REVIEW ARTICLE

Effect of *Gymnema sylvestre* in the Control of Diabetes: A Review

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ABSTRACT

Gymnema sylvestre is a plant of the Asclepiadaceae family that grows worldwide. It is one of the most potent medicinal plants. *G. sylvestre* leaves are commonly utilised in the treatment of diabetes mellitus.In Indian herbal medicines, it is used as a diuretic drug. The most important active chemical ingredient taken out from the *Gymnema* plant are gymnemic acids which help prevent glucose absorption. This herb is famous for its antihelmentic, anti-inflammatory, diuretic and stomach-friendly qualities. Leucoderma, constipation, hemorrhoids, jaundice, cardiopathy, asthma, bronchitis and dyspepsia are said to be treated with this plant. The *Gymnema* leaves are chewed to reduce the appetite for sweet and bitter items and applied on the affected body regions to heal a variety of illnesses. An examination of the literature found that the plant has anti-inflammatory, anti-obesity, hypolipidaemic, antidiabetic, free radical scavenging and antibacterial properties. According to literature reviews, *Gymnema* is an extensively used plant for the cure and management of a lot of disorders and is a key constituent in numerous ayurvedic formulations. However, scientists have not made much effort to prove its efficacy. The current review focuses on *G. sylvestre's* folk and ayurvedic usage and pharmacognostic, pharmacological and phytochemical research. *G. sylvestre* may aid weight reduction by reducing sweet cravings and controlling blood sugar levels. This review highlights the plant description, literature and phytochemistry of *G. sylvestre*. It also talks briefly about diabetes mellitus and how *G. sylvestre* can be useful in the treatment of it. We also discuss about the side effects and toxicity of it.

Keywords: Gymnema sylvestre, Diabetes, Anti-diabetic, Phytochemistry, Saccharine.

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INTRODUCTION

Gymnema sylvestre is a woody perennial vine found in Australia, Africa and Asia. Ayurvedic medicine has made use of it for a very long time.It has been used in herbal medicine for a long time and offers a wide spectrum of medicinal characteristics. Common names of *G. sylvestre* are Gurmar (sugar destroyer), *Gymnema*, madhunashini and Australian Cowplant. *G. sylvestre* is one of the herbs that has powerful antidiabetic qualities. This plant helps a lot in managing diabetes.It is a powerful antidiabetic herb which has been utilised in ayurveda, folk and homoeopathic medicine for centuries.Asthma, eye ailments, inflammations, and snake bites are all treated with it.[1] This plant helps a lot in managing diabetes. Themajor active ingredients of this plant are a group of acids known as gymnemic acids, the main bioactive elements which come in contact with the taste buds of the tongue to inhibit the sweet sensation for a short period of time.[2] The *G. sylvestre* leaves' sweet paralysing power is well known, and it has been used to avoid craving for sweets.

Plant Description

Gymnema is an endangered species. It grows slowly and is a perennial medicinal woody climber found in Peninsular and central India. It's a powerful antidiabetic herb that's been utilized in folk, ayurveda, and homeopathic medicine for centuries. *G. sylvestre* is a large, woody climber with a pubescent appearance. It's sometimes cultivated for medicinal uses. The leaves of this plant are elliptic, ovate or opposite while the flowers are tiny, yellow, and have umbellate cymes. Follicles are lanceolate and terete, measuring up to the length of 3 inches.[1]

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Diabetes Mellitus

Diabetes is a metabolic disorder defined by persistently high blood sugar levels caused by the tissues' diminished capacity or total inability to use carbohydrates and alterations in the electrolyte, fats, water and protein metabolism. Diabetes can be described as a collection of disorders characterized by altered carbohydrate, protein and lipid metabolism, hyperglycemia and an elevated risk of cardio-vascular consequences. Polyuria, polydipsia, polyphagia, dehydration and general weakness are some common symptoms of diabetes mellitus. If diabetes is left untreated or ignored, it leads to a variety of health problems. Diabetes mellitus can cause a variety of acute health problems such as ketoacidosis, hyperglycemia, vulvitis or balanitis and mortality. Kidney disorders persisting for a huge amount of time, strokes, ulcers in the foot, cardiovascular disease, damage to the eye and nerves, cognitive impairmentare all critical long-term risks. The main reason for diabetes is the shortage or less effectiveness of the insulin hormone which is secreted by the pancreatic cells.

