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Luteolin and its derivatives as potential antidiabetic drug ingredients

Ayusman Swain*[1]

[1]*Lecturer of Chemistry, Department of Mathematics and Science, Government Polytechnic Kendrapara, Odisha 754289, India*

Email: ayusman.iitd@gmail.com

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Abstract: Luteolin is a flavone class natural product that occurs as a free or as in glycoside form in nature and is often derived from plant sources. Though it is reported as a natural antioxidant like other flavonoids, many studies found it as a potent ingredient for diabetic management. Its antidiabetic activities both *in vitro* and *in vivo* are reviewed from recent works of literature found from the articles searched in PubMed, ScienceDirect and Google Scholar. Luteolin and its derivatives were studied for their potential anti-bacterial, anti-fungal, anti-inflammatory, antioxidant, anti-apoptotic, anti-allergic along with its anti-hyperglycemic activities. The antidiabetic effect of luteolin was supported by different mice model experiments, enzyme inhibitory assays and molecular docking studies. The review suggests further clinical studies with a larger sample size for the determination of appropriate doses and synergistic actions.

Keywords: Luteolin, Anti-hyperglycemic, Antioxidant, α-Glucosidase, Enzyme inhibition, Insulin resistance

Introduction

Luteolin ($C_{15}H_{10}O_6$) is found in many edible and medicinal plants, such as pepper, onion, apple, artichoke, cabbage, celery, carrot, and spinach. Many phytochemical studies have reported the presence of luteolin as aglycone or in glycoside form in plants belonging to different families such as Asteraceae, Rosaceae, Leguminosae, Cyperaceae, Gentianaceae, Scrophulariaceae, Clusiaceae, Lamiaceae, Caprifoliaceae, Passifloraceae, Plantaginaceae and Polygonaceae [1]. Luteolin possesses strong antioxidative, anti-inflammatory and potential anti-cancer activities as reported by earlier works of literature [2,3]. Studies have also claimed the enhancement of insulin resistance in diabetic mice was due to the bioactivity of luteolin [4,5]. The biological activities of luteolin (Fig 1) have been attributed due to the

position of hydroxyl (-OH groups) moieties and the C_2= C_3 double bond in ring B [6].

The plant secondary metabolites like phenolics and flavonoids are of pharmacological importance as they are the ingredients for many drugs, functional foods and preservatives [7]. Several studies reported the flavonoids from different food materials could control lipid profile, glucose metabolism, regulate enzyme functions and thus can protect the human body from oxidative stress, obesity, diabetes, inflammations and other complications [8]. The flavone, luteolin has an array of biological functions as an anti-oxidant, anti-tumorigenic, anti-mutagenic, anti-apoptotic, anti-allergic, anti-inflammatory and anti-estrogenic [1,3]. Luteolin, when administered, maybe in free form or glucuronide form while it circulates in the plasma. Luteolin has been reported to act as a therapeutic agent for many nervous system disorders and mediates the modification of different signaling systems (e.g. AKT/GSK 3β, and AKT/PKB pathway) [9].

Materials and methods

The biological activities of luteolin were searched from different search engines like PubMed, ScienceDirect and Google Scholar. The keyword luteolin was searched in combination with antidiabetic activity, natural α-glucosidase inhibitor, anti-hyperglycemic drug, flavonoid activities in the management of diabetes, biological activities and pharmacological importance. Among the searched literature, the relevant publications of luteolin activities relating to anti-diabetic properties were reviewed.

