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Luteolin in the Management of Type 2 Diabetes Mellitus

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Abstract

Diabetes is an increasing pandemic and several million people are affected by this disease worldwide. The treatment of diabetes includes lifestyle modifications, oral antidiabetic drugs and insulin. The chronic use of oral antidiabetic drugs produces undesirable side effects. Hence safe alternative medicines are always sought after. Plant phytochemicals are the best alternatives as they possess a wide spectrum of pharmacological activities. Flavonoids are an important class of phytocomponent which is commonly present in fruits and vegetables. Luteolin belongs to flavone class of flavonoid which has multiple health benefits like antioxidant, antidiabetic, anti-inflammatory and anti-cancer properties. Luteolin mediates several pharmacological actions of which the role of luteolin in the treatment of diabetes is well studied. In this review, the use of flavonoids as antidiabetic agents is discussed, with special reference to luteolin. Luteolin mediates its anti-diabetic potential by maintaining blood glucose levels and improving the sensitivity of body cells to insulin and these mode of actions have been discussed here.

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Introduction

Diabetes is the oldest known metabolic disorder characterized by hyperglycemia, insulin deficiency and/or insulin resistance and associated imbalance in the homeostasis of glucose, lipid and protein. The prevalence of diabetes is increasing steadily and it is estimated that 439 million people would be diagnosed with type 2 diabetes (T2DM) by the year 2030. The most common type of Diabetes Mellitus (DM) is T2DM and its occurrence can be attributed to the interaction betweenvarious genetic, environmental and lifestyle factors.[1,2,3]

Chronic hyperglycemia results in various short term orlong term microvascular complications in kidney, eyes, heart and periphera. These complications account for the morbidity and mortality seen in patients with T2DM.[2]

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Management of T2DM includes diet interventions, lifestyle modifications, oral hypoglycaemic agents, insulin secretagogues, insulin sensitizers and insulin. Antidiabetic drugs have serious side effects like hyperlipidemia, fatigue and gastrointestinal tract disturbances. Also, these oral hyperglycemia drugs lose their efficacy in due course of time.[4] Weight gain and hypoglycaemia are the commonly reported side effects of insulin injections. Hence proper control of diabetes continues to intrigue doctors and diabetics.[4] These undesirable side effects of antidiabetic drugs can be side-lined by alternative therapies.

According to World Health Organization, about 80% of the world population relies on Complementary and Alternative Medicine (CAM) for primary health care. CAM modalities include medicinal herbs, acupuncture, excercises, etc.[3] Medicinal plants and the phytoconstituents present in medicinal plants are safe alternatives to synthetic oral antidiabetic drugs. Plant phytoconstituents play multiple beneficial roles apart from lowering blood glucose levels. They function as antioxidants, anti-lipidemic agents and enhance insulin secretion as well.[3,5] This review summarizes antidiabetic potential of flavonoids in general and luteolin in particular.

Alternative Medicine for Diabetes Therapy

Traditional medicine is used for management of diabetes in many countries. The herbs used in traditional medicine are readily available, cost effective and have very low side effects unlike drugs used in conventional medicine. More than 800 medicinal plants used in Ayurveda and other Indian medicine practices possess antidiabetic activity. These plants exert their antidiabetic potential by inhibiting enzymes involved in glucose generation or by promoting secretion of insulin.[6,7] The antidiabetic activity of the medicinal plants is contributed to the secondary metabolites such as glycosides, alkaloids, terpenoids and flavonoids present in various parts of the plants. This review focuses on the role of flavonoids, luteolin in particular, in the management of diabetes.[8]

Flavonoids

Flavonoids are plant secondary metabolites that form a large class of compounds with polyphenolic structures. They are widely found in nuts, fruits, vegetables, grains, beverages and herbs. Flavonoids are structurally made up of two six-membered aromatic rings (A and B)linked by a three carbon chain which may or may not be a part of a third ring (C).[9,5] Based upon the functional group on rings, the position of attachment of ring B to ring C and the structure of ring C, flavonoids are classified in to subgroups. They are flavones, flavonols, flavanols, flavanones, isoflavones, and anthocyanins. The individual flavonoids are differentiated by the hydroxylation and conjugation patterns.

