The potential effects of dietary flavones on diabetic nephropathy; a review of mechanisms

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ABSTRACT

Diabetes as a chronic metabolic disorder affects the worldwide population with high incidence of morbidity and mortality. Different complications such as nephropathy, neuropathy, ocular diseases, and cardiovascular disease are common in patients with diabetes that threaten the patient's lifestyle. Diabetic nephropathy (DN) usually is related to some major structural alterations in the kidney which characterized by generation of toxic reactive oxygen species (ROS) or inhibition of antioxidant systems in kidney tissue. Different natural agents have been introduced to be used as a complementary treatment to prevent diabetic kidney disease. Flavones (apigenin, luteolin, nobiletin and chrysin) as a subgroup of flavonoids are natural occurring substances which have several pharmacological activates, including antioxidant, anti-apoptotic, anti-inflammatory, and anti-tumor efficacy. Recent evidence indicated that flavones may be effective for prevention and treatment of diabetes complications in experimental models. The present study was designed to review the relationship between flavones administration and diabetes and diabetic kidney disease by focusing on the possible molecular pathway. The findings indicate that flavones have protective effects against diabetic kidney disease by modulation of different pathways related to oxidative stress, inflammation, and apoptosis in animal models. Therefore, more clinical investigations are suggested to be conducted to find the protective effects of flavones in patients with diabetes.

Implication for health policy/practice/research/medical education:
Reactive oxygen species overproduction in diabetes is known to be associated with the pathways generally lead to inflammation in renal tissue, endothelial dysfunction, and renal fibrosis.

Introduction

Diabetes as a chronic metabolic disorder is characterized by hyperglycemia related to lack of insulin (type I) and presence of insulin resistance (type II) (1). Although the etiology of this disorder is not clear yet, different factors such as autoimmune disease, viral infection, and environmental causes have been suggested (2). Diabetes accompanied by numerous complications in patients which commonly affects the cardiovascular system, peripheral nerves, kidney, eye, ear, and skin and consequently, these are too costly in terms of quality and longevity of life (3).

Diabetic nephropathy (DN) or diabetic kidney disease is one of the most serious complications of diabetes which causes end-stage renal failure in these patients. Recently, diabetic kidney disease has been reported to involve about 15% to 25% of patients with type I diabetes (4) and 30% to 40% of type II diabetes patients (5). Diabetic kidney disease is clinically recognized by a progressive increase of albumin level in urine (albuminuria) and a subsequent decline in the glomerular filtration rate (GFR) (6). The pathogenesis of diabetic kidney disease usually is related to some major structural alterations in the kidney such as glomerular capillaries enlargement, renal hypertrophy, thickening of glomerular basement membrane due to excessive deposition of extracellular matrix, and mesangial expansion (7). Chronic hyperglycemia affects the function of numerous renal cells. Thereby, podocytes, cells of the tubular and collecting ducts the glomerular endothelial cells, smooth muscle cells, and mesangial

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cells may subsequently conduct the activation of several pathological processes leading to diabetic kidney disease (8). Several mechanisms have been defined to determine the underlying effects of hyperglycemia in induction of tissue damage. Oxidative stress has been demonstrated as a major culprit in kidney disease in diabetes which significantly disrupts renal hemodynamics known to be related to diabetic kidney disease (9). Oxidative stress, which referred to an imbalance between production of pro-oxidants and antioxidant defenses, plays a crucial role in the pathogenesis of diabetes (10). Pro-oxidants are chemical components are characterized by the generation of toxic reactive oxygen species (ROS) or inhibition of antioxidant systems. Therefore, ROS plays a critical role in high glucose-induced renal dysfunction (5). Accordingly the compounds are involved in the accumulation of ROS are known as antioxidants. Endogenous antioxidants have an important role in regulation of cellular functions (11). The most efficient enzymatic antioxidants involve superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) (12).

Free radicals, the reactive chemical species with unstable configuration have a single unpaired electron in an outer orbit which provides energy to react with adjacent molecules such as lipids, proteins, nucleic acids, and carbohydrates (13). Recent studies provide growing evidence that the ROS overproduction in diabetes is known to be associated with the pathways generally lead to inflammation in renal tissue, endothelial dysfunction and renal fibrosis (14).

