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Review

A Review on Antidiabetic Activity of Orientin

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Abstract

Diabetes mellitus is a long-term metabolic condition characterized by increased blood sugar levels caused by insulin resistance, reduced insulin secretion or both. Even while synthetic antidiabetic medications are readily available, their prolonged use is linked to adverse effects, which makes the search for natural alternatives necessary. Orientin, a bioactive flavonoid glycoside that is mostly present in *Phyllostachys nigra* (black bamboo leaves), *Passiflora incarnata* (passionflower), and *Ocimum sanctum* (holy basil), has drawn a lot of interest due to its possible antidiabetic effects. This review examines the pharmacological processes that underlie orientin's antidiabetic actions, such as its capacity to improve glucose absorption, control insulin signaling pathways, and alter oxidative stress. Studies have demonstrated that orientin increases GLUT4 translocation, inhibits AMP-activated protein kinase (AMPK), and activates AMP to produce its hypoglycemic effects.

Keywords: *Diabetes mellitus, Phytochemicals, Antidiabetic agents, Adverse effects*

INTRODUCTION

Diabetes mellitus is characterized by hyperglycemia (very high blood glucose levels) and glucose intolerance, which can be caused by either a relative lack of insulin secretion or a decrease in the efficiency of insulin's ability to promote glucose absorption. If treatment is not provided, serious repercussions may arise. [1] These adverse effects include oxidative stress, enzymatic protein glycation, and among these adverse effects include hyperlipidemia, oxidative stress, and enzymatic protein glycation. Chronic hyperglycemia is the hallmark of diabetes mellitus, a common and complex metabolic syndrome brought on by abnormalities in insulin production, insulin receptor or post receptor events, and disturbances in the metabolism of proteins, lipids, and carbohydrates. [2] A WHO estimate from 2014 states that 8.5% of people over the age of 18 have diabetes. In 2019, there were 1.5 million deaths from diabetes, with 48% of the deaths occurring in people under 70. Additionally, high blood glucose levels were connected to nearly 20% of deaths from cardiovascular disease, and diabetes was a contributing factor in an additional 460,000 deaths from

kidney disease. The standardized death rates from diabetes increased by 3% between 2000 and 2019. The death rate linked to diabetes rose by 13% in lower-middle-income nations. However, the chance of passing away from any of the four main non-communicable diseases-cancer, diabetes, chronic lung disease and globally, there was a 22% decline in cardiovascular diseases or respiratory issues among people aged 30 to 70.[3]

Types of Diabetes

Long before abnormal insulin secretion starts, type 1 diabetes (T1D) can be detected, with a steady decline starting at least two years before diagnosis [4]. Around the same time, β-cell sensitivity to glucose decreases. A compensatory mechanism may be indicated by the last insulin response increasing while the initial insulin response declines. Insulin responsiveness continues to deteriorate at an accelerated rate in the early postdiagnosis phase. There has been a two-phase decrease in insulin secretion in the initial years following diagnosis, with the first year being steeper than the secondary After a diagnosis, the reduction in insulin secretion may continue for years until little or no insulin is produced. despite being within the typical range. Glucose levels change dramatically as T1D progresses. It might be possible to predict the onset of diabetes Following. When T1D develops, there is a considerable variation in glucose levels. Predicting the onset of diabetes may be possible. Years may pass after a diagnosis until there is little to no insulin generated because to the decline in insulin secretion. Elevated glucose levels are a sign of type 1 diabetes even though They fall inside the typical range. There is a significant fluctuation in glucose levels when T1D develops. [5] Type 2 diabetes (T2D). One important contributing element to the pathogenesis of type 2 diabetes (T2D) is defective insulin production. Insulin production varies according to insulin sensitivity in order to maintain appropriate glucose levels. The disposition index measures the curvilinear correlation between secretion and insulin sensitivity. [6] Additionally, because they have a low disposition index, patients with type 2 diabetes are unable to efficiently raise their insulin production in order to combat insulin resistance. Even though the absolute insulin levels of insulin-resistant obese T2D patients are higher than those of insulin-sensitive lean control subjects, they are nonetheless unacceptable due to the severity of their insulin resistance. [7] The first phase of glucose stimulation results in a significant reduction or elimination of insulin production. In patients with type 2 diabetes, the proinsulin to insulin (C-peptide) ratio is higher. Peak insulin production is much decreased, as is the increase of insulin responses to non-glucose stimuli brought on by hyperglycemia.

Gestational diabetes

During pregnancy, hyperglycemia raises the risk of injury to the fetus, mother, and unborn child. [8] pregnancy-related type 2 diabetes that was identified before to or during pregnancy. The risk of developing diabetes as an adult is higher for newborns whose mothers have gestational diabetes. Adult-onset diabetes is more likely to occur in newborns whose mothers have gestational diabetes.