- Flavones are an important subgroup of flavonoids and are found in fruits, leaves and flowers. Commonly found flavones are Luteolin and apigenin.
- Flavonols are the most common flavonoids. They possess a ketone group and are precursor molecules of proanthocyanins. Commonly studied flavonols are quercitin, kaempferol and rutin.
- Flavonones are citrus flavonoids, also called dihydroflavones. Flavonones are different from flavones only at the bond between position 2 and 3 in the C ring, which is saturated in flavonones. Commonly found flavonones are hesperitin and naringenin.
  Flavanols, the 3- hydroxyl derivatives of flavanones, are primarily found in fruits. The common flavanol is catechin.
- Isoflavonoids are also called phytoestrogens and are mainly found in leguminous plants. The B ring is attached at to C ring at C 3 rather than the usual C 2 position. The best studied isoflavonoids are genestein and daidzein.
- Anthocyanins are plant colouring pigments often found in berries. The well-studied anthocyanins include pelargonidin and cyanidin. The colour of anthocyanin depends on the acetylation or methylation of the hydroxyl groups of the flavonoid skeleton.[10]

The potential benefits of flavonoids are well established by several scientific reports. The wide spectrum of pharmacological advantages of flavonoids includes anti-oxidant,anti-inflammatory, anti-microbial, anti-diabetic, anti-ulcer, anti-atherosclerotic, anti-thrombotic, anti-neoplastic, anti – angiogenic, anti – tumorigenic activities. Flavonoids also protect the cardio-vascular, hepatic, renal and gastric systems.[9,11,12,13]

Luteolin

Luteolin is 3',4',5,7-tetrahydroxy flavone belonging to the flavone group of flavonoids. The molecular formula of Luteolin is $C_{15}H_{10}O_6$.The biological activities of luteolin are attributed to its hydroxyl moieties and the double bond present between C2 and C3 (Figure 1).

Luteolin is present in a variety of fruits and vegetables. Carrot, cabbage, celery, artichoke, peppers, onion, apple and apple peels are rich in luteolin. Luteolin is mostly present as its glycosylated form in plants. Luteolin is heat stable and hence losses due to cooking do not incur.[14] Post absorption by the intestinal mucosa, luteolin is converted into its free form or as glucoronide. It circulates in the plasma as free luteolin, glucuronides or sulphate conjugates.[15] Luteolin can permeate the blood brain barrier and hence acts as a therapeutic agent for an array of nervous disorders.[14]

Luteolin is an active flavonoid with a wide range of biological activities. The well-known pharmacological activities of luteolin such as anti-oxidant, anti-inflammatory, anti-estrogenic, anti-tumorigenic, anti-mutagenic, anti-apoptotic, anti-allergic and anti-diabetic have been established scientifically.[15] Luteolin exerts beneficial immunomodulatory effects and thus assists in the treatment of neurodegenerative diseases.[16] Luteolin mediates its pharmacological activities through the modification of signalling systems like AKT/GSK 3β, AKT/PKB and NFκB-AF1 pathways.[17,18]

Flavonoids in Glucose Homeostasis

Several *invitro* and *invivo* approaches have proposed that flavonoids possess antidiabetic activity and consumption of flavonoids can mitigate the risk of diabetes. Flavonoids can improve insulin secretion by the pancreatic cells[19] and increase sensitivity to insulin.[20] Flavonoids can alter metabolic pathways of glucose homeostasis. They can promote glycolysis and glycogenesis, inhibit gluconeogenesis and glycogenolysis.[21,22] Flavonoids have been proved to promote insulin uptake by modifying GLUT4.[23] Studies also claim that flavonoids exhibit hypoglycaemic activity by inhibiting carbohydrate hydrolyzing enzymes such as amylase, glucosidase and disaccharidases.[24,25] The complications associated with diabetes are the contributing factors for the morbidity and mortality seen in diabetic populations. The microvascular complications are promoted by the accumulation of sorbitol, a product of polyol pathway. Glucose is converted to sorbitol by aldose reductase and the ensuing accumulation of sorbitol results in osmotic imbalance which culminates in cataract, nephropathy and neuropathy. Inhibition of aldose reductase by flavonoids has been reported to control diabetes and its pathophysiology.[26]

