 14.
Class II : Glucose transporter proteins 5, 7, 9 and 11.
Class III : Glucose transport proteins 6, 8, 10, 12 and HMIT (high affinity myo-inositol transporter)[21].

The fourteen glucose transport proteins are comprised of ~ 500 amino acid residues and composed of 12 transmembrane segments, a single site of N-linked glycosylation, a relatively large central, cytoplasmic linker domain exhibit topologies with both their N and C termini positioned in the cytoplasm. Glucose transport proteins are expressed in almost every human cell types. By tissue-specific expression of one or more glucose transport proteins the rate of glucose entry into the cell is determined.

Glucose transporter-1 transport glucose, galactose, mannose, glucosamine and reduced ascorbate though glucose is the main physiological substrate of glucose transport -1 protein. By the cell stressors such as azide[22], osmotic stress[23], methylene blue [24] and glucose deprivation[25] the activation of glucose transport-1 is mainly occurred.

Flavonoid rich medicinal plants exert promising effects in up-regulation of glucose transporter protein-1 expression levels. Genisetin derivatives have been demonstrated promising effects in the treatment of type 2 diabetes mellitus because these compounds significantly stimulated the glucose uptake through elevating glucose transport- 4 and glucose transporter-1 mRNA expressions levels in L6 myotubes .

Glucose transporter -2 is involved in glucose-sensing in pancreatic β- cells, liver and the hypothalamus as well as triggering the glucose - mediated insulin secretion cascade [26]. It could be involved in the pathogenesis of diabetes mellitus. It is proved that glucose transporter-2 expression is down-regulated in pancreatic β-cells, while the hepatic expression of this glucose transporter is enhanced in diabetic animal models. In the liver of experimental animals [27], hesperidin and naringin have been demonstrated to reduce protein expression of glucose transporter-2.

Glucose transporter -3 is also known as neuron specific glucose transporter. It plays an important role in the alterations of placental function observed in diabetic pregnancies [28]. The predominant site of expression of this protein is brain. It is responsible for uptake of glucose into the neurons.

Glucose transporter- 4 exist in small vesicles in cytoplasm and can be stimulated by both insulin and muscle contraction which induce the translocation of this glucose transporter isoform to the plasma membrane where it serves as portal though which glucose uptake takes place. Glucose transporter - 4 plays a vital role in glucose- sensing although only 15% is absorbed by adipose tissue and the remaining 85% by muscle in healthy individuals [29]. Various studies have suggested the role of flavonoids and phenolic compound in enhancement of Glucose transporter- 4 expressions and glucose uptake. Epigallocatechingallate has been suggested to increase glucose uptake and promote translocation of Glucose transporter-4 to plasma membrane in skeletal muscle cells. Quercetin possesses anti-diabetic properties by up-regulation of mRNA level of Glucose transporter-4 and its translocation to the cell membrane in adipocytes and skeletal muscle cells [30-31].

Activation of insulin receptor, leads to phosphorylation of insulin receptor substrate which in turn triggers the activation of phosphoinositide 3- kinase. Phosphoinositide 3-kinase then phosphorylates the lipid phosphatidylinositol 4, 5- bisphosphate (PIP_2) to yield phosphatidylinositol 3, 4, 5- triphosphate (PIP_3). This then activates phosphoinositide- dependent protein kinase1 (PDK1). PDK1- mediated phosphorylation of protein kinase B (Akt), in turn allows phosphorylation of the Rab GTPase- activating protein AS160 and leads to transloation of GLUT-4 from intracellular storage vesicles to plasma membrane and enhances the glucose uptake.

Glycose synthase kinase-3 inhibited by activation of AKT,which then phosphorylated and deactivates glycogen synthase. The forehead box protein O1 (FOXO1) also phosphorylated by AKT , which deactivates the expression of glucose-6-phosphate(G6Pase) and phosphoenol pyruvate carboxy kinase (PEPCK) and suppresses gluconeogensis in the hepatocyte[32]. Adenosine monophosphate-activated protein kinase is an important regulator of the cellular metabolism which is also represses the hepatic glucose production through the modulation of PECK(phosphoenol pyruvate carboxy kinase) and G6Pase (Glucose- 6-phosphatase)[33].

A serine / threonie kinase AMPK (adenosine monophosphate – activated protein kinase) is involved in regulating anabolic and catabolic processes and maintaining balance of cellular energy. Through the cellular energy changes AMPK is activated. Some unknown factors, however, from immune and metabolic tissues/ cells can coordinate to regulate this protein kinase [34]. The intracellular ATP is reduced and AMP level is increased under high cellular energy demands. This increased in AMP/ATP is reduced and AMP level in increased under high cellular energy demands. This increased in AMP/ ATP ratios activates LKB1: STRAD:MO25 complex which in turn phosphorylates Thr172. The phosphorylation of Thr172 eventually leads to AMPK activation. The alternate pathway to activate AMPK is through activation of Ca^{++}/ calmodulin- dependent protein kinase (CaMKKβ) in response to activation of Ca^{++} level in cell cytoplasm. The activated AMPK, decrease hepatic glucose production by inhibiting

gluconeogenic enzymes phosphoenol pyruvated carboxy kinase (PEPCK) and G-6Pase and translocated GLUT-4 and GLUT-1 which ultimately increase glucose uptake. Lipid metabolism is also stimulated by AMPK through decreasing malonyl CoA levels in response to inhibition of acetyl CoA carboxylate (ACC) and activation of malonyl CoA decarboxylase (MCD) .