Mechanism

Glucose is the main fuel and energy source for human cells. It originates from food that is consumed, broken down by the body, and then transported through the circulation to target cells. It is vital that glucose be able to flow through the plasma membrane. [9]After a while, glucose powers the body's metabolic functions, which is created when lipids, proteins, and carbohydrates mix. The several processes that comprise glucose metabolism include glycogenesis, glycolysis gluconeogenesis, and glycogenolysis.[10]. Cells catabolize glucose and convert it to pyruvate through a metabolic process called glycolysis, which is performed by enzymes The Glycogenolysis and gluconeogenesis.[11]. Through a metabolic process known as glycolysis, which is carried out by enzymes, cells catabolize glucose and transform it into pyruvate. The cytosol and mitochondria of hepatocytes engage in a range of metabolic processes that produce glucose from non-carbohydrate substrates in order to maintain steady blood sugar and glucose levels throughout the fasting state. It is regulated by cortisol, glucagon, and insulin.[12] Moreover, the pancreas releases glucagon during a fast, which starts the breakdown of glycogen. Glycogen is broken down into glucose and glucose-1- phosphate by a biological process known as glycogenolysis. Glycogenesis is the process by which glucose molecules combine with glycogen to become glycogen [13]. Blood glucose levels are regulated by the circadian cycle. The early hours of the day are when human tolerance to glucose for metabolism peaks. The reason for this is that whereas glycogen storage rises sharply in the evening, pancreatic beta cells are primarily activated in the morning. Adipose tissue responds violently to insulin after lunchtime. The glucose metabolism chain is made up of the several energy consumption strategies that occur during the day. After three to four hours of fasting, the usual blood sugar level is between 80 and G0 mg/dl. The blood sugar level can normally reach 120-140 mg/dL after a meal, but the body's feedback system brings the glucose down to normal in short time.High blood glucose causes blood glucose levels to rise, which simultaneously causes the extracellular space to give way to the intracellular space, which triggers the secretion of insulin. However, the decrease in secretion of blood glucose levels triggers the release of glucagon, which in turn causes blood glucose levels to rise. This is clinically significant since insufficient insulin production is the cause of diabetes mellitus. [14]

Glycemic control can be enhanced by lifestyle modifications, but long-term medication will be required to adequately treat the condition. Inhibitors for the management of type 2 diabetes comprise sodium-glucose transport protein 2

(SGLT2) inhibitors, oral glucagon like peptide 1 (GLP-1) receptors, bile acid sequestrants, dopamine agonists, sulfonylureas, meglitinides, alpha glucosidase inhibitors, dipeptidyl peptidase IV (DPP-IV) inhibitors, and sodium-glucose transport protein 2 (SGLT2) inhibitors [15].

Pharmacological management of type 1 diabetes in patients

Insulin therapy is the primary treatment for type 1 diabetes. However, as a result of study, noninsulin supplements are currently being employed in lab settings and clinical trials to discover new approaches to managing diabetes. The most popular drug for diabetes is metformin, a biguanide. Insulin therapy is the primary treatment for type 1 diabetes because it occasionally interacts with amylin analogizes and GLP-1 receptors [16].

Pharmacological treatment of type 2 diabetes mellitus

The many drugs used to treat people with type 2 diabetes mellitus have different ways of preventing the symptoms of hyperglycemia by lowering blood sugar levels.

Sulfonylureas

Diabetes has long been treated with sulfonylureas, which are insulin secretagogues. They are usually broken down in the liver, and occasionally they are eliminated by the kidneys. [17] Regardless of blood glucose levels, sulfonylureas cause the pancreas to release insulin. [18] Sulfonylureas also increase insulin sensitivity in peripheral tissues, decrease hepatic insulin clearance, and suppress glucagon secretion [19].

Meglitinides

Meglitinides are glucose-dependent drugs that increase the pancreatic release of insulin, reducing the risk of hypoglycemia. It can be used to correspond with the postprandial rise in glucose and has a brief duration of action. [20]

Metformin

increases hepatic insulin sensitivity and decreases hepatic glucose synthesis. In peripheral tissues, it also reduces insulin resistance by lowering blood glucose, triglycerides, and free fatty acids [20]. Despite its antihyperglycemic effect, insulin secretion is unaltered [21].

Sodium-glucose transport protein 2 (SGLT2) inhibitor

sodium-glucose transport protein 2 inhibitors (SGLT2) Adults with type 2 diabetes can use this sort of oral antidiabetic medication to reduce their blood glucose levels. It is not impacted by body insulin levels or insulin resistance.
Symlin (pramlintide) Amylin can be synthesized as pramlintide. It is used orally and is soluble in nature. The pancreas uses insulin to secure amylin in response to dietary inputs. It delays stomach emptying, reduces hunger, and lowers postprandial glucagon secretion.