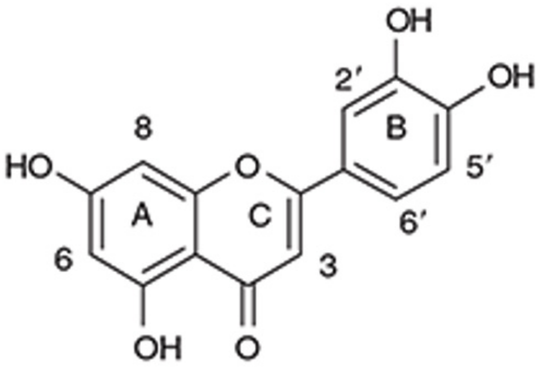

Fig. 1: Structure of luteolin

Antidiabetic Activity of Luteolin

Luteolin is a potential flavonoid with multiple benefits and has been reported to mediate multiple functions that collectively promote luteolin as a remarkable antidiabetic agent. Luteolin is considered to be a safe antioxidant. The generation of free radicals followed by oxidative injury to the islet cells of pancreas cause diabetes. Luteolin can prevent the generation of Reactive Oxygen Species (ROS) by inhibiting the enzymes that generate ROS, can scavenge ROS and can protect the components of other antioxidant systems.[14] The antioxidant activity of luteolin coupled with its hypoglycaemic potential protects the pancreas and promotes insulin secretion. The inhibition of free radical generation and repression of lipid peroxidation has been proved using experimental diabetic animal models.[18] ROS is generated by the progression of diabetes wherein glycation of proteins culminates in oxidative stress. The increase in ROS generation during disease progression is curbed by luteolin in experimental mice.[27] The free radical scavenging activity of luteolin is reportedly through Nrf2 pathway.[28] Diabetic humans and experimental diabetic animals have a down-regulated eNOS (nitric oxide synthase) pathway. NOS interacts with superoxide dismutase and its down-regulation results in injury by free radicals. Luteolin, reportedly, activates the eNOS pathway and enhances SOD activity.[29]

Antioxidants, though, prevent the onset of oxidative stress, a balance between antioxidants and pro-oxidants is highly important for a tissue/organ to be stress-free. Pro-oxidants promote the generation of non-radical ROS and the disturbance in the balance between pro-oxidant mechanisms and antioxidant defences results in diseases and disorders, especially diabetes.[30] Luteolin, surprisingly exhibits pro-oxidant effect apart from its antioxidant potential. The mechanism underlying the dual action is yet to be investigated. However, the micro-environment of the cell is said to influence the anti or pro-oxidant status of any compound. The presence of ions such as iron and copper and the concentration of these ions can determine the status of luteolin.[14]

Luteolin is reported to improve insulin sensitivity by influencing the Akt2 kinase.[31] Akt2 prevents the dephosphorylation of the insulin receptor and thus prevents attenuation of the insulin-signaling process. Akt2 is also responsible for the regulation of uptake of glucose and this effect is mediated by the translocation of GLUT4 glucose transporter to the surface of the cell.[32]

Luteolin can maintain fasting blood glucose in normal levels and thus prevent lipolysis. This helps in maintaining the triglyceride and total cholesterol levels in near normal limits and thus preventing the onset of diabetic cardiomyopathy.[18] Zhang *et al.,* suggest that Luteolin hinders the onset of diabetic cardiomyopathy via the AKT/GSK 3β pathway. In addition, luteolin has been proved to protect diabetic hearts by activating the NOS pathway and ameliorates ischemia/reperfusion injury.[29]

Hemeoxygenase-1 (HO-1) is an antioxidant and a cytoprotectant. Luteolin increases HO-1 expression and phosphorylation of AKT and prevents morphological destruction of renal tissues and diabetic nephropathy.[18] Luteolin alleviates diabetic neuropathy as well.[27] It presents its beneficial effects by improving nerve blood flow and thereby improving nerve conduction velocity. These effects attenuated nerve damage and prevented diabetic nephropathy.[27] Lu *et al.,* [33] have reported on the protection offered by luteolin in diabetes induced retinal neuro degeneration.

Several reports established the correlation between inflammation and diabetes.[27,34,35] The inflammatory cytokines reduce beta cell function and induce insulin resistance.[27] Luteolin attenuates inflammation induced diabetes and diabetes induced inflammation.[5] The flavonoid exerts its protective effect by ameliorating the hyperglycemia induced increase in inflammatory markers.

Conclusion

Luteolin, a flavone type of flavonoid possesses various pharmacological activities and has been proved to exert its beneficial effects in several experimental disease models. Luteolin exhibits appreciable antidiabetic potential which has been well studied. The underlying mechanisms and the signalling pathways involved in its antidiabetic role are reported. However, the synergistic effect of luteolin and other flavonoids in management of diabetes needs more exploration and must be established in both invitro and invivo models. This will help to ascertain relatively safe doses of luteolin in the treatment for diabetes.

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Conflict Of Interest

The authors do not have any conflict of interest.

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