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Review

Luteolin: protective effects against diabetes and diabetes associated complications

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Abstract

Diabetes is known to be associated with a deficiency of insulin affecting directly or indirectly other important parts of the human body. There are various forms of treatment in Ayurveda and other traditional medicinal systems which use naturally occurring compounds for the treatment of diseases. One such widely studied phytochemical is Luteolin. Luteolin is known to be present in a wide variety of plant species, especially edible plants like carrots and cucumbers. Luteolin belongs to the group of flavonoids having its unique properties and is known to inhibit pro-inflammatory cytokines. The cellular actions and properties make luteolin a potent anti-diabetic compound. Luteolin's antioxidant function, together with its hypoglycemic ability, protects the pancreas and facilitates the secretion of insulin which makes it effective and important for medicinal studies. In this review, we will focus upon the ability of luteolin to treat diabetes and its related complications.

Keywords: luteolin, phytochemical, diabetes, diabetic nephropathy, reactive oxygen species.

Introduction

Diabetes is one of the oldest known diseases, which was mentioned in the Egyptian Manuscript some 300 years ago (13). Diabetes is a group of metabolic conditions which is described by hyperglycemia, associated with insulin deficiency (type 1), and insulin resistance (type 2) (1). The causes of these diseases are not known yet, but some possible causes are autoimmune diseases, obesity, genetic history, family background, alcohol consumption, sedentary lifestyle, and environmental causes (2, 68–70). A number of complications is seen under diabetes which commonly affects the cardiovascular system, the peripheral nerves, the kidney, eyes, ears, and skin (3, 71–73). The people who are having type 1 diabetes were confirmed to have a high rate of bone turnover, resorption, and decreased level of 1-25-hydroxycholecalciferol (prehormone which produced in the liver by hydroxylation of vitamin D_3 by the enzyme cholecalciferol 25-hydroxylase) (5–7). Negative protein balance and disturbance in hormonal balance are the other risk factors for osteoporosis in type 1 diabetes (8). In many studies, the bone density decreases in type 1 diabetes compared to non-diabetic subjects (5, 8–9).

The most common form of diabetes is type 2 diabetes also known as non-insulin-dependent diabetes, which is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency (10, 14). The risk of gestational diabetes for people relates to the underlying occurrence of type 2 diabetes (11, 12). The interaction between genetic, environmental, and behavioral risk factors results in type 2 diabetes (15, 16), while other risk factor includes changes in primary lifestyle (17). It is expected that in the next two decades the prevalence of type 2 diabetes in adults will increase and majorly affect the patients between 45 and 64 years of age (18). Physical inactivity, a sedentary lifestyle, cigarette smoking, and generous alcohol consumption are the lifestyle factors for type 2 diabetes (19). Obesity was found to be the leading cause of type 2 diabetes in 55% of cases. According to the IDF Diabetes atlas, it was estimated that there were 451 million (age 18–95 years) people with diabetes in 2017 worldwide. This was expected to increase to 693 million by 2045. Additionally, it was estimated that almost half of all people (about 49.7%) living with diabetes are undiagnosed. In 2017 approximately 5 million death worldwide were attributed to diabetes in the 20–99-year age range (4).

Several medicines are in use to treat diabetes, but long-term use of synthetic medicines causes side effects in diabetic patients which include hypoglycemia episodes, gastrointestinal problems (vomiting, nausea, and diarrhea) (30). From ancient times the use of traditional medicine gained significance in the treatment of diabetes. Many forms of traditional medicine such as Ayurveda and Unani medicine is being used worldwide. Many countries serve traditional medicine as the main source of health care because of their affordability, cultural acceptability, and trust by the people (28). A 80% population of the world relies on traditional medicine as the primary source of health care (29). Medicinal plants contain proteins, essential oils, triterpenoids, saponins, flavonoids, tannins, and coumarins. The therapeutic activity of these medicinal plants depends on the interaction of several classes of phytochemicals (31). There are more than 1200 species of medicinal plants that were evaluated for their anti-diabetic activity, approximately 200 pure bioactive compounds were reported to possess potent hypoglycemic properties (32). Phytochemicals are bioactive chemical components extracted from plants and are responsible for the medicinal plant extracts that have pharmacological effects (23). From these the polyphenolic compounds, especially flavonoids are the most productive chemical groups with a broad range of health-promoting practices and pharmacological effects, such as antioxidant, anti-diabetic, anti-inflammatory, neuroprotective, anticancer, and cardioprotective effects (24).

