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A Review on flavonoids as anti-diabetic and antioxidant agents

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Abstract
Pharmacological property of flavonoids acts as potent antioxidant and antidiabetic activity play an important role in the improvement of diabetes mellitus. Flavonoids are polyphenol compounds that exert many probable health benefits, including diabetes type-II, which is the third most common disease that causes death, right after cancer and cardiovascular diseases. The extremely high level of blood glucose has been believed to trigger type II diabetes. The aim of this review is to describe the flavonoid's ability as an alternative treatment for diabetes type-II patients and explore the antioxidant and antidiabetic properties of some flavonoids to identify key positions responsible This paper also addresses several aspects in which flavonoids may impart a essential role in starch digestion, such as the interaction of flavonoids with enzymes involved in starch hydrolysis, the role of flavonoids in inhibiting glucose absorption, as well as the interface of flavonoids with starch to form a complex resistant to hydrolysis.

Key Words: *Flavonoids, Diabetes, Antioxidant*

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I. Introduction

Diabetes

Diabetes mellitus is a condition which distresses the person's ability to control their own blood sugar levels, either because their body doesn't produce enough insulin or because of insulin resistance when cells don't respond to the insulin that is produced (1). High blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), weight loss and lethargy. Insulin is the principle hormone that regulates uptake of glucose from the blood into most cells, primarily muscle and fat cells (2).

Flavonoids as Hyperglycemia Regulators

Dietary flavonoids are well known for their profitsconcerning glucose homeostasis. Flavonoids are capable of inhibiting carbohydrate digestions and glucose absorptions, along with the parameter of insulin secretions via multiple signaling pathways [1]. Flavonoids can simply inhibit carbohydrate-digesting enzymes and glucose transporters, which aids in achieving normoglycemia within the blood circulation.

Inhibitors of α-Glucosidase

α-Glucosidase is among the most important membrane-bound enzyme in carbohydrate digestion found in the small intestine epithelium. The events of α-glucosidase correlate to maltase-glucoamylase (MGAM) and sucrase-isomaltose (SI), which are located in the intestinal border [2]. Glucose is unconstrained from the non-reducing end through the hydrolysis of linear $\alpha-1\longrightarrow4$ and branched $\alpha-1\longrightarrow6$ linkages of oligolinkages [2]. The inhibition of α-glucosidase can delaythedeprivation of complex sugars into glucose, which helps interruption the absorption of glucose in the small intestine, ultimately decreasing postprandial blood sugar levels. Flavonoids, mainly astragalin, rutin, isoquercetin, and kaempferol-3-O-rutinoside in Morusatropurpurea leaves, can suppress α-glucosidase activity [3]. Among these four flavonoids, rutin and astragalin have shown remarkable α-glucosidase inhibitory activities of IC50 values (13.19 ± 1.10 and 15.82 ± 1.11 μM, respectively). α-glucosidase activity significantly reduced via competitive inhibition by apigenin [3]. Furthermore, molecular stimulation of apigenin is bound to a site near the α-glucosidase active site, which could trigger the channel closure to restrict the access of substrate, ultimately leading to α-glucosidase inhibition. Geranylated flavonoids, namely, 3′-O-methyl-5′-O-methyldiplacone, 4′-O-methyldiplacone, 3′-O-methyldiplacone, 4′-methoxyflavanone, mimulone, 4′-O-methyldiplacol, and 3′-O-methyldiplacol isolated from Paulownia tomentosa and it was a significant inhibitory effect on α-glucosidase with IC50 values ranging from 2.2 to 78.9 μM [6]. Besides that, rutin, kaempferol hexose, and catechin were the most abundant flavonoids found in

the extraction of R. roxburghii fruits dispersion. Among these components, catechinhas the greatest inhibitory effects on α-glucosidase with the highest IC50 value [4].

Inhibitors of Glucose Cotransporter

A glucose mimic from a carbohydrate-rich diet is a major essential metabolic substrate that is absorbed from the border of the intestine into target cells via the bloodstream. In this process, integral transport proteins act as shuttles in the processes of glucose transport across plasma membranes. These glucose cotransporters can be divided into two categories: (i) sodium-dependent glucose transporters (SGLTs) and (ii) facilitative glucose transporters (GLUTs) [4].