Table 1. Reported biological activities of luteolin and its derivatives

Compounds studied	Biological activity	Reference
Luteolin	Antidiabetic, Anti-inflammatory and anti-oxidative effects	[5]
	Antioxidant activity, antibacterial activity and hypoglycemic effect	[31]
	Effective in ameliorating ethanol-induced hepatic steatosis and injury in mice.	[18]
	Protection against the development of diabetic nephropathy	[4]
	Inhibition of α-glucosidase and α-amylase	[21]
	Antimicrobial activity against *S. aureus* and *L. monocytogenes*.	[32]
	Antioxidant, anti-inflammatory and anti-allergic activities	[3]
	Cardiovascular protective effect	[20]
	Potential anticancer activities	[33]
5-hydroxy-3′,4′-dimethoxyflavone-7-O-(rhamnoside) and 5-hydroxy-3′-methoxyflavone-4′-O-(penthenyl-4-one)-7-O-(2″-(rhamnosyl) rhamnoside)	Antibacterial activity against Gram-positive bacteria	[34]
Luteolin-7-O-glucoside	Antidiabetic, Anti-inflammatory and anti-oxidative effects	[5]
Luteolin-7-O-glucoside	Antibacterial activity against *Salmonella typhimurium* and antifungal activity against *Alternaria alternate.*	[35]

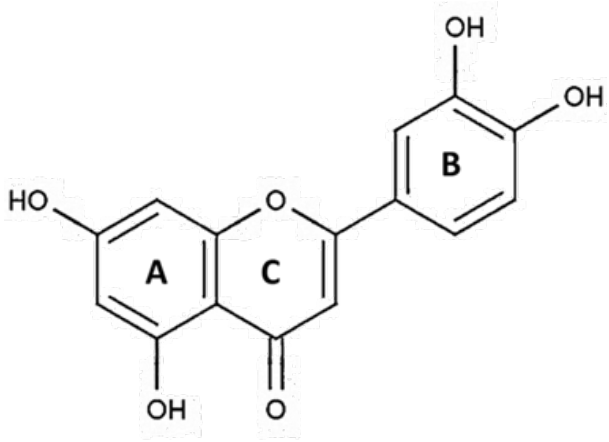

Fig. 1. Structure of Luteolin

Results and Discussion

Flavonoids in glucose homeostasis

Several *in vitro* and *in vivo* studies revealed the potential bioactivities of flavonoids in managing diabetes and improving insulin secretion and sensitivity. Flavonoids also can alter metabolic pathways of glucose homeostasis [10]. Some reports also claim that flavonoids exhibit inhibitory activities against amylase, glucosidase and other sugar hydrolyzing enzymes [11–13]. Aldol reductase converts glucose to sorbitol and excess sorbitol causes osmotic imbalance leading to the development of cataracts, nephropathy and neuropathy. Flavonoids are potential inhibitors of aldol reductase and thus, can work for controlling diabetes. The flavonoids such as quercetin and taxifolin have been extensively studied and reviewed for their various biological activities, particularly anti-diabetic properties [14,15]. The present review makes an effort to outline the anti-diabetic studies of luteolin and its derivatives as these compounds are widely distributed in nature in plants of several families.

Antidiabetic activity of luteolin

Luteolin and its derivatives or glycosides have been studied by various research groups for its important biological activities and disease suppression potential (Table 1). Diabetes can be due to the oxidative injury to pancreatic islet cells by Reactive Oxygen Species (ROS) or excess free radicals [16]. Luteolin possesses ROS scavenging activity to protect the components of physiological systems and the pancreas [17]. Along with its antioxidant activity, it also promotes insulin secretion [5,9,18]. Activation of the nitric oxide synthase pathway and enhancement of superoxide dismutase (SOD) activity was also regulated by the luteolin molecule and thus it can prevent free radical-mediated injury [5,19,20].

Inflammation and diabetes are correlated as the insulin resistance is induced by the reduction of beta-cell (β-cell) function by inflammatory cytokines.Luteolin can minimize inflammation-induced diabetes. The flavonoid exerts its protective effect against inflammatory markers [5,21,22]. The anti-inflammatory activity of luteolin has a large impact on the reduction of insulin resistance in rat model experiments [9]. Diabetes treatment is being carried out with oral anti-hyperglycemic drugs and insulin injection Common drugs used in oral administration are commercially available anti-hyperglycemic drugs, such as glycosidase inhibitors, sulfonylureas, biguanides, and thiazolidinedione derivatives. These types of medications have specific toxic and adverse effects leading to other disorders and reduced insulin receptor sensitivity [23,24]. Administration of flavonoids may exert antioxidant, antimicrobial, anticancer, antitumor, anti-inflammatory and cardiovascular actions inside the human body [1,11,13]. Recent *in vivo, in vitro* and *in silico* studies have greatly supported the anti-diabetic properties of some flavonoids like quercetin, taxifolin and luteolin [6,9,12,14,25].