Mainly, there are 3 kinds of diabetes mellitus

- Type 1 diabetes is because of the destruction of pancreatic beta cells due to which the pancreas fail to secrete enough of the hormone insulin. Type 1 diabetes is also known as "insulin-dependent diabetes mellitus" or "juvenile diabetes".[3-4] Destruction of beta cells is caused by an auto-immune reaction.[3] This auto-immune response's aetiology is unclear. It has a slow onset.
- In Type 2 diabetes, loss of beta cells and resistance to insulin are both present. Levels of insulin might be low, normal or high but are unable to overcome insulin resistance or decreased tissue sensitivity to insulin causing hyperglycemia. As the condition worsens, there is a deficit of the hormone insulin and the patient might need exogenous insulin. Type 2 diabetes is also known as "non-insulin dependent diabetes mellitus" or "adult-onset diabetes".[3] It has a gradual onset. Obesity is the most common cause of diabetes.
- Gestational diabetes is the third most frequent kind of diabetes, and it is diagnosed when glucose intolerance is diagnosed for the first time during pregnancy.

Diabetes is on the rise at an alarming rate, and it is quickly becoming a global issue. The focus on diabetes-related pharmacological research has seen a considerable shift away from standard pharmaceuticals and toward therapies based on bioactive phytomolecules generated from natural sources. Gymnemic acids, which are found in *G. sylvestre*, slow the absorption of glucose into the blood. The gymnemic acids are thought to prevent glucose absorption in the small intestine, while the specific mechanism is uncertain. One or more mechanisms might be involved.[5] G. *sylvestre*'s leaf extract, particularly the peptide 'Gurmarin', interferes with the tongue's capacity to taste sweet and bitter. People using it are thought to reduce their consumption of suggary foods because it inhibits the sweet taste experience.[5]

Traditional Use of *G. sylvestre*

The biological activity of naturally occurring chemicals has sparked a steady increase in people's interest in recent years. In reality, it is well known that the use of dietary supplements and other natural products-based compounds has increased, which are frequently neither standardised nor adequately evaluated in terms of their potential benefits or drawbacks. This necessitates diligent and thorough research into natural chemicals with the goal of utilizing them to supplement or replace manufactured medications, which are plagued with adverse results and elevated prices.Traditional medicine refers to knowledge, practises, procedures, and beliefs held by many people which are collected on the basis of findings, results and conclusions inherited from one generation to another to prevent and cure mental, bodily, and social well-being imbalances.[6]

Gymnema is among the most popular potent plants with therapeutic properties andis a woody climber that grows year after year found in arid woods up to 600 metres high Southeast Asia. The plant is huge, with elliptic/ovate opposing leaves with little yellow blooms. This herb is used to cure a variety of diseases in traditional medicine, particularly in India.[1] For instance, the leaves of this plant are chewed to reduce the appetite for sweet and bitter items and applied on affected body regions to heal illnesses. It is also advised to treat urinary difficulties and stomachaches and is utilizedin controlling diabetes mellitus in decoctions and disorderscaused by stress. The extract of *Gymnema* leaf is also used to cure corneal opacity. It's used as an aperitive and to eliminate unpleasant odours from breast milk in glycosuria. It is bitter and acrid, diuretic and digestive, laxative and anti helmentic, vomitive, analgesic, expectorant, cardiotonic, antipyretic, and stimulant, according to Ayurveda. In addition, the leaf extract has long been used to treat conjunctivitis, jaundice, and leucoderma, as well as hepatosplenomegaly, amenorrhoea, and haemorrhoids.[6]

G. sylvestre has outstanding hypoglycemic qualities, and in the ancient medicinal system, it serves as the foundation for diabetic therapies.[7]

In the morning, the Junglee Irulas of the Nilgiri highlands eat green leaves to ensure pure urine. The Kol tribe of Chhattisgarh, as well as ethnic tribes in Rajasthan, Andhra Pradesh's Godavari area, Maharashtra's Kandla, and Karnataka's Nayaks, utilise leaves to cure gastrointestinal disorders, diabetes, glycosuria, urinary ailments, and eye difficulties.[8]