Phytochemicals are used in the treatment of diabetes; as they can control blood sugar levels in the body. Flavonoids are a very common group of polyphenols which is having a general structure of a 15-carbon skeleton consisting of two benzene rings attached via a heterocyclic pyrene ring, in a C6–C3–C6 arrangement (21). At present, there are more than 8000 flavonoids that are classified into different sub-groups, such as chalcones, flavones, flavanols, flavanones, flavanols, anthocyanins, and isoflavones (25). Luteolin (3′,4′,5,7-tetrahydroxy flavone) is a wide group of polyphenolic low molecular weight compounds specific to plants (26). This is because flavone has inhibited pro-inflammatory cytokine production (22). It is naturally found in a glycosylated form that occurs in various vegetables and fruits like broccoli, chilly, pepper, thyme, and celery (27).

On the perusal of the above literature, we can say that luteolin is found abundantly in plants like celery, green pepper, chamomile tea, and have several health benefits like anti-mutagenic, anti-tumorigenic, anti-oxidant, anti-diabetic and anti-inflammatory. In this review article, we discuss how luteolin is being used as an anti-diabetic agent and in treating diabetes-related complications.

Sources of luteolin

Luteolin is one of the most common flavonoids present in edible plants. For example, it has been found in carrots (*Daucus carota* L.), peppers (*Capsicum annuum* L.), celery (*Apium graveolens* L.), olive oil (*Olea europaea* L.), peppermint (*Mentha piperita* L.), thyme (*Thymus vulgaris* L.), rooibos tea (*Aspalathus linearis* (*Burm.f.*) *R.Dahlgren*), buckwheat sprouts (*Fagopyrum esculentum Moench*), turnip (*Brassica napus* L.), capers (*Capparis spinosa* L.) and cucumber (*Cucumis sativus* L.). In lemons, beets, brussels sprouts,

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cabbage, cauliflower, chives, fennel, harwort, horseradish, kohlrabi, parsley, spinach, and green tea; luteolin has also been found (33). The plants which are used in traditional medicine, also have luteolin in them, for example, *Terminalia chebula* Retz (33, 34). It is found in the leaves, barks, rinds, and pollen of the plant. Luteolin is a flavone aglycone found in the largest genus of Plantaginaceae (formerly Scrophulariaceae), Veronica, which consists of approximately 500 species. The species of Veronica have gained interest due to their common uses and biological activities (35). Luteolin was also isolated from the aromatic flowering plant *Salvia tomentosa* Mill., which is traditionally used to alleviate wound healing (36).

Structure of luteolin

Luteolin, 3′,4′,5,7-tetrahydroxyflavone, is part of a group of naturally occurring compounds called flavonoids which are commonly present in the plant kingdom. Flavonoids are polyphenols that play an important role in the protection of plant cells against micro-organisms, insects, and UV irradiation (37). Evidence from cell culture, animal, and human population studies have suggested that flavonoids are also beneficial to human and animal health. Because of their abundance in foods, (e.g. vegetables, fruits, and medicinal herbs), flavonoids are common nutrients that are antioxidants, anti-diabetic, estrogenic regulators, and antimicrobial agents (38). Luteolin belongs to the flavone group of flavonoids and has a composition of C6-C3-C6 and has two benzene rings (A, B), a third oxygen-containing (C) ring, and a double bond of 2-3 carbons. Luteolin also has carbon 5, 7, 3', and 4' hydroxyl groups (39). Hydroxyl molecules and 2-3 double bonds are important luteolin structural features associated with its biochemical and biological activities (40) (Figure 1).