In vivo anti-hyperglycemic activities of luteolin

Diabetic nephropathy is due to alterations in specific renal morphology and functions. High glucose-induced renal injury can be stimulated by ROS [26]. Wang et al suggested that the intracellular ROS also leads to the pathogenesis of diabetes or diabetic nephropathy [4]. In this context, the luteolin action can change the (SOD) activity, the malondialdehyde (MDA) level and the Heme Oxygenase-1 expression via antioxidative properties. Wang et al studied the streptozotocin (STZ) induced diabetic mice where the blood glucose level (BGL) of the STZ induced mice were measured before and after diabetes induction. After confirmation of diabetes, luteolin was fed at a dose of 200 mg/kg. After eight weeks when a high BGL was confirmed in controlled mice, the blood samples, urine samples and kidneys were collected and biochemically analyzed with the due procedure [4].

The results showed that in the diabetic group the BGL reached more than four times higher compared to that of the control group after 48 h of incubation. After 8 weeks there was no significant change in BGL in the diabetic group. The luteolin-treated diabetic group showed a decrease in BGL (from 21.73 to 13.66 mmol/L) within 8 weeks. Luteolin also protected the rats from bodyweight loss. Administration of luteolin at 200 mg/kg brought back the Blood urea nitrogen (BUN), creatinine and 24-h urea protein to close to the normal values which were increased in STZ-induced diabetic rats. The levels of serum triacylglycerol (TG), total cholesterol (TC), and low-density lipoprotein (LDL) were increased in STZ-induced diabetic rats while the respective values increased in the luteolin-treated group of rats. The level of high-density lipoprotein (HDL) was significantly increased in the luteolin-treated group of rats. A significant enhancement in SOD activity and reduction in MDA level in the kidney homogenate sample was observed due to luteolin treatment. The histological study showed an improvement in the damaged glomerulus and tubulointerstitial lesions. The western blot analysis also showed an elevation of the expression of cytoprotectant enzyme Heme Oxygenase-1. Luteolin improved nerve blood flow and thus improves nerve conduction velocity. These effects of luteolin treatment prevented diabetic nephropathy and retinal neurodegeneration [27].

Luteolin reportedly improves insulin sensitivity when it influences the AKT2 kinase. Luteolin also maintains normal levels of fasting blood glucose to prevent lipolysis. This helps in maintaining the TG and TC levels in reference limits. Diabetic cardiomyopathy via the AKT/GSK 3β pathway is also regulated by luteolin treatment and the diabetic hearts are protected by activating the nitric oxide synthase pathway preventing oxidative injury [4,28].

Zang et al studied the antidiabetic properties of luteolin and luteolin-7-O-glucoside using KK-A^y mice [5]. The mice were divided into 3 groups: the control group (CON group); the luteolin treated group (LU group) and luteolin-7-O-glucoside treated group (LUG group). Equimolar luteolin and luteolin-7-O glucoside were added in the respective diets. In their experiment, the mice were anesthetized after regular food intake for 28 days. Then by cardiac puncture, the blood was collected for analysis. The BGL, serum HbA1c, HOMA-IR index, and insulin levels in KK-A^y mice were found to be significantly lower in the LU and LUG groups than those in the CON group indicating the reduction in hyperglycemia and hyperinsulinemia. LU has shown to have stronger antidiabetic activity than LUG though both were showing a reduction in BGL. The TC and TG levels were decreased and HDL levels improved in both serum and liver by administration of LU and LUG. Inflammation and oxidative stress are related to the pathogenesis of diabetes. TNF-α, which affects the β-cell function and induces insulin

resistanceis a pro-inflammatory cytokine [29]. A decrease in the serum TNF-α, liver TBARS, TNF-α mRNA expression was observed in the LU and LUG groups. The overall result indicated that LU and LUG can be effective drug ingredients against diabetes and LU activity was better than LUG.