To have an important role in translocation of GLUT- 4 to plasma membrane, P13/AKT, participation of CAP/ Cb1/TC10 pathway has been well documented. Activation of insulin receptor, recruits the adapter protein APS to the insulin receptor β subunit and subsequently phosphorylates Cb1 proto-oncogene. Cb1 and Cb1 associated protein (CAP) then interact and bind to the lipid raft protein flotillin in the plasma membrane resulting in the recruitment of CrKII. CrKII then binds to the exchange factor C3G which catalyze the exchange of GDP to GTP on the lipid-raft-associated protein TC10. The TC10 downstream effectors are known to translocate GLUT-4 on plasma membrane and facilitate glucose uptake.

In response to enhanced glucose levels in blood circulation, insulin is secreted from pancreatic circulation. Through GLUT- 2 glucose is transported into the β-cells. The increased intracellular concentrations of glucose leads to increase in the production of ATP, and an increase in the ATP/ADP ratio; which ultimately leads to closure of potassium channels on the cell membrane. The membrane depolarizes and leads to voltage-dependent calcium influx. The increased Ca^{++} concentration eventually promotes insulin secretion [35-36].

Flavonoids and their antidiabetic properties:

For instant, Apigenin-6-C-β-L-fucopyranoside and quercetin have been reported to reduce blood glucose level and improve insulin secretion in hyperglycemic rats [37].

Cyanidin- 3-O-β-glucoside and its metabolite protocatechuic acid have been demonstrated to exert insulin- like effects by up-regulating PPARγ activity which results in regulation of adiponectin and translocation of GLUT-4 in human omental adipocytes [38].

In vivo and *in vitro* the positive effect of anthocyanins in glucose homeostasis has been investigated [39]. Studies revealed that the antidiabetic activity of anthocyanins derived from purple sweet potato through inhibition of JNK and IKKβ activation caused by oxidative and ER stress in the liver of high-fat-diet mice [40]. These studies suggested that the protective effect of epigallocatechin gallate from FFAs-induced peripheral insulin resistance through inhibition of oxidative stress and PKC activity. In high-fat diet rats, the ability of epigallocatechin gallate to improve insulin signaling by decreasing the levels of toll-like receptor 4, IKKβ, NF- κB, TNF-α, and IL-6 has been reported [41]. Emerging evidence indicated the hypoglycemic effect of naringin by regulation of PEPCK and G6pase as well as anti-oxidative stress property of this flavanone glycoside antioxidant in the improvement of insulin resistance and lipogenesis [42]. It has been reported that naringin and hesperidin attenuate hyperglycemia-mediated oxidative stress and pro-inflammatory cytokines production where, the increased levels of MDA, NO, TNF-α and IL-6 have been reversed in HFD/STZ-induced diabetic rats after administration of naringin and hesperidin [43].

Kaempferol is a member of the flavonol group of flavonoids and is abundant in apple, grape, tomato, tea, potato, broccoli, spinach, and some edible berries [44]. Kaempferol extracted from *Bauhinia forficata* leaves reduced hyperglycemia and enhanced glucose uptake in the rat soleus muscle similarly to the action of insulin [45]. *In vitro* results confirmed that kaempferol treatment (10 μM) promoted cell viability, repressed cellular apoptosis, and reduced caspase 3 activities in β cells and human islets continually exposed to hyperglycemic conditions. These defensive effects were related to the improved expression of anti-apoptotic Akt (also known as protein kinase B (PKB)) and Bcl-2 proteins, enhanced cAMP signaling, and increased secretion and synthesis of insulin in β cells [46]. Moreover, kaempferol stimulated glucose uptake in the rat soleus muscle via the PI3K and protein kinase C (PKC) pathways and the synthesis of new glucose transporters [47].

The anti-diabetic effect of quercetin was also investigated in streptozotocin (STZ)-induced diabetic mice; treatment of quercetin resulted in the reduction of hyperglycemia-stimulating GLUT4 and glucokinase, increased liver glucose uptake, and decreased hepatic glycogenolysis and gluconeogenesis [48-50]. Dietary supplementation of 0.5% quercetin in the diet for two weeks enhanced serum insulin concentrations and lowered blood glucose in STZ-induced diabetic mice.