There has also been shown that neutralization of free radicals can significantly inhibit the development of diabetes complications, although there is still some controversy about administration of antioxidants and its effectiveness in lowering the risk of diabetes development and its complications (15). Various antioxidants have been suggested for treatment of hyperglycemia-induced damages in diabetes. Vitamins, some components of plants and fresh fruits (16). Additionally, many diabetic patients prefer to select some alternative and complementary therapies along with mainstream anti-diabetic medications, which can be protective against the complications of diabetes (17).

Flavonoids, as a large family of compounds with common chemical properties are synthesized by plants (18). Flavonoids can be further divided into six major subclasses according to their chemical structure (with C ring generic structure); flavonols (quercetin, rutin kaempferol, morin and myricetin), flavanones (eriodictyol, hesperetin, narigin, taxifolin, fisetin, and naringenin), flavans-3-ol (catechin), isoflavonoids (genistein, genistin, daidzein, and glycitein), flavones (apigenin, luteolin, nobiletin, chrysin), and anthocyanins (delphinidin, cyanidin, pelargonidin, malvidin, peonidin, and petunidin). Flavonoids represent a large class of at

least 6000 phenolic compounds; and some have been demonstrated to act as the anti-diabetic agents (19). Polyphenols extracted from these natural sources can be used as a supplementary treatment for repairing the diabetes-induced damages due to their biological features (20). In addition to the potent antioxidant properties, dietary flavonoids also improve glucose and lipid metabolism and exhibit anti-inflammatory properties (18). Additionally, natural and plant source agents, such as flavonoids with a more specific focus on diabetic renal injury, would cause less treatment-related morbidity (21).

In the present review, we focused on the connection between flavones and diabetic kidney disease on the basis of recent studies. The anti-diabetic functions and the underlying molecular signaling of the flavones found in dietary plants, fruits have been investigated using basic and clinical researches.

Flavones

Flavones (Figure 1) are known as important and powerful subgroups. The most famous flavones are luteolin (LUT), apigenin, nobiletin, and chrysin (22). These compounds have a diversity of activities, which contribute to plants adaptation to a terrestrial environment. In addition to the different biochemical, physiological, and ecological activities in plants, flavones also exhibit biological functions on animals, considering as valuable nutrients (23).

To discuss the health benefits of flavones, it should be noted that, these components have this ability to scavenge ROS. Analysis of structural-activity classification of flavonoids identified that LUT is one of the most potent suppressors of xanthine oxidase which known as a key enzyme in ROS production (24). Besides, apigenin prevents endothelial cells from lipopolysaccharide-induced damage during acute inflammation and modulates mitochondrial activity by reducing ROS (25).

Furthermore, the anti-inflammatory functions of flavones seem to be related to their ability to modulate the toll-like receptor/ nuclear factor-kB (NF-kB) which is responsible for the regulation of inflammatory mediators e.g. tumor necrosis factor α (TNFα), interleukin1β (IL1β) and cyclooxygenase-2 (26). Several
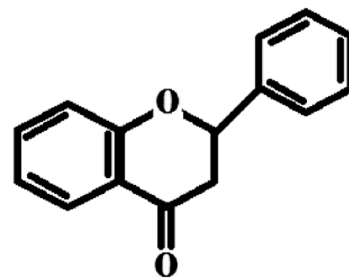

Figure 1. Chemical structure of flavone.

interventions have shown that consumption of flavones can enhance the activity of blood antioxidant enzymes, including glutathione reductase, SOD, GPx, and CAT (27). Consistent with the ability of flavones to decrease oxidative stress and regulate inflammation, interventions on the flavone enrich diet showed anti-diabetic properties too (28).

Effect of flavones on diabetes nephropathy
Luteolin

LUT, as an anti-diabetic flavone can be found in large amounts in common consumed fruits and vegetables e.g. cabbage, carrots, celery, peppers, onion leaves, apple skins, parsley, broccoli, and chrysanthemum flowers (29). Various biological functions of LUT are induced by inhibition of oxidative stress and inflammation. It has been shown that LUT mediates its effects by modulation of different molecular targets such as transcription factors (nuclear factor-kB [NF-kB] and activating protein-1 [AP1]), cytokines (TNFα, IL1, IL6 and chemokines), and enzymes (inducible nitric oxide synthase inhibitor) (30). Moreover, the antioxidant property of LUT has been found to be related to its Nrf2 activating capability in previous studies (31).