Thiazolidinediones

The peroxisome proliferator activated transcription factor is bound by the insulin sensitizer thiazolidinedione.

Insulin

The best drug for decreasing blood sugar is still insulin, particularly for people with elevated HbA1c levels. Starting insulin therapy presents a number of difficulties, such as time restraints and unfamiliar insulin compositions. insufficient knowledge of new insulin formulations and patient discomfort with self-injections. insufficient knowledge of new insulin compositions [22], [23]. Data from a retrospective cohort study including over 81,000 individuals in the UK Clinical Practice Research database may be explained by these obstacles revealed that for patients receiving 1, 2 or 3 oral glucose-lowering medications, the median duration to insulin therapy intensification was >7.1, >6.1, or 6.0 years, respectively. [24] Together, the patient and the prescribing doctor will decide whether to add insulin, taking into consideration the patient's age, motivation, overall health, risk of hypoglycemia, and potential cardiovascular consequences. [25]

Phytochemicals in the management of diabetes mellitus

- **Phenols**
- **Ellagic acid**

The majority of fruits and nuts contain the polyphenolic component ellagic acid. Numerous studies conducted both in vitro and in vivo have demonstrated the significant anti-diabetic effects of ellagic acid therapy. In insulin-resistant type 2 diabetic albino mice, repaglinide (0.5 mg/kg) and ellagic acid (10 mg/kg) given combined for two weeks improved glucose balance, lipid profiles, and insulin signaling. [26]. According to the oral glucose tolerance test conducted by Fatima et al. (30), a dose of 25 mg/kg of ellagic acid had no appreciable effect on glucose tolerance in type 2 diabetic rats. However, dosages of 50 and 100 mg/kg improved glucose tolerance. [27]

Alkaloids

Aegelin, marmesin, and marmelosin are key alkaloids found in the plant Aegle marmelos that aid in pancreatic β cell regeneration and insulin secretion. These botanicals help, heal pancreatic β cells and sustain insulin levels by boosting insulin gene expression, secretion, and inhibition. Patients with Type 1 Diabetes Mellitus (T1DM) lack functioning β cells, resulting in depletion and reliance on exogenous insulin. Several botanicals, including *Tribulus terrestris* extracts, β carbolines, *Achyranthes aspera* extracts, *Xanthocercis zambesiaca,* Berberine, and *Castanospermum australe*, have been demonstrated to inhibit DPP-IV and regulate hyperglycemia in rats. [28]

Coumarin

Since ancient times, there have been notions about using natural ingredients to cure ailments. *Aegle marmelos* Corr., a Rutaceae plant that contains marmesin (furocoumarin),is commonly used in Indian Ayurvedic medicine to treat diabetes. [29] The hypoglycemic effects were studied *in vitro* and in a diabetic mouse model. Osthole has been shown to treat hyperlipidemia, hyperglycemia and insulin resistance. Steroid transcription factors that intervene in the expression of many target genes associated with fatty acid storage and glucose metabolism directly inhibit peroxisome proliferator-activated receptors (PPAR). [30] Osthole was shown to significantly lower blood glucose levels in obese diabetic db/db mice when given in various ways. Oshole may therefore be a dual PPAR inhibitor, significantly reducing hyperglycemia and making it a promising therapeutic drug for the treatment of diabetes mellitus, based on the results of the in vitro and animal model investigations. [31]

Flavonoids

Rutin

Reduced absorption of carbohydrates from the small intestine, increased uptake of glucose, suppression of gluconeogenesis, stimulation of β-cells to produce insulin, and protection of the islets of Langerhans against degeneration are some of the anti-diabetic properties of rutin. Additionally, rutin prevents the production of sorbitol, reactive oxygen species, pro-inflammatory cytokines, and precursors of advanced glycation end products. [2G] [32]

Morin

A naturally occurring flavonoid, morin is mostly found in fruits like figs and guava. well as traditional medicinal plants like *Prunus dulcis* and *Chlorophora tinctoria* L [33]. In animal models, oral morin treatment for 30 days greatly reduced insulin resistance, hyperglycemia, and glucose tolerance. After morin administration, lipid peroxides and antioxidant levels were Diabetic rats showed a reduction [34]. Morin effectively reduces inflammatory cytokines including TNF-α and IL-6. Morin improved leptin sensitivity in animal studies, while hepatic insulin reduced hyperlipidemia and liver lipid accumulation. Morin affects hepatic enzymes differently, reducing the activity of FDP ase and G6Pase and enhancing the activity of hexokinase and G6PD.

Orientin and its uses

The IUPAC classifies orientin as a water-soluble C-glycoside flavonoid. 2-(3,4- dihydroxyphenyl)-5,7-dihydroxy-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6- (hydroxymethyl)oxan-2-yl] is chromen-4-one. Its molecular weight is 448.376G g/mol, and its chemical formula is C21H20O11.