SGLT is an energy-dependent sodium/glucose cotransporter that plays an essential role in glucose absorption. SGLTs are in the intestine and in the proximal tubules of the kidney and allow glucose absorption. These carrier proteins transport glucose through active transport [5]. SGLT uses the movement of sodium ions down its electrochemical gradient to transport glucose into target cells. SGLT1 and SGLT2 are SGLT isoforms, with SGLT2 having a lower affinity and found almost exclusively in the kidney, where plasma glucose transport from the glomerular filtrate occurs [6]. SGLT2 has become a major drug target because inhibition of SGLT2 can reduce glucose reabsorption by increasing urinary glucose excretion while simultaneously controlling blood glucose levels. Formononetin compounds derived from Sophoraflavescens, which are also frequently used in traditional Chinese medicine, showed potent SGLT2 interrupting activity [7]. On the other hand, although SGLT1 has a high affinity and is found primarily in the small intestine, it is also expressed in the kidney to restore any remaining glucose to prevent glucose loss in the urine. Quercetin 4′-O-glucoside (Q4′glc), a flavonoid from onion, has the strongest inhibitory effect on SGLT1 in hyperglycemic mice [7].

SLC2 genes are responsible for encoding GLUT proteins, which are responsible for the transport of monosaccharides, small carbon compounds and polyols across plasma membranes using a diffusion gradient. GLUTs show different substrate specificities, tissue expression profiles and kinetic properties. Many members of the GLUT family express themselves differently. GLUT1 is expressed almost ubiquitously in all normal tissues, often in association with one or more other GLUT isoforms to maintain a basal glucose supply. GLUT2 and GLUT3 are involved in fundamental processes such as pancreatic insulin secretion [13] and neuronal glucose [8]. Several flavonoids have demonstrated their inhibitory effects on GLUT2, However, GLUT4, which is mostly found in the heart and brain, is responsible for insulin-stimulated glucose transport. Note that GLUT7, which has a high affinity for both glucose and fructose, showed high levels in the ileum responsible for sugar uptake at the end of a meal when sugar concentrations gradually decrease [9].

Flavonoids of various plants and their hypoglycemic effects

Over the years, flavonoids from plant sources have shown antidiabetic activity through several mechanisms in vitro and in vivo. Common flavonoids with hypoglycemic properties include quercetin, kaempferol, rutin, naringenin, fisetin, and morin. Plants such as Fagopyrumtataricum, Gynuraprocumbens, and Tetraceraindica, which consist of flavonoids, have also been reported to have significant hypoglycemic effects [10].

Plant flavonoids.

Quercetin

Quercetin (3,5,6,3′,4′-pentahydroxyflavone) is a naturally occurring flavonoid commonly found in plants and fruits. Some of the many plants that consist of quercetin are green leafy vegetables, seeds, nuts, broccoli, onions, olive oil, pepper, tea leaves and red wines, as well as fruits such as apples, cherries and blueberries [11]. Quercetin from plant sources was effective in lowering blood glucose levels. It can regulate glucose absorption leading to glucose homeostasis through interaction with various molecular targets in skeletal muscle, pancreas, small intestine, and liver in the body [12]. The hypoglycemic action of quercetin includes inhibition of intestinal carbohydrate digestion, glucose transporter activity and hepatic glucose production, and improvement of glucose utilization in peripheral tissues as well as protection against pancreatic islet damage [12].

Quercetin-rich extracts from Vacciniumvitis-idaea exhibit antidiabetic activity through stimulation of the AMP-independent protein kinase (AMPK) insulin signaling pathway and

subsequent basal glucose uptake in skeletal muscle cells [13]. The molecular mechanism of action of quercetin in L6 myotubes and found that quercetin improves glucose uptake through the AMPK signaling pathway in muscle cells [14]. In skeletal muscle, activation of the AMPK pathway can increase glucose uptake by translocating glucose transporter 4 (GLUT4) to the plasma membrane. On the other hand, the AMPK pathway reduces hepatic glucose production through the downregulation of enzymes involved in gluconeogenesis, such as glucose-6 phosphate and phosphoenolpyruvate carboxylase [15]. In addition, quercetin has the potential to suppress glucoside uptake activity that is mediated by SGLT 1 in human intestinal epithelial cells (Caco-2) through interaction with transporters. Quercetin lower blood glucose levels by inhibiting α-

glucoside activity, which is involved in carbohydrate digestion [16]. Both sucrase and maltase activities were found to be significantly inhibited after treatment with quercetin in vitro and in

vivo at a dose of 50 mg/kg. Quercetin could protect against islet beta-cell damage and promote beta-cell regeneration [17].