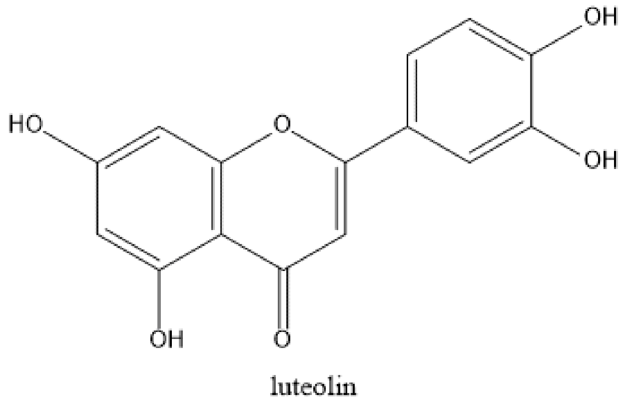

Figure 1: Structure of Luteolin

Bioavailability, oral absorption of luteolin

Previously it was thought that the oral bioavailability of flavonoids is very limited. However, the bioavailability of luteolin in peanut hull extracts was investigated in one study (45). The analysis showed that the efficient permeability with the constant rate of absorption of pure luteolin is 5.0 μg/ml. Peanut hull extracts have greater efficient permeability and the constant rate of absorption of the pure luteolin. In a single dose of pure luteolin, the oral absorption is 14.3 mg/kg in rats (45). 5,7,3',4'-Tetramethoxyflavone (TMF) luteolin analog is a methoxy flavone isolated from *Kaempferia parviflora* (46). The bioavailability of TMF after absorption was 14.3%. An excretion study confirmed that after 48 hours, 0.81% of the oral TMF given was mostly faecally excreted in its pure form while only 0.05% was urinary excreted; indicating that TMF was mainly excreted as the metabolites developed (46). This gives us information that luteolin and its analogs may be very useful.

Toxicity: The safety profile of luteolin is unclear till now (47). For mammalian cells, the luteolin and its analogs may be deleterious and affect the endocrine system (48). Since the oral absorption of luteolin is 15%, the concentration of luteolin present in the available dietary supplements is unlikely to reach the concentration capable of inducing toxicity (48).

Anti-diabetic activity of luteolin

Luteolin is an effective multi-benefit flavonoid and has been identified to activate different functions that collectively promote luteolin as an outstanding anti-diabetic agent (Figure 2). Luteolin is recognized to be a relatively secure antioxidant. The formation of free radicals accompanied by oxidative damage to the pancreatic islet cells causes' diabetes. By inhibiting the enzymes that produce ROS, luteolin may prevent the development of reactive oxygen species (ROS) and can absorb ROS and secure the constituents of other antioxidant systems (49). Luteolin's antioxidant function, together with its hypoglycemic ability, protects the pancreas and facilitates the secretion of insulin. Using experimental diabetic animal models, the free radical generation, and suppression of lipid peroxidation have been proven (50). ROS is caused by the development of diabetes in which protein glycation results in oxidative stress. Luteolin in experimental mice curbs the increase in ROS generation during disease progression (51). Luteolin's free radical scavenging activity is reportedly documented via the Nrf2 (nuclear-related factor2) pathway (52). Luteolin stimulates the eNOS (nitric oxide synthase) pathway and boosts the SOD (Superoxide dismutase) function. Experimental diabetic animals and diabetic humans have a down-regulated eNOS pathway and the NOS interacts with superoxide dismutase causing free radical generation (53). For the organs to be stress-free the balance between the pro-oxidants and antioxidants is very important. Pro-oxidants promote the generation of non-radical ROS and the disturbance in the balance between pro-oxidant mechanisms and antioxidant defenses results in diseases and disorders, especially diabetes (54). Luteolin, apart from its antioxidant ability, unexpectedly displays a pro-oxidant effect. The status of luteolin can be determined by the presence of ions like iron and copper (55).

AKT2 (Protein kinase B) prevents insulin receptor dephosphorylation and thereby prevents the insulin signaling mechanism from being attenuated. The regulation of glucose uptake is also the duty of Akt2, and this effect is mediated by the translocation of the GLUT4 (Glucose transporter) glucose transporter to the cell surface (56). Luteolin is known to promote insulin sensitivity by affecting kinase Akt2 (57). Luteolin can also control the normal level of blood glucose and thus minimize lipolysis, which helps to maintain the levels of triglycerides and total cholesterol and avoids the development of diabetic cardiomyopathy (58). By activating the NOS pathway and reducing ischemia/reperfusion injury, luteolin has been shown to protect diabetic hearts (53). Luteolin enhances the production of HO-1(Hemeoxygenase-1) and phosphorylation of AKT and reduces renal tissue cytogenetic degradation and diabetic nephropathy (58).

Luteolin also helps reduce diabetic neuropathy (51). Luteolin demonstrates its beneficial effects by enhancing the blood flow of the nerve and thereby enhancing the rate of nerve conduction by this effect the reduced nerve damage and avoided diabetic neuropathy (51, 56). Luteolin minimizes diabetes-induced inflammation and inflammation-induced diabetes (59). Liu et al., 2014 recently demonstrated that by reducing

