LUTEOLIN FLAVONOID AS ANTIDIABETIC AGENT - A REVIEW

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Abstract

Diabetes is a chronic disease which is one of the leading cause of mortality worldwide. Though various allopathic treatments are available for this disease, but they have several adverse effects. Thus safe alternative method can be opted. Plant phytochemicals are the alternatives for the prevention to this disease. Flavonoids are common plant ingredients used as traditional remedies which posses various pharmacological properties. A subclass of flavonoids called luteolin has been extensively studied for potential medicinal uses and health benefits. Luteolin is a possible agent for the prevention and treatment of diabetes which is supported by numerous researches. In this review, the mode of actions of flavonoids as antidiabetic agents is discussed, with special reference to luteolin that mediates its anti-diabetic potential by maintaining blood glucose levels and improving the sensitivity of body cells to insulin.

KEYWORDS: *Diabetes mellitus, Luteolin, anti-diabetic, flavonoids , phytochemicals .*

Introduction

Diabetes mellitus is a chronic metabolic disorder which is the fastest growing global health crisis stated by the current 9th edition of the world diabetes atlas. As per the International Diabetes Federation, diabetes affects 463 million people in 2019 worldwide, the figure expected to increase to 578 million by 2030 and 700 million by 2045. Thiazolidinediones Sulfonylureas, biguanides, meglitinides and alpha glycosidase inhibitors are among the five types of oral hypoglycemic. Diabetes mellitus (Type-II) is an endocrine and metabolic disorder, that is mainly characterized by inadequate insulin secretion and excessive or inappropriate glucagon secretion, in which glucose, a principal source of energy, cannot enter the cells due to insufficient insulin as a result glucose increase in bloodstream.[1] Type 2 diabetes mellitus (T2DM) is a major global public health concern and its global prevalence is indicated to rise 10.1% by 2030. [2] The International Diabetes Federation predicts that there were 463 million adults with diabetes globally in 2019 and that number will grow to 578.4 million by 2030. The nations with the highest numbers of people with diabetes in 2019 were China (116.4 million), India (77 million), and the United States (31 million). Patients with type 2 diabetes mellitus (T2DM) account for >90% of all diabetes patients and suffer from abnormal oxidative stress and liver tissue damage, which further aggravate T2DM progression and eventually lead to a variety of complications. Chronic hyperglycemia results in various short term or long term micro-vascular complications in kidney, eyes, heart and periphery. These complications account for the morbidity and mortality seen in patients with T2DM.

Symptoms of T2DM include hyperglycemia, hyperlipidemia, and decreased body weight. The absorption of body fuels is hindered by high blood glucose levels, and as a result, loss of weight occurs from the energy-dense compounds that escape with urine. In T2DM the pancreas is malfunctioning thus the production of energy from carbohydrates does not take place, resulting in high glucose levels (hyperglycaemia) which leads to polyuria, polyphagia and polydipsia.

The use of the allopathic treatments might result in unpleasant side effects such as tiredness, memory loss, nausea, diarrhea, and gastrointestinal discomfort. Therefore, it is essential to find safe and beneficial phytochemical that might potentially reduce diabetes and its other consequences.

Flavonoids

Flavonoids are a significant group of natural products; particularly, they are a class of plant second-generation metabolite with a polyphenolic composition that is prominent in fruits, vegetables, and some beverages. . Nearly 6,500 flavonoids have been discovered.They have plenty of invaluable biochemical and antioxidant characteristics related with health conditions including cancer, Alzheimer's disease (AD), atherosclerosis, and diabetes. Flavonoids exhibit the protective effects against human diseases. [3]

These compounds can be classified into different subgroups depending on the carbon of the C ring on which the B ring is linked and the degree of unsaturation and oxidation of the C ring. The compounds in which the B ring is linked in a place 3 of the C ring are titled isoflavones. Those in which the B ring is attached in position 4 are titled neoflavonoids, while these in which the B ring is associated in position 2 can be likewise subdivided into multiple subgroups on an aspect of the structural elements of the C ring. These subgroups are: flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins and

chalcones.[4] There are variety of class and sub–class of flavonoids and their major source is depicted in the following table 1.

Table 1.The list of different class and sub class of flavonoids along with their source.