The hypoglycemic effect of quercetin has been studied in animal models. Quercetin remarkably reduced plasma glucose levels in streptozotocin-induced diabetic rats on day 21 of treatment compared to control rats. Another study also revealed that consuming a diet containing quercetin at different concentrations (0.04% and 0.08%) for six weeks significantly reduced blood glucose levels by up to 15% and 31% in mice with type 2 diabetes compared to control group. group without quercetin [18]. An in vivo study claimed that quercetin reduced oxidative damage and increased glucose uptake in rats through AMPK activation [19]. Quercetin also has the ability to reduce intestinal glucose uptake and lower postprandial blood glucose levels in diabetic mice through inhibition of the glucose transporter GLUT2 [20]. In addition, Allium cepa L. peel extracts containing quercetin as their major flavonoids were shown to alleviate insulin resistance and hyperglycemia in STZ-induced diabetic rats fed a high-fat diet through upregulation of glucose uptake in peripheral tissues as well as downregulation of liver gene in inflammation [21]. Therefore, it is suggested that quercetin can be further developed as a natural antidiabetic agent. High quercetin content is commonly found in many plants including Allium fistulosum, Calamusscipionum, Camellia sinensis, Capsicum annum and Euonymus alatus [22].

Kaempferol

Kaempferol (3,5,7-trihydroxy-2-[4-hydroxyphenyl]-4H-1-benzopyran-4-one), also known as kaempferol-3, kaempferide, and the flavanolkaempferol, is a major flavonoid aglycone that can be isolated from plants [23]. It consists of the following characteristics: high antioxidant activity, anti-inflammatory activity, anti-cancer activity and anti-diabetic properties [24]. Ingested kaempferol will be absorbed in the small intestine and then further cleaved into glucuronide- and sulfo-conjugated forms [25].

Kaempferol can stimulate insulin secretion and reduce glucose absorption in the small intestine or regulate blood glucose levels. The effect of kaempferol concentration (50, 100 and 200 mg/kg) on plasma glucose levels in normal and STZ-induced diabetic rats [26]. Oral administration of kaempferol does not significantly alter blood plasma glucose levels in normal rats; however, it significantly reduced plasma glucose levels in diabetic rats after 45 days of treatment. However, it has also been shown to increase plasma insulin in diabetic rats. It demonstrated a maximal hyperglycemic effect at the highest concentration (200 mg/kg) of treatment. kaempferol exhibited a strong inhibitory effect on α-glucosidase [27]. In CD spectra analysis, the addition of kaempferol

to α-glucosidase increased the tendency of α-helix and random coil content (from 30.8% to 34.2% and from 27.6% to 29.8%, respectively). It indicates that kaempferol reacts with α-glucosidase to form a complex, kaempferol-α-glucosidase. The insertion of kaempferol into human islets exposed to chronic hyperglycemia, and caspase-3 activation is significantly reduced. Kaempferol is able to protect beta-cells against hyperglycemia-induced beta-cell toxicity [28] it could also restore Bcl-2 protein expression in beta-cells and islets. The expression of AMPK and GLUT4 proteins in skeletal muscle and adipose tissue of mice fed a HF diet [29]. The expressions of AMPK and GLUT4 are significantly reduced in skeletal muscle and adipose tissue of obese mice, while treatment with 0.05% kaempferol increased the expression. In addition, kaempferol has been shown to have potent antidiabetic properties with high potential for development as an antidiabetic agent [30]. Fruits and vegetables such as tomatoes, grapes, broccoli, cabbage and cabbage also contain kaempferol. In addition, it is also found in medicinal plants such as Ginkgo biloba, Tilia spp. and Sophora japonica [30]. However, data on the long-term effects and toxicity levels of kaempferol intake on the human body are insufficient. Thus, more clinical and in vivo studies with different concentration of kaempferol are needed [31].

Rutin

Natural rutin (3′,4′5,7-tetrahydroxy-flavone-3-rutinoside) is a citrus flavonoid glycoside that is abundant in plants. Rutin is also called quercetin-3-rutinoside, rutoside, and soforin. The name "rutin" comes from the plant Rutagraveolens, which contains rutin [32]. In recent years, rutin appears to be widely used as an additive in health supplements and medicine [33]. Rutin has many benefits such as powerful antioxidants, radical scavenging effects, antidiabetic effects and anti-inflammatory effects [34]. Low levels of antioxidants in the blood generally show a higher risk factor for the development of chronic disease, and antioxidants are important in the prevention of DM [35]. After rutin enters the human body, it can be degraded into small metabolites by intestinal bacteria. Initially, rutin is metabolized to quercetin 3-O-glucose by loss of rhamnose and then loses glucose molecules and is converted to leucocyanidin [36].