Gymnema is classified as an anodyne, antipyretic, anthelmintic, alexipharmic, bitter, stomach - friendly, laxative, astringent, diuretic stimulant and uterine tonic, and is utilized to cure and manage asthma,amenorrhea, conjunctivitis, bronchitis, cough dyspepsia, constipation, haemorrhoids. The plant's leaves are used to treat diabetes mellitus, and a paste made from the leaves of *Gymnema* is utilized to reduce inflammation. The bark of the roots of *G. sylvestre*may be useful as an analgesic, expectorant and emetic for bodily aches, while the juice from the root has been praised by Bhav Prakash Nighantu as a good therapy for snakebite. Phlegm, colic pain, piles, eye problems, dropsy, cardiac, and respiratory disorders can all be treated with *Gymnema*.[8] The bitter, thermogenic fruit is used to alleviate disorders related by phlegm or vata (wind). *Gymnema* is listed in Nighantu Ratnakaram as being

helpful in eradicating cough and toxicants, as well as healing eye problems. *Gymnema* leaves are utilised as a component in many antidiabetic compositions in the Siddha and Unani systems of medicine.[8]

Phytochemistry of *G. sylvestre*

Triterpene saponins from the oleanane and dammarane classes are found in the leaves of *Gymnema*. Gymnemic acids and *Gymnema* saponins belong to the oleanane saponin family, whereas *Gymnema* sides belong to the dammarane saponin family.[9,10] Flavones, pentatriacontane, hentriacontane, anthraquinones, resins, phytin, formic acid, stigmasterol, lupeol, tartaric acid, butyric acid,calcium oxalateand -amyrin related glycosidesare some of the other phytoconstituents present in *G. sylvestre*.[11]

The existence of alkaloids in plant extracts of this plant have been discovered. *Gymnema* leaves contain anthraquinones, acidic glycosides, and their derivatives.[12] *Gymnema* has a collection of 9 closely related acidic glycosides, the most important of which are gymnemicacid A–D, which may be seen in all sections of the plant.Shoot tips have the most gymnemic acid (54.29 mg-g^1 DW) while seeds have the least.

The anti- saccharin property of gymnemic acid A1 considerably diminished when converted to A2, whereas zero activity was detected in gymnemic acid A3, showing that the anti-sweet action of triterpene saponins is conferred by the genin component's ester group of gymnemic acid. The molecular structures of gymnemic acids A3 and A2 have galactose and glucoronic acid but gymnemic acid A1 had solely glucuronic acid as a constituent.[13] The several members of the gymnemic acids family aregymnemic acids I–VII, *Gymnema* saponins and gymnemosides A–F. Gymnemic acids are methylbutyryl, acylated tigloylgroup substituted components produced from a 3-O-glucuronide of *Gymnema* genin (3, 16, 21, 22, 23, 28, hexahydroxy-olean-12-ene), deacylgymnemic acid (DAGA). Gymnemic acids A4, A3, A2 and A1 constitute gymnemic acid A, also known as *Gymnem a*genin. This component is a hexahydroxy-triterpene D-glucuronide which esterifies with the help of acids. Later on, the gymnemic acids XII, XI, X, IX and VIII were also extracted and described. The aglycone moiety of *Gymnema* saponins III which is another anti-sweet chemical identified from *G. sylvestre* has been revealed to include 23 hydroxylongispinogenin glycosylated with one or two glucose molecules at the 23 and 28 hydroxyl groups. The anti-sweet impact of these compounds was lower than that of gymnemic acids.[14]

Gurmarin is a 35 amino acid peptide that is extracted from *G. sylvestre* and has a molecular weight of 4209. Electrophysiological taste reactions of six people (three women, three men) aged 20–55 were used to test the sugar suppression activity of this drug. The anti-sweet action of gurmarinis very particular to the taste of sweetness on the tongue, which is altered by pH changes. This polypeptide was shown to have the strongest anti-sweetening properties at its iso-electric point.[15] Gurmarin's inhibitory effect is very particular to the taste of sweetness on the tongue. The most efficient pH for gurmarin activity on the tongue was around the isoelectric point of it. It has a three-dimensional structure having a hydrophobic amino-acid residue-rich domain. Gurmarin has a half-life of around 40 minutes in the circulation, and the hydrophobic interaction, rather than the ionic contact, is important for gurmarin to adequately connect to the target molecules.[8] The hydrophobic interaction, rather than the ionic, is important in gurmarin's proper binding to the target molecules. *Gymnema* sins A, B, C, and D, as well as alkaloids, are additional key elements isolated from leaves.[8]