Class of flavonoids	Sub-class	Source
Isoflavones	Genistein Daidzein Glycitein Daidzin	Soya beans, chickpeas, pea- Nuts, pistachios
Flavanols	Catechin Epicatechin Epigallocatechin Epicatechingallate	Tea, cocoa, hops, beers, red wine
Anthocyanin	Delphinidin Cyanidin Malvidin Peonidin	Red grapes, merlot grapes , raspberries, bilberries
Chalcone	Phloretin Chalconaringenin Arbutin Philoridzin	Tomatoes, pears, straw -berries and certain wheat products.
Flavonols	Quercitin Kemprferol Rutin Myricetin	Lettuce, apples, grapes, kale Onions.
Flavones	Apigenin Luteolin Tangeretin Baicalein	Celery, parsley, red peppers, Mint, ginkgobiloba

Luteolin

Luteolin was first isolated in pure form and named in 1829 by the French chemist Michel Eugene Chevreul. The luteolin empirical formula was determined by the Austarin chemists Heinrich Hlasiwetz and Leopold Pfaundler in 1864. In 1896, the English chemist Arthur George Perkin proposed the correct structure of luteolin. Perkin's proposed structure was confirmed in 1990 when the Polish-Swiss chemist Stainslaw Kostanecki(1860-1910) and his students A. Rozycki and J. Tambor synthesized luteolin.Luteolin is bioactive flavonoid; it is present in the form of its glycoside (luteolin-7-O glucoside or luteolin- G). Other name for luteolin are Lutelol, Digitoflavone, flacitran, luteoline .

Source of Luteolin

Source of luteolin are Celery, broccoli, green pepper, parsley, thyme, dandelion, perilla, chamomile tea, carrots, olive oil, peppermint, rosemary, navel oranges, oregano. [5-6]. Vegetables are a good source of luteolin with 37.96 mg/100 g. The richest source of luteolin among herbs is oregano having 1,028.75 mg/100 g. In terms of fruits and plants, raw lemons without peel along with fresh sage contain 1.50 and 16.70 mg/100 g luteolin respectively. [7]

Table2. List of different plants containing Luteolin and its derivatives. [8-13]

S.No.	Plant Name		Bioactive Constituent
	Species	Family	
1	*Abutilon indicum*	Malvaceae	Luteolin, luteolin 7-O-beta-glucopyranoside
2	*Capsicum annuum*	Solanaceae	luteolin 7-O-beta-D-apiofuranosyl-(1-->2)-beta-D-glucopyranoside, luteolin7-O-[2-(beta-d-apiofuranosyl)-4-(beta-d-glucopyranosyl)-6-malonyl]-betad-glucopyranoside, luteolin-7-O-(2-apiofuranosyl-4-glucopyranosyl-6-malonyl)-glucopyranoside, luteolin 6-C-beta-D-glucopyranoside-8-C-alpha-L-arabinopyranoside
3	*Charysenthemum morifolium*	Astreaceae	luteolin-7-O-beta-D-glucoside, luteolin
4	*Rosemarius officinalis*	Lamaecae	luteolin 3'-O-beta-D-glucuronide, luteolin 3'-O-(4''-O-acetyl)-beta-D glucuronide, luteolin 3'-O-(3''-O-acetyl)-beta-D-glucuronide
5	*Ballotanigra*	Lamiaceae	luteolin-7-lactate, luteolin-7-glucosyl-lactate
6	*Vitexagnus-castus*	Lamiaceae	luteolin 6-C-(4''-methyl-6''-O-trans-caffeoylglucoside), luteolin 6-C-(6''-O trans- caffeoylglucoside), luteolin 6-C-(2''-O-trans-caffeoylglucoside), luteolin 7-O-(6''-p-benzoylglucoside), luteolin, orientin

Chemical Structure of Luteolin

Luteolin is a polyphenolic flavones. [14] It is 3', 4', 5, 7-tetra hydroxyl composed of C_6-C_3-C_6 carbon and three benzene rings. It has the chemical formula $C_{15}H_{10}O_6$ with a MW of 286.24. The rings A and B are all benzene, while the third C ring includes an oxygen and carbon double bond at positions 2-3. Hydroxyl groups can also be found in the structure of luteolin at carbons 5, 7, 3', and 4'.[15] The hydroxyl group and the moiety of 2-3 bonds are important components of luteolin's structure as they are connected to the substance's pharmacological and biochemical characteristics. [16]

Physiochemical Properties of Luteolin

Luteolin is insoluble and slightly soluble in cold water and in hot water respectively. [16] In plants, the luteolin molecule is found as an aglycone molecule without a sugar moiety and as a glycoside molecule having a sugar moiety linked to it. [17]