Numerous studies have shown that rutin inhibits two enzymes that catalyze the digestion of carbohydrates, α-glucosidase and α-amylase. Inhibition of these enzymes blocks the small intestine from absorbing glucose molecules, thereby preventing a sharp rise in blood glucose [36]. An in vivo study of an oral

glucose tolerance test (OGTT) biochemical study in normal and diabetic rats [37]. In rutin-treated diabetic mice, liver glycogen and serum insulin levels are significantly decreased. Rutin reduced plasma glucose, glycosylated hemoglobin, serum tumor necrosis factor alpha (TNF-alpha), interleukin-6 (IL-6), and high-density lipoprotein (HDL) in diabetic rats [38]. Rutin treatment also improved islet cell structure. Increased glucose uptake in rat muscle in response to insulin is controlled by signaling through the insulin receptor and phosphoinositide 3-kinase (PI3K). PI3K in rutin signaling pathways, activating several proteins such as protein kinase B (PKB), akt substrate 160 kDa (AS160) and protein kinase C (PKC). These proteins significantly translocate GLUT4 from the intracellular pool to the plasma membrane [38]. There is no doubt that pancreatic beta-cells play a key role in insulin secretion, and insulin is released into the bloodstream when blood glucose levels are high. Insulin promotes glycolysis and excess glucose is removed from the blood [39]. However, insulin secretion and insulin resistance are dependent on calcium homeostasis. Changes in calcium concentrations can activate voltage-gated calcium channels, and insulin secretion is highly dependent on voltage-activated Ca2+ influx [39]. Rutin can alter Ca 2+ uptake in isolated pancreatic islets followed by an increase in Ca 2+ uptake. Rutin is safe at a concentration of 2000 mg/kg and intake of rutin from food sources does not cause any
toxic effects [53]. Rutin is widely distributed in plants such as Rutagraveolens, Morus alba, asparagus and buckwheat [39].

Naringenin

Naringenin (4,5,7-trihydroxy-flavanone) is a dietary flavonoid widely found in citrus and grapefruit. Several studies of naringenin have demonstrated its antidiabetic, antidyslipidemic, antiatherogenic and anti-inflammatory properties. The hypoglycemic effects of naringenin have been investigated both in vivo and in vitro. In an in vitro study, naringenin was found to ameliorate the effects of fructose and palmitate-induced insulin resistance by improving glucose uptake through insulin stimulation and translocation of the glucose transporter GLUT4 in L6 myotubes and skeletal muscle through AMPK activation [40]. The anti-diabetic activity of naringenin and found that naringenin increased skeletal muscle glucose uptake through AMPK activation [40]. Sambucusnigra L. (elder flower) represents naringenin because one of its main bioactive components significantly increases glucose uptake in primary cultures of porcine myotubes from animals [41]. Effects of naringenin on pancreatic β-cells and demonstrated that naringenin was able to increase insulin secretion through glucose stimulation and protect beta-cells from apoptosis [41].

Furthermore, several in vivo studies have investigated the results of naringenin treatment in streptozotocin-induced animal models.The hypoglycemic properties of naringenin and revealed that a short-term five-day treatment with naringenin could significantly reduce plasma glucose levels in streptozotocin-nicotinamide-induced diabetic rats [42]. A study that investigated the effects of naringenin extracted from orange peel revealed that naringenin could increase insulin receptor beta-subunit, GLUT4 and tissue insulin sensitivity in STZ/NA-induced diabetic rats [42]. Also, another study in STZ-induced diabetic rats fed a high-fat diet and treated with naringenin showed a significant reduction in postprandial blood glucose levels by inhibiting intestinal α-glucosidase activity, which prolongs carbohydrate intake. absorption in rats [42].

A reduction in plasma glucose after consumption of a citrus polyphenol extract containing naringenin for 12 weeks [42]. However, naringenin has also been found to exhibit hypoglycemic effects by inhibiting gluconeogenesis through upregulation of AMPK, which has a similar antidiabetic effect to metformin, a type of drug that is intended to treat DM [42]. This suggests that naringenin has the potential to be further explored as an alternative anti-DM drug. Naringenin can be extracted from various medicinal plants such as Madagascar periwinkle, Catharanthusroseus and Elaeodendroncroceum [42].

Fisetin

Fisetin (3,3′,4′,7-tetrahydroxy flavone) is structurally related to flavan-3-ol and is found in various types of plants such as apples, strawberries, grapes, persimmon, cucumber and onion at concentrations of 2–160 μg /g [100]. Fisetin plays a huge role in pharmacological properties that include anticancer, anti-inflammatory, antiproliferative and antihyperglycemic activities [43]. In addition, fisetin has antidiabetic effects and can reduce methylglyoxal-dependent glycation of proteins. It contributes to the reduction of DM complications [43]. Glucose homeostasis may also be improved by fisetin by weakening the body's carbohydrate metabolism enzymes. During oral treatment with fisetin administered at a dose of 10 mg/kg continuously for 30 days, a decrease in glycated hemoglobin (Hb1Ac) could be observed. In addition, blood glucose levels and protein level expression of gluconeogenic genes have also been shown to decrease. At the same time, there is also an increase in plasma insulin concentration [43].