Gymnemic acid (saponin; gymnenin) decreases blood sugar levels by increasing the production of endogenous insulin and inhibiting glucose receptors. Gymnemic acid increases insulin permeability in normal rats while lowering cholesterol in hypertensive rats. For 15 minutes to 24 hours, gurmarin impairs the tongue's capacity to taste sweet items.[16]

***G. sylvestre* Against Diabetes**

Type 1 diabetes (IDDM: insulin-dependent diabetes mellitus) is an autoimmune disease in which the pancreas' - cells die, resulting in insulin deficiency. Patients with type 1 diabetes require a continual dose of insulin from the outside to survive. Diabetes mellitus type 2 is the quickest developing metabolic disorder in the world, accounting for around 90% of diabetics.[17] Insulin resistance and obesity result from a decreased receptor concentration, IRS-1 concentration, phosphorylation, kinase activity, PIK activity, intracellular enzyme activity and glucose-transporter translocation.[18]

G. sylvestre lowers the glucose in urine in diabetics and suppresses the hyperglycaemic reaction to epinephrine as well as adrenohypophyseal activity, all of these actions are thought to be mediated *via* gluconeogenetic and phosphorylase activity.[19] The plant's hypo-glycemic action in normal diabetics has been widely demonstrated. Enzymes dependent on insulin such as glyceraldehydes 3-phosphate dehydrogenase, glycogen synthetase, hexokinase, and glucose 6-phosphate dehydrogenase had reduced activity in the diabetic tissues of rabbits, but enzymes independent of insulin such as glycogen phosphorylase, glucose 6-phosphatase, gluconeogenic enzymes,sorbitol dehydrogenase and fructose 1,6-diphosphatase, of polyol pathway, In untreated diabetics, activity was dramatically enhanced, but this was reversed when G. *sylvestre* was administered.[8] In mice treated with beryllium nitrate with disrupted CHO metabolism and liver injury. *Gymnema* leaves helped control blood sugar levels and suppressed the activity of hexokinase in the liver. In rabbits, dogs and rats with alloxan-induced diabetes, the therapy restored blood glucose and serum insulin balance.[20] This could be attributed to β cell regeneration or repair in the islets of langerhans.

GS4 therapy for eighteen to 20 months lowered lipids in plasma in people with type 2 diabetes (non-IDDM)[21]. Sulfonylureas and biguanides, on the other hand, control blood glucose homeostasis by increasing the secretion of insulin from the pancreas and suppressing gluconeogenesis.[8] Both of these medicines have significant adverse effects, such as increased plasmacholesterol, free fatty acids and triglycerides and their efficacy on lipid metabolism diminishes with time. *Gymnema* extract was given to rats on a high-fat diet for 10 weeks, which reduced body weight gain, liver lipid

accumulation, interaperitoneal fat deposition, and plasma triglyceride levels.[21,22]

However, no anti-hypolipidemic or anti-diabetic advantages were discovered in a recent research of the anti - hypolipidionic and anti-hyperglycemia effects of *Gymnema* leaves in alloxan-diabetic and non- diabetic rats. The discrepancy in results between one research which found zero anti-hypolipidionic and anti-hyperglycemia effect from G. *Sylvestre* and another which found them might be related to the usage of a glycoside combination by other researchers (GS4 and gymnemic acid). G. *sylvestre*, it appears, will need more experimental and clinical studies before it can be recommended for use in the treatment of diabetes.[23]