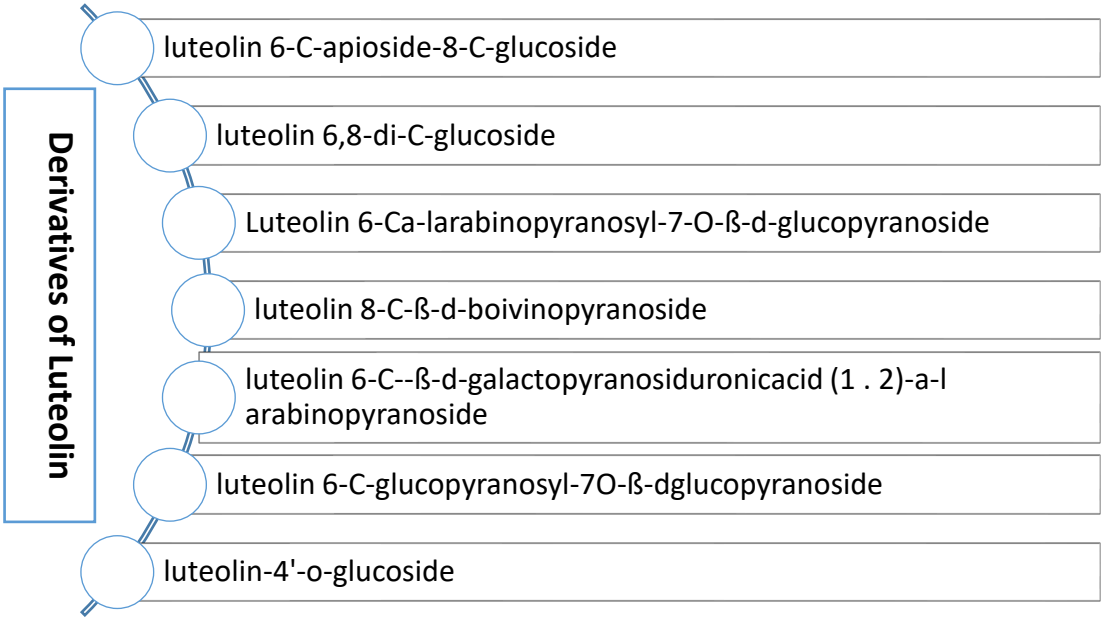

Fig 1.Derivatives of Luteolin

Pharmacokinetic Profile of Luteolin

The manner in which that luteolin is consumed influences the plasma concentrations of it. Highest concentrations of luteolin are obtained after one to two hours, and they remain in the plasma for several hours. This indicates that part of the physiological benefits of luteolin are achieved by the flavonoids due to its comparatively high bioavailability and low metabolism.[17] According to studies, luteolin is present in small amounts in the urine (6.6%) and faeces (31.3%), and a significant amount of it is likely to be metabolized into other metabolites. When rats were administered 200 mg/kg of Chrysanthemum morifolium extract orally, the luteolin compound was quickly absorbed, with the greatest plasma levels of the luteolin compound (4 g/mL) appearing 1.1 hrs after the amount taken.[18]

It was initially thought that luteolin-like flavonoids had minimal oral absorption. But based on recent studies, 5.0 g/ml of luteolin administered orally show little impacts of absorption in the duodenum and jejunum but significantly boosts absorption in the colon and ileum. [19]

A luteolin-loaded nanoparticle's bioavailability was discovered to be about five times greater than free luteolin employing a nanoparticle drug delivery system. The luteolin concentration in plasma also enhanced as shown by lower concentration peak time (t_{max}), higher plasma peak concentration (C_{max}), and increased area under the concentration-time curve from zero to the last detectable concentration (AUC_{0-t}).[20]

Role of Luteolin in Treatment of Diabetes

The pancreas can be protected and insulin secretion can be increased by luteolin's antioxidant activity and hypoglycemic potential. [21] In diabetes ß-cell death causes the pancreas to become dysfunctional and unable to release enough insulin for glucose metabolism. The production of insulin for glucose metabolism may rise as a result of luteolin's ability to induce ß-cell renewal. Luteolin works in the pancreas by reducing ROS, promoting pancreatic cell proliferation, and inhibiting pancreatic apoptosis. Several signaling molecules

are involved in luteolin-induced pancreatic regeneration.[22] Insulin deficiency leads to metabolic irregularities in diabetes.[23]

Lutein, luteolin 7-O-ß-glucoside, and luteolin 7-O-ß-glucuronoside can improve the shape of the pancreatic islets and the activity of the enzyme glucose-6-phosphate dehydrogenase (G6PDH) in diabetic rats. [24]