Various studies have supported the anti-diabetic characteristics of LUT. LUT was shown to improve action of insulin and upregulate the expression of peroxisome proliferator-activated receptor-γ (PPARγ) target genes in 3T3-L1 adipocytes and primary mouse adipose cells (32). The metabolic pathways related to the insulin resistance has been shown to be beneficially affected by this substance. Furthermore, LUT attenuates the pathophysiology of DM by suppressing the circulating levels of inflammatory chemokines such as monocyte chemoattractant protein-1 and resistin (33). Moreover, LUT has been proven to increase the levels of insulin in uric acid-induced pancreatic β-cells damage by suppressing the reduction of the mast cell function-associated antigen and particularly through signaling pathways related to the NF-kB and inducible nitric oxide synthase–nitric oxide (iNOS–NO) (34). Wang et al evaluated the effects of LUT on DN in streptozotocin (STZ)-induced diabetic rats and proven that the LUT induced its protective effects using lowering BUN and creatinine and regulating the SOD activity, the MDA content and protein expression of Heme Oxygenase-1 (HO1) in diabetic animals (35). It should be noticed that HO1 is an enzyme, thought to have antioxidant and cytoprotective characteristics and is capable to change the heme into carbon monoxide, equimolar amounts of iron, and biliverdin (36). Additionally, Chen et al demonstrated that oral administration of LUT (10 and 20 mg/kg/d for 4 weeks) protected the mice against STZ-induced diabetic renal damage through the regulation of insulin signaling pathway and receptor-interacting protein 140 (RIP140)/NF-kB pathway (37).

Apigenin

Apigenin (40,5,7-trihydroxyflavone) belongs to the flavone subclass of flavonoids which is mostly extracted from the plant kingdom. Glycosylated apigenin is mainly distributed in significant amount in fruits (oranges), vegetables (parsley, onions and celery), herbs (chamomile, thyme, oregano and basil), and plant-based beverages (beer and tea), nuts and soy (38). Apigenin has been attributed with a wide range of biological functions. The anti-diabetic activity of apigenin has also been extensively studied. In has been reported that apigenin administration can reduce hyperglycemia in diabetic mice (39). Moreover, Suh et al stated that apigenin ameliorates damage in pancreatic β-cells by suppressing the signaling involved in oxidative stress (40). Intraperitoneal administration of apigenin had a significant anti-hyperglycemic impact in STZ-induced diabetic rats (41).

Recent studies have been reported the administration of apigenin can be beneficial in diabetic complication as such cardiovascular defects which ameliorates endothelial dysfunction in thoracic aorta of diabetic rats (42). To confirm the free-radical scavenging activity, oral consumption of apigenin (0.78 mg/kg BW) for 10 days has been reported to enhance the hepatic antioxidants content in diabetic mice induced by alloxan (43). As an antioxidant, apigenin reduced the apoptosis of clonal β-cells in the 2-deoxy-D-ribose-induced toxicity through enhancing the mitochondrial membrane potential (44). As a well-known activator of AMP-activated protein kinase (AMPK), apigenin was shown to be 200 times more potent than metformin. Additionally, apigenin decreases the phosphorylation of acetyl-CoA carboxylase and impeded lipid accumulation in HepG2 cells exposed to high glucose, suggesting that apigenin has valuable effects on diabetes and dyslipidemia by regulating metabolic pathway related to the AMPK-dependent signals (45). Furthermore, different studies proved the beneficial effects of apigenin against renal dysfunction in diabetes. Malik et al reported that the treatment of rats with apigenin (20 mg/kg) significantly normalized serum creatinine, blood urea nitrogen, and urinary albumin level which improved renal dysfunction in diabetic rats. They showed that apigenin mitigated STZ-induced DN in rats by regulation of oxidative stress and reducing the kidney fibrosis via TGF-β1- mitogen-activated protein kinases (MAPKs)-fibronectin and MAPK/NF-κB/TNFα pathways (46). In an *in virto* study, Zhang et al proved that apigenin (100 and 200 μM) protected the human renal epithelial cell (HK-2) against induced by high glucose (exposed to hyperglycemia) through regulating the NF-E2-related factor-2 (Nrf2) pathway (47).