Orientin's chemical composition shows that it is primarily made up of phenol groups, along with two ether groups and one ketone group. A polar solvent, such as methanol, ethanol, or water, is required to extract orientin from medicinal plants.

Chemical formula =C21H20O11 From Plants to Orientin

Orientin has been isolated from a variety of medicinal plants, including *Osmium sanctum*, Phyllostachys species (bamboo leaves), Passiora species (passion flowers), Trolli u s species (Golden Queen), and *Jatropha gossypifolia* (bellyache bush). *Osmium sanctum*, which is cultivated in India and is renowned for its medicinal qualities, is also referred to as Indian holy basil or Tulsi in Sanskrit.

Several *Osmium sanctum* components are used in the ancient Indian medical system known as Ayurveda to treat skin conditions, snakebites, malarial fever, coughs, and common colds. *Osmium sanctum* in addition to other flavonoids including luteolin, molludistin, apigenin, apigenin-O-glucuronide, and luteolin--O- glucuronide Likewise, orientin was extracted from the same plant sections by Uma Devi et al. for in vivo radioprotective effect studies.

Orientin's Therapeutic Properties

Orientin's antioxidant properties

The antioxidant properties of orientin have been the subject of numerous studies. Studying orientin's significant radical scavenging activity, the capacity to donate electrons and its electron affinity, electronegativity, electrophilic index, and adiabatic ionization potential can help explain its antioxidant qualities. Orientin's antioxidant qualities are further demonstrated by its effect on hydrogen peroxide- induced β-galactosidase activity. Orientin decreased the H_2O_2-induced β-galactosidase activity, but H_2O_2- treatment alone increased the enzyme activity. [35] Research conducted on animals has also demonstrated orientin's antioxidant qualities. After several weeks of D-

galactose therapy, Orientin was administered to old mice. According to An et al., orientin significantly improved the mice's overall health and brain weights. Age-treated. Furthermore, orientin-treated mice showed increased levels of catalase, glutathione peroxidase, and superoxide dismutase in their brain, liver, and kidneys, but considerably reduced amounts of malondialdehyde, a biomarker of oxidative stress, and lipofuscin, an age pigment. [36]

Antibacterial and antiviral

The creation of novel antibiotics benefits from orientin's antiviral and antibacterial qualities Orientin's antiviral and antibacterial properties aid in the development of new antibiotics. Orientin has been shown to have moderate to strong antiviral activity against the Para 3 virus by Lin et al. [37] and Li et al. [38]. Additionally, the flavonoid mixture of kaempferol, quercetin, rutin and orientin completely decreased Herpes Simplex Virus Type 2 (HSV-2) of various viral titres (1, 10, 100 TCID50) on Hep-2 cells at the maximal safe dose of 0.048 μg/mL [3G].

Anti-Inflammatory

issue uses inflammation as a biological defence against damage or infection. There are two phases to inflammation. [39] Neutrophils and monocytic leucocytes are indicative of the acute phase, whereas macrophages and lymphocytes are indicative of the chronic phase [40, 41]. Nevertheless, hypertension drugs only have a 60% maximum efficiency rate, and two or more diuretic. To create high efficacy in individuals, adrenergic medications, calcium channel blockers, or angiotensin converting enzyme or receptor blockers are needed. Additionally, vasodilator classes typically need to be done concurrently. [42] Vasorelaxant is therefore a necessary drug for hypertensive people in order to lower their high blood pressure and shield them from cardiovascular illnesses. [43,44] Neuroprotective or Antidepressant-Like Effect Progressive disorders of the central nervous system are caused by neurodegenerative diseases, which are deteriorating and incurable conditions in which misfolded intracellular and extracellular proteins aggregate and deposit [45,46]. They have been highlighted among aging disorders due to their ineffective treatment, inability to be cured, and related societal and financial costs. [47]

CONCLUSION

Orientin, a flavonoid glycoside present in a variety of medicinal plants, has demonstrated promise antidiabetic activity via numerous pharmacological pathways. Its capacity to improve glucose absorption, modulate insulin signaling, block carbohydrate digesting enzymes, and protect pancreatic β-cells from oxidative stress makes it a encouraging natural option for the treatment of diabetes. Furthermore, its anti-inflammatory and antioxidant properties ward off diabetes-related complications like cardiovascular disease and nephropathy. Despite these promising results, most investigations on orientin's antidiabetic activity have been limited to in vitro and preclinical models, with no large-scale clinical trials to establish its efficacy and safety in humans. More research is needed to determine its pharmacokinetics, bioavailability, dosage optimization and potential interactions with traditional antidiabetic medications.

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