Based on these results, it is envisaged that luteolin may be treated as a drug ingredient to enhance the redox balance and prevent the damage of the physiological components due to diabetes mellitus. The high antioxidant activity of luteolin may have a pronounced effect on prevention of the diabetic nephropathy progression.

In vitro enzyme inhibition studies

Luteolin and its derivatives such as amentoflavone, luteolin 7-O-glucoside, and daidzein were strong inhibitors of α-amylase and α-glucosidase as reported by Kim et al [21]. The *in vitro* enzyme inhibition assay was performed with a standard procedure where the inhibitor was tested for its inhibitory potential against α-amylase where starch was taken as substrate. The inhibitory potential against α-glucosidase was tested by taking PNPG (4-Nitrophenyl α-D-glucopyranoside) as substrate [7,21,24]. Luteolin showed 36% inhibition against α-glucosidase at 0.5 mg/mL and was shown to be a better inhibitor than acarbose (the most widely prescribed drug). The result suggested that luteolin may suppress postprandial hyperglycemia in patients. Luteolin also inhibited α-amylase but with less potent than acarbose. Earlier reports claim that that the catechol system on the ring B, the presence of C_2=C_3 double bond and the ketonic group at C_4 position altogether enhances bioactivity, particularly the antidiabetic effects [30]. The double bond position and the substituent position were also studied theoretically in molecular docking and kinetics experiment. Along with the C_2=C_3 double bond the position of the substituent on B-ring (carbon no. 3' and 4') and A-ring (carbon no.5 and 7) of any flavonoid have an important role in α-glucosidase inhibition kinetics [6,12]. Luteolin exhibited α-amylase with IC_{50} value 78 μM and was observed to show a competitive inhibition [6]. Structure-activity relationship studies were performed for varieties of flavonoid compounds and were found that many flavonoids have the potential to be used as an alternative to the widely prescribed drug, acarbose. The structure of flavonoids, number and position of -OH groups determine the intended properties of the flavonoids [12]. Luteolin showed better α-glucosidase inhibiting potential (IC_{50} value 46 μM) compared to acarbose (IC_{50} value 607 μM). Hence potentially effective flavonoids like quercetin, taxifolin, luteolin and others can be used as drug ingredients for type-II diabetes therapeutics. Dong et al [31] synthesized luteolin–manganese(II) complex and performed glucose digestion assay in HepG2 cell line. The complex has Mg(II) ion bonded to the chelation sites of 5-hydroxy and 4-carbonyl in two luteolin molecules. It was observed that the complex had a higher anti-hyperglycemic effect than luteolin. Even the antioxidant and antibacterial activities were improved after complexation.

Conclusion

Luteolin has many beneficial effects proved in experimental disease models *in vitro* and *in vivo* to support luteolin and its derivatives as an alternative to the commonly administrated α-glucosidase inhibitors for diabetic management along with potential antioxidant, antimicrobial, anti-allergic and cardiovascular protective effects. Protecting the physiological components and maintaining the desired level of BGL, TC, TG, LDL, HDL, and SOD activities in mice model experiments set the benchmark of the antidiabetic potential of luteolin. The antioxidant and enzyme inhibition potential of

luteolin and its derivatives were reproduced in different experimental researches and supported by *in silico* studies as well. Significant anti-hyperglycemic activity of luteolin in both animal and enzyme models suggested its pharmacological importance as a natural antidiabetic drug ingredient. More clinical studies are required with a larger sample size to explore the synergistic effects and future drug prospective of luteolin.

Conflict of interests

The author declares that there is no conflict of interest

Abbreviations:

BGL: Blood glucose level; **HDL:** High-density lipoprotein; **HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance; **HbA1c:** Hemoglobin A1c; **LDL:** Low-density lipoprotein; **MDA:** Malondialdehyde; **PNPG:** 4-Nitrophenyl α-D-glucopyranoside; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide dismutase; **STZ:** Streptozotocin; **TBARS:** Thiobarbituric acid reactive substances; **TC:** Total cholesterol; **TG:** Triglycerides; **TNF-α:**Tumor necrosis factor-alpha

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