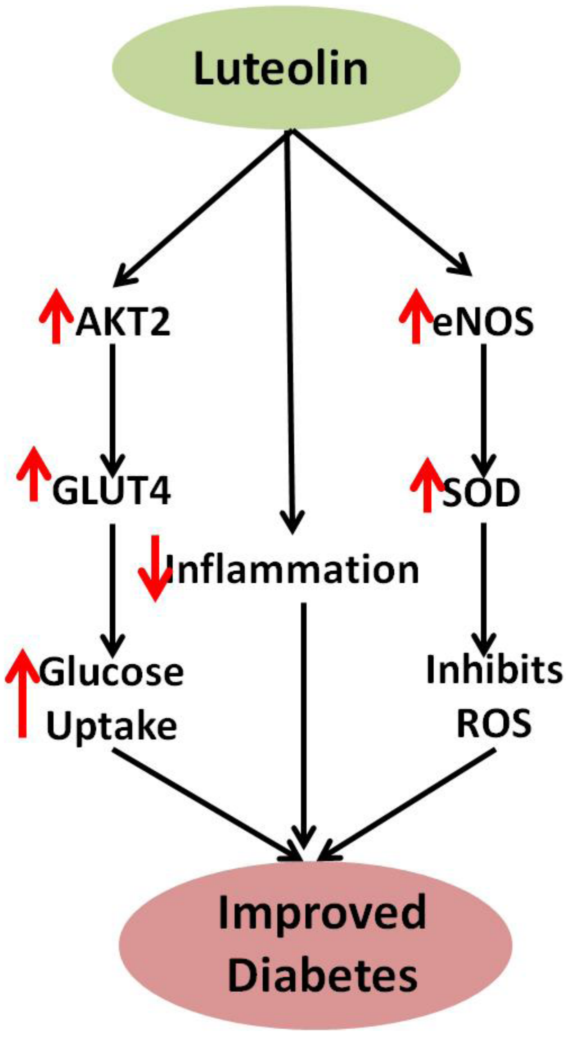

Figure 2: Role of luteolin in improving diabetes.

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neuronal injury and lipid peroxidation function, treatment with luteolin (50 and 100 mg/kg) can reduce cognitive impairment in streptozotocin-induced diabetes (60). Therefore, by these approaches, we can say that oral luteolin supplementation may be a preventive approach for reducing cognitive impairment associated with diabetes.

Role of luteolin in the treatment of diabetic nephropathy

Luteolin is an anti-diabetic flavone, the inhibition of oxidative stress and inflammation causes different biological functions of the luteolin. It modulates different molecular targets and shows its effect by modulating transcription factors like cytokines (TNFα, IL6, chemokines), enzymes (inducible nitric oxide synthase inhibitor), nuclear factor-kB (NF-kB), and activating protein-1 (AP1) (61). In comparison, with previous studies, the antioxidant activity of luteolin is correlated with its Nrf2 activating potential (62). In 3T3-L1 adipocytes and primary mouse adipose cells, luteolin has been shown to enhance the function of insulin and control the function of peroxisome proliferator-activated receptor-γ (PPARγ) target genes (63). By blocking the circulating levels of inflammatory chemokines like monocyte chemoattractant protein-1, luteolin attenuates diabetes epidemiology (64).

In uric acid-induced pancreatic β-cell damage, luteolin also has been shown to increase insulin levels by disrupting the decrease of the mast cell function-associated antigen and specifically by signaling pathways similar to NF-kB (nuclear factor-kB) and inducible nitric oxide synthase-nitric oxide (iNOS–NO) (65). In streptozotocin (STZ) induced diabetic rats, Wang et al examined the impact of luteolin on diabetic nephropathy and demonstrated that luteolin induced its beneficial role by reducing the activity of BUN (blood urea nitrogen) and creatinine and by monitoring the SOD, MDA (Malondialdehyde) levels, and protein expression of Heme Oxygenase-1 (HO1) in diabetic animals (66). The HO1 is an enzyme that is known to have antioxidant and cytoprotective properties and can transform the heme into carbon monoxide, equimolar iron, and biliverdin quantities (67). In another study, luteolin was tested in vivo in db/db mice where it ameliorated interstitial fibrosis and glomerular sclerosis by inhibiting ROS production (74). In another experiment done on the Sprague-Dawley rat, luteolin was able to delay the DN progression (75). Another report showed that luteolin was able to restore dyslipidemia, insulin resistance, renal inflammatory cell infiltration, and hyperuricemia in STZ-induced mice (76).

Conclusion

Luteolin possesses anti-diabetic activity that has been studied worldwide. Studies done on cell lines and animal models have supported the fact of it being a good anti-diabetic agent. Persistent high blood glucose levels often cause complications like nephropathy, neuropathy, cardiomyopathy, and atherosclerosis. Luteolin is an important bioactive flavonoid that also shows neuroprotective and nephroprotective effects. Many studies have been reported where researchers studied the role of luteolin in DN progression. Results were quite significant as they ameliorated DN to a great extent.

Conflict of Interest

The authors declare that no conflict of interest exist with the publication of this work.

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