Many studies have been conducted to investigate the antidiabetic properties of fisetin in rats. In an in vivo study, NF-κB p65, serum nitric oxide (NO), hemoglobin A1C (HbA1c), and blood glucose levels were shown to be significantly reduced by fisetin treatment [43]. On the other hand, there is no indicative change in blood glucose levels in control rats during the experimental period. The antidiabetic and antioxidant activity of fisetin in streptozotocin-induced rats [43]. The results showed a significant reduction in blood glucose and an

increase in plasma insulin after treatment with fisetin. This can be demonstrated by the absence of sugar in the urine of diabetic rats treated with fisetin. In another report, fisetin was shown to regulate hyperglycemia-mediated oxidative stress, inflammatory processes, and programmed cell death. These finally showed improvement in the development of diabetic cardiomyopathy in STZ-induced DM rats [43].

In an in vitro study, fisetin was shown to reduce both glycogenolysis and gluconeogenesis. Fisetin can inhibit glucose, lactate, and pyruvate that are released from endogenous glycogen. A Revis concentration of 200 mMfisetin could produce maximal inhibition of glycogenolysis (49%) and glycolysis (59%). Meanwhile, 300 mMfisetin could inhibit gluconeogenesis from lactate and pyruvate or fructose [44]. In addition, cytokine production induced by glucose biomolecules in monocytes is inhibited by fisetin, which would possibly prevent DM [44]. In addition, fisetin plays an essential role in enhancing hexokinase activities. Reduction of glucose-6-phosphate dehydrogenase (G6PD) and glucose-6-phosphatase (G6Pase) activity has been demonstrated with fisetin [44]. Fisetin is a flavonoid dietary component found in the smoke tree (Cotinuscoggygria) [73] and rich sources of fisetin can be found in plants such as Butea frondosa, Gleditsiatriacanthos, Quebracho Colorado, Curcuma longa, Rhusverniciflua, Acacia greggii, and Acacia berlandieri [44].

Morin

Morin (3,5,7,2′,4′-pentahydroxyflavone) is a natural bioflavonoid and is also a major component of traditional medicinal herbs, which is primarily isolated from members of the Moraceae family. Morin appears as a pale yellowish pigment and is a component of many herbs, fruits and wine [45]. In addition, morin is also available in Psidiumguajava (Indian guava). Guava contains antioxidant properties and is traditionally considered an effective antidiabetic plant [45]. Morin has many benefits for human health and has been reported for its potent antioxidant and other pharmacological properties, including antimutagenesis, anti-inflammatory [45], cardioprotection and antiallergic [45]. Through in vivo and in vitro studies, many previous investigations have shown and demonstrated the antioxidant, anti-inflammatory and anti-proliferative effects of morin [45]. Furthermore, morin as an insulin-mimetic flavonoid has been shown to have antidiabetic properties.

In addition, insulin levels in diabetic rats also increase in a fisetin-dependent manner. Potentiation of pancreatic insulin secretion from existing beta-cells or by its release from the bound form may be a possible mechanism formorin's hypoglycemic effect [46]. Whereas the results in diabetic rats treated with a higher dose of 30 mg/kg per day, there was a significant (< 0.05) reduction in blood glucose levels and at the same time, insulin levels were significantly (< 0.05) increased comparedto untreated diabetic rats [46]. In animal models, oral administration of morin for 30 days has been shown to significantly improve hyperglycemia, glucose intolerance, and insulin resistance. There was also a reduction in lipid peroxide levels and concomitant improvement in antioxidant competence inmorin-treated diabetic rats [46].

In addition, morin is proven for its anti-inflammatory effects, as it can effectively reduce the levels of inflammatory cytokines such as IL-6 and TNF-α [84]. Morin exhibits a systemic protective effect and helps reduce the negative side effects of several drugs without interfering with their functions. In addition, in vitro and in vivo studies have shown that morin exhibits very low levels of toxicity. In addition, its chronic administration is well tolerated. It has been suggested that morin could be used either alone or in combination with other drugs to prevent many human pathologies. In addition to Psidiumguajava, morin can also be found in seed weeds, almonds (Prunusdulcis), figs (Chrozophoratinctoria), and Osage orange (Maclurapomifera) [46].

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