In diabetic people, the usage of B.pilosa, either alone or in combination, might dramatically lower fasting blood glucose and glycosylated haemoglobin A1c (HbA1c). B. pilosa consistently raised fasting insulin levels. Additionally, B.pilosa in conjunction with other anti-diabetic medications improved glucose control compared to B.pilosa alone. According to findings from the homeostatic model assessment (HOMA), B. pilosa's antidiabetic action was likely caused by the maintenance of -cell function. [25] Effect of luteolin on insulin release is aided to reduce the diabetes complications. Luteolin inhibit the generation of Reactive Oxygen Species (ROS) by restricting the enzymes that generate ROS and scavenge ROS. [26]

Luteolin regulates diabetes via various signaling pathways including mTOR, cytokine, AMPK, and p53, which can also be impacted by ROS/superoxide dismutase (SOD)[27]. The level of ROS is influenced by NADPH oxidase, eNOS, and mitochondria. Luteolin blocks eNOS and lessens the quantity of ROS they create [28]. NOS interacts with SOD, free radical damage results from its down regulation. Luteolin increases SOD activity[29].

The NRF pathway is stimulated, which improves cell mobility and proliferation while reducing cell death, oxidative stress.[30] Through modifying the production of SOD, eNOS, p53, NRF, mTOR, and cytokines, luteolin give significant anti-diabetic impact[31].

Luteolin is suggested to improve insulin sensitivity by influencing Akt2 kinase[32]. Insulin receptor dephosphorylation is inhibited by Akt2, which results in a reduction in the insulin signaling pathway. The glucose transporter GLUT4 is moved to the cell's surface to facilitate the regulation of Akt2, which is also responsible for controlling glucose absorption. As it binds to enzymes at low and high doses, thus luteolin is a non-competitive inhibitor (Placeholder1)of alpha-glucosidase [33].

A healthy liver helps to keep blood glucose within in normal range and protect against excessive fluctuations which is vital in hyperglycemia and hypoglycemia ,conditions which can be dangerous for human body. Cumulative data indicates that luteolin may be viewed as a regulator of insulin resistance and diabetes due to its critical function in regulating gluconeogenic and lipogenic capacity[34-35]. The lipid-lowering effects of luteolin in vitro may be partially mediated by AMPK signaling, which is accompanied by a higher level of expression of the carnitine palmitoyltransferase 1 gene (CPT1) and reduced levels of the sterol regulatory element linking protein 1c 65 gene (SREBP-1c) as well as fatty acid synthase (FAS) genes [36].

Additionally, a study on obese mice given with luteolin or luteolin-rich extract showed improvement in hepatic steatosis through decreased gluconeogenesis and lipogenesis, indicating a positive impact on impeded liver glucose generation.[37] The role of luteolin in regulating glycolipid metabolism is correlated with AMPK pathway activity.[38] In a research, LUT from Grifolafrondosa's ethanolic extract was extracted and showed that the substance is capable of enhancing lipid metabolism[39].

Conclusion

Diabetes has a negative socioeconomic effects. The prevalence of diabetes among younger people is rising, which worries society. It has been estimated that nearly 592 million adults become diabetic patients by the year 2035 due to aging, high population growth size, increased urbanization, high prevalence of obesity, rise in living standards and the spread of calorie rich, fatty and fast foods. A number of potentially fatal health issues are exacerbated by diabetes, one of the most prevalent diseases impacting the world's population. There haven't been many studies done on LUT's hypoglycemic characteristics. It is believed that LUT had ineffective anti-hyperglycemic effects and that structural alteration was necessary to improve its anti-hyperglycemic action. Luteolin is able to treat and prevent the diabetes by increasing insulin secretion by its anti-oxidant activity and by acting on signaling pathway (mTOR, ROS, eNOS, AMPK) as well as influencing Akt2 kinase, gluconeogenesis and lipogenesis. An intriguing biomolecule for both treatment and prevention can be one created from natural food sources. Because they are natural chemicals found in all plant materials and ingested in food this creates the foundation for a variety of strategies.This paves the way for a variety of methodologies to be utilized in research aimed at improving human well-being. Further research and confirmation in both *in-vitro* and *in-vivo* models are necessary to figure out the synergistic impact of luteolin in treatment of diabetes. Many previous studies of luteolin, for anti-diabetic effect, on animals showed positive result. This assists in determining generally the safe luteolin dosage for the treatment of diabetes.

Thus this phytochemical agent; luteolin may be utilised in preclinical studies as an anti-diabetic agent to combat diabetes mellitus.

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