Chrysin

As an active flavone, chrysin (5,7-dihydroxyflavone) naturally presents in propolis, honey, chamomile, even

in mushroom and passion flowers and other plant sources (48). This compound exhibits strong biological characteristics and anti-diabetic effects of chrysin also were investigated. Singh et al reported that mixture of Baicalin and chrysin showed cyto-protection effects against diabetic induced tubular injury through modulation of inflammation, oxidative stress, and RAGE (49). The protective effects chrysin against the DN were investigated in different studies. Kang et al showed that chrysin (1-20 μmol/L) inhibited the diabetes-induced kidney tubulointerstitial fibrosis via suppressing the transition of epithelial to mesenchymal (50). In the other study, Kang et al showed, chrysin (1-20 μmol/L) ameliorated podocyte injury through inhibition of the protein kinase RNA-like endoplasmic reticulum kinase (PERK)/ eukaryotic initiation factor 2α (eIF2α)/ activating transcription factor / and C/EBP homologous protein (CHOP) pathway involved in the endoplasmic reticulum stress (51). They also showed that chrysin (1–20 μM) inhibited kidney fibrosis related to the advanced glycation end products (RAGE) in renal mesangial cells and diabetic kidneys through reducing the accumulation of matrix proteins and myofibroblast-like cells (52). Additionally, Singh et al reported that the mixture of baicalin (75mg/kg b.wt.) and chrysin (10 mg/kg b.wt) exhibited cytoprotective effects against the methylglyoxal-induced cytotoxicity and diabetic tubular injury via modulation of oxidative stress, inflammation and also regulation of receptor proteins synthesis (49).

Nobiletin

Nobiletin (5,6,7,8,3′,4′-hexamethoxyflavone) is a nontoxic dietary polymethoxyflavones that can be in citrus fruits such as citrus sinensis (oranges), *Citrus depressa* (shiikuwasha), and *Citrus limon* (lemons) (53). Nobiletin has been reported to exhibit pharmacological activities including anti-oxidation, anti-tumor, anti-inflammatory, and neuroprotective features (54). Furthermore, the anti-diabetic characteristics of nobiletin have been mentioned in several studies. Lin et al reported that nobiletin suppressed the expressions of pro-inflammatory cytokines, including IL-1, IL-6 and TNFα in mouse macrophages (55). Likewise, Saito et al demonstrated that nobiletin enhances the differentiation and lipolysis of 3T3-L1 adipocytes, but does not act as a PPARγ ligand (56). Lee et al stated that nobiletin improved hyperglycemia and insulin resistance in obese diabetic ob/ob mice by regulation of glucose transporter (Glut)1 and Glut4 expression in white adipose tissue and muscle, and adipokines expression in white adipose tissue (57).

Based on the evidence, the protective effects of nobiletin against the diabetes complication such as neuropathy has been detected (58). The nephroprotective effects of nobiletin have been demonstrated for cisplatin induced acute renal injury too (59). Additionally, Liu et al reported that nobiletin suppressed the high-glucose-induced inflammation and extracellular matrix (ECM) accumulation in human mesangial cells via signal transducer and activator of transcription 3 (STAT3)/NF-κB pathway (60).

Conclusion

Flavones as naturally occurring agents present in a wide variety of vegetables, fruits, and beverages. This substance has a wide range of pharmacological and biological functions which induce many potential beneficial activities in animal studies mainly in diabetes and diabetes complications. To protect the kidney against the diabetes induced injury, flavones exhibit antioxidant and anti-inflammatory properties, which these should be further explored. Additionally, future clinical trials are suggested to be performed to confirm the potential effects of flavones in diabetic patients.

Authors' contribution

LM and MZ made substantial *contributions* to conception. LM, AM and MZ have been involved in drafting the manuscript or revising it critically for important intellectual content. MZ has given final approval of the version to be published.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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