The Functioning of Gymnemic Acids

Gymnemic acids promote insulin production by the pancreas. When consumed, it brings about the same effect by lowering blood sugar levels. Similar to how sugar molecules load and activate taste receptors, gymnemic acids achieve the same thing, albeit without unpleasant side effects.[14] Blood sugar levels are lowered as a result of its binding to a receptor on the gut wall, which blocks sugar absorption. Gurmarin, which blocks taste receptors for both sweet and bitter, works through a similar manner. Gymnemic acids' hypoglycemia impact is the consequence of a chain reaction that starts with the stimulation of insulin production and secretion as a result of a shift in incretin activity.[24] It boosts the renewal of islet cells of the pancreas, resulting in improved glucose absorption through enzymes. This mechanism impairs the capacity of mouth and gut receptors to detect sweetness as in the small intestine. It reduces fatty acid and glucose absorption.[14] Gymnemic acid's activity has previously been described in the literature to be comparable to those of incretin-mimetic mechanisms of action.[25]

Antidiabetic Property of *G. sylvestre*

The triterpene saponins gymnemic acids, gymnema saponins, and gurmarin are responsible for the sugary inactivation effect of the herb. Experimental trials on rats treated with beryllium nitrate and streptozotocin validated G. *sylvestre*'s hypoglycemic impact. In diabetic rats treated with G. *sylvestre*, there was a modest rise in body weight and protein and a considerable drop in fasting blood sugar. The outcomes were comparable to mice treated with insulin and glibenclamide.[14]

An experimental investigation also studied the hypolipidemic and antidiabetic potential of *Gymnema*'s dried and powdered leaves. Non-diabetic and alloxan-diabetic rats were given *G. sylvestre* leaf extract to see what impact it had. The leaf extract of G. *sylvestre* had zero effect on reduced glycemia generated by a balanced diet or the injection of glucose or amylose, but it did raise blood lipid levels following SOC therapy. However, chronic and sub-acute treatment with G. *sylvestre*'s extract showed zero influence on water and food intake, increased body weight or blood sugar and differences in lipid levels between diabetic alloxan rats and control rats.[14] However, the herbal preparation must be clinically approved and scientifically validated before treating diabetes and hyperlipidemia.[23] Finally, the research revealed that the plant has antidiabetic characteristics and sugar-inactivation properties.[25-36]

Side Effects and Toxicity of *G. sylvestre*

The antibacterial, anti-protozoal, anti-fungal, and anti-viral properties of G. *sylvestre* shoot extracts are well-documented. The intraperitoneal administration of water and ethanol extracts of *Gymnema* to mice resulted in an LD_{50} of 375 mg/kg.[8]

Gymnema might produce moderate gastrointestinal discomfort if taken on an empty stomach. In those who are hyperglycemic, extremely high dosages can cause hypoglycemia. Changes in insulin dose or other antidiabetic drugs, such as antidepressants and salicylates, can improve antidiabetic efficacy, but some stimulants, such as *Ephedra* sp., can diminish it.[8]

CONCLUSION

The ancient Ayurvedic system of medicine was built on medicinal herbs. Herbal treatments are now becoming popular as molecular drug targets in research and in pharmacological usage. The increased prevalence of illnesses and problems connected with commercial pharmaceuticals presents a severe threat to humanity. Naturopathic therapies provide relief from the high expense of pricey pharmaceuticals and the benefit of being relatively safe and having fewer side effects. Screening plants with pharmacological importance as a foundation for the creation of novel and more efficient medicines is thus very important. *G. sylvestre* is a globally distributed plant. It's one of the most powerful medicinal herbs on the planet. *G. sylvestre* leaves are commonly utilized in the management of diabetes. It is diuretic in Indian herbal medicine. Gymnemic acid is the major active chemical ingredient extracted from *G. sylvestre*. It helps limit glucose absorption.G. *sylvestre* must be grown and maintained as an important medicinal plant and source of bioactive chemicals. Since ancient times, the plant has held varied pharmacological importance as a naturopathic remedy, and it is gaining appeal in the modern day as well. The plant has been demonstrated to possess digestive, anti-helmentic, diuretic, and anti-inflammatory qualities. This plant is supposed to help with leucoderma, constipation, hemorrhoids, jaundice, cardiopathy, asthma, bronchitis, and dyspepsia. The leaves of this plant are eaten to curb sweet and bitter cravings and applied to the afflicted areas of the body to cure a variety of problems. G. *sylvestre* is a very useful plant in today's modern-day world therefore, this plant should be utilized properly up to its full potential. More research must be done to discover other uses or qualities of this plant. This review tries to highlight the properties of this plant with already done and provided research.

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