Rutin (a glycosylated quercetin, also known as rutoside, quercetin-3-*O*-rutinoside, and sophorin), which can be normally extracted from natural plant sources such as buckwheat, grapes, oranges, lemons, limes, peaches, and berries, was also reported to have anti-diabetic functions [51-52]. Diabetic mice fed with 100 mg per kg rutin in the diet showed significant reductions in plasma glucose levels and increased insulin levels along with the reestablishment of glycogen content and the activities of carbohydrate metabolic enzymes [53].

Rutin was also found to activate liver enzymes linked with the gluconeogenic and lipid metabolic processes. Rutin was shown to influence glucose uptake in the rat soleus muscle through the phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways [54]. The flavonoid also reduced the levels of fasting blood glucose, blood urea nitrogen, and creatinine and the intensity of oxidative stress, with a significant increase in phosphorylation of mothers against decapentaplegic homolog 7 (SMAD7), an inhibitory SMAD, I-SMAD. SMAD7 belongs to the transforming growth factor β (TGFβ) superfamily of ligands and is a TGFβ type 1 receptor antagonist that blocks the association of the TGFβ type 1 receptor and SMAD2, a receptor-regulated SMAD, R-SMAD. Rutin was also reported to reduce the levels of plasma glucose, hemoglobin A1C (HbA1c, a glycated (beta-*N*-1-deoxy fructosyl) hemoglobin), and cytokines, including IL-6 and TNF-α. The flavonoid also led to the reestablishment of antioxidant status and serum lipid profile in STZ-treated diabetic rats fed a high-fat diet (HFD/STZ) [55]

Oral administration of apigenin (0.78 mg per kg body weight) for 10 days was reported to reverse the reduction in hepatic antioxidants in alloxan-induced insulin-dependent diabetic mice, confirming the free-radical scavenging activity [56]. Intraperitoneal administration of apigenin had a significant anti-hyperglycemic effect [57] in STZ-induced diabetic rats.

Morin shows numerous health benefits by preventing diabetes. It is a natural flavonoid found in almonds and other plants in the *Moraceae* family. In diabetic rats, morin treatment improved the antioxidant ability and decreased lipid peroxides thus normalizing the serum lipid and lipoprotein profile. For 30 days oral administration of morin in animal models significantly enhanced glucose intolerance, hyperglycemia, and insulin resistance. In diabetic animals, morin treatment reduced the elevation of inflammatory cytokines, including IL-1β, IL-6, and TNF-α [58]. Morin significantly reduced the levels of blood glucose, G6Pase, and fructose 1, 6-diphosphatase (FDPase, also known as fructose 1, 6-bisphosphatase) and increased the levels of insulin, hexokinase and G6PD (or G6PDH) [59].

Morin impaired the hepatic SphK1/S1P signaling pathway and ameliorated high fructose-induced reduction of hepatic NF-κB activation, subsequently decreasing the levels of IL-1β, IL-6, and TNF-α in the rat liver and BRL3A cells. Administration of morin was reported to improve hepatic insulin and leptin sensitivity, followed by subsequent decreases in blood lipid and liver lipid accumulation [60]. As an inhibitor of protein-tyrosine phosphatase1B (PTP1B, also known as tyrosine-protein phosphatase non-receptor type 1), dietary morin sensitized and activated insulin receptor-mediated metabolic pathways [61].

Naringenin (Flavonones) are found in citrus fruits e.g., tomatoes, grapes, oranges possess anti-diabetic activity. Naringenin improved glucose metabolism by modulating the decrease in blood glucose [62].

Conclusion

Flavonoids are well known for their multi- directional biological activities including anti- diabetic efficacy. The prospect of using natural products to treat diabetes has not been widely examined. Emerging studies have described the promising role of flavonoids in treating diabetes as well as their associated metabolic diseases. The anti-diabetic potential associated with flavonoids are very large given their regulatory effects on blood sugar transporters by increasing insulin secretion, reducing apoptosis, promoting pancreatic β-cell proliferation, and reducing insulin resistance, inflammation, and oxidative stress in the muscle. Determining the molecular mechanisms involved in glucose metabolism in diabetes would provide insight into the field of drug development, and future discoveries are expected to yield therapeutic benefits. With the rapidly increasing incidence of diabetes worldwide, there is a great need for safe and effective functional biomaterials with anti-diabetic activities. Therefore, additional studies are needed to promote the development of nutritional flavonoids for treating diabetes, and their complications.This review emphasize that diabetes have been treated with several medicinal plants for a very long time, whereby the medicinal plant extracts were found to improve the diabetic control and mean while reduce side effects in comparison to synthetic ones. Thus, the search for more effective and safer anti-diabetic compounds (flavonoids) has become an area of active research. Flavonoids are a potential alternative treatment strategy for the development of effective and safe anti-diabetes drugs.

Conflict of Interest Statement

We decline that we have no conflict of interest.

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