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Review

Clinical applications of *Gymnema sylvestre* against type 2 diabetes mellitus and its associated abnormalities

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Summary. Diabetes mellitus (Madhumeha) is one of the leading metabolic disorder prevalent in the developing countries which is characterized by high blood sugar level and is associated with macrovascular and microvascular complications. The Indian Ayurveda describes several herbs for the management and treatment of diabetes mellitus among which *Gymnema sylvestre* (Asclepiadaceae) is revered as a potential antidiabetic herbal drug which has the capability of simultaneously regenerating β-cell and stimulating insulin secretion. *Gymnema sylvestre* also possesses anti-obesity, anti-hyperlipidemic, anti-inflammatory, and anti-cancerous activities. This review updates the recent developments in the experimental studies conducted on the *Gymnema sylvestre* as an effective remedy for diabetes mellitus evidenced by both animals and human studies. Moreover, this study also discussed the toxicity of *Gymnema sylvestre* and future challenges in the roadmap of formulation for prevention and control of diabetes.

Key words: Diabetes Mellitus, *Gymnema sylvestre*, Anti-diabetic, Anti-hyperlipidemic, Anti-inflammatory, Anti-Cancerous

Introduction

Plants have been used practically in all civilizations as a source of medicine. The World Health Organization (WHO) projects the rampant use of plants based preparations as medicines by almost 80% populace inhabiting the developing nations (1). Countries in Asia are considered to provide crucial information in using herbal species for the treatment of various metabolic conditions (2).The modern pharmacopoeia contains at least 25% of plant-derived drugs. Ayurveda of the Atharva Veda enlists the usage and efficacy of herbal formulations in the healing of diabetes. Diabetes is a cluster of inter-related metabolic anarchy symbolized by hyperglycemia and carbohydrate, lipid and protein metabolic disorders which ultimately results in discrepancies either in the secretion of insulin or its efficacy or both (3). According to WHO, approximately 171 million people were worldwide suffering from diabetes in 2000 and the prevalence is projected to 366 million by 2030 (4).

Gymnema sylvestre-A Potential Herbal Cure

Gymnema sylvestre (Gurmar/Madhunashini) is one of the natural herbals that has been extensively used in traditional medicine for almost two thousand years. It is a woody, plant species native to India, particularly in South Indian forests. It is also found in tropical Africa and in Australia as well as in Asia, Malaysia, Japan, Vietnam and Sri Lanka (5). The main plant parts of *Gymnema sylvestre* used for herbal preparations are its leaves and roots (6). The leaf powder is yellow in

color and soft in nature having poor flow ability and compatibility (7). G*ymnema* possesses hepatoprotective and sugar suppressing potential (8, 9). The age-old use of G*ymnema* includes the usage of its dried leaf and root, for ailments such as cough, leprosy, skin diseases and wounds. Liquid extract procured from the roots of *Gymnema* has been used to cure nausea, vomiting, and dysentery and while the paste formed from the plant when mixed with mother's milk is effective enough to cure mouth ulcer (10, 11).

This present review aims at providing the latest developments on the pharmacological and clinical research conducted to establish the hypoglycemic effect of the plant, unraveling its active hypoglycemic constituents in the treatment of diabetes. Moreover, the study discussed other activities of *Gymnema sylvestre* such as anti-microbial, anti-cancerous and anti-arthritic activity.

Various applications of *Gymnema sylvestre*

Gymnema sylvestre is highly preferred by Ayurvedic physicians to dexterously combat and manage diabetes. This figure explains the antidiabetic, antihyperlipidemic, anti-Obese, anti-oxidant, immunomodulatory and wound healing activities *Gymnema sylvestre* (Fig.1).

Antidiabetic activity of Gymnema sylvestre based on animal studies

The antidiabetic activity of *Gymnema sylvestre* has been studied in diabetic rats by administering them with the alcoholic extract of leaves (100 mg/kg/day) for a period of one month (20). The average blood glucose level was significantly lowered in the animals treated with *Gymnema sylvestre* extract from the second week of therapy. As no effect of *Gymnema sylvestre* was noted on the level of thyroxine even in corticosteroid-induced diabetes mellitus rat, hence it was concluded that possibly *Gymnema sylvestre* does not affect thyroid hormone-mediated type 2 diabetes mellitus.

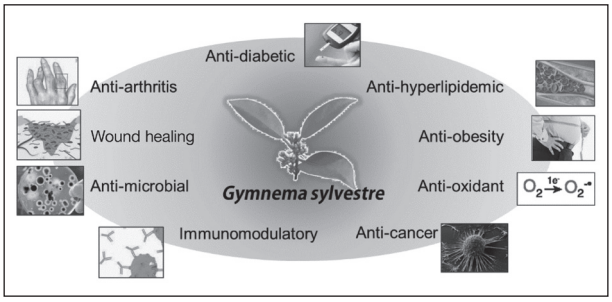

Figure 1. Various roles of *Gymnema sylvestre* in health protection. Anti-diabetic (9), anti-hyperlipidemic (12), anti-obesity (13), anti-oxidant (14), anti-cancer (15), Immunomodulatory (16), anti-microbial (17), wound healing (18), anti-arthritis (19).

While in the diabetic rabbits experiment, *Gymnema sylvestre* demonstrated improvements in glycogen synthesis, glycolysis, gluconeogenesis, and hepatic and muscle glucose uptake (21) (22) and facilitated the hitch of hemoglobin and protein glycosylation (23). Studies carried out by Srivastava and co-workers (1985) have illustrated the anti-hyperglycemic and life-protracting upshot of aqueous extract of the dried leaves of *Gymnema sylvestre* that had been given in four different single doses (of amounts 0.2 g, 0.4 g, 0.6 g, and 0.8 g respectively) in alloxan-induced diabetic rats with various ranges of blood glucose levels. The highest reduction in the level of blood glucose was obtained in the moderately diabetic rats treated with *Gymnema sylvestre* at a dose of 0.6 g. The same group also exhibited highest life-expectancy. While the administration of over 0.6 g of *Gymnema* extract showed no further amelioration in the management of blood glucose (24).

Gymnema sylvestre also possesses insulinotropic activity, the administration of *Gymnema sylvestre* has reduced the fasting glucose levels (at significant variation, $P < 0.001$) together with a considerable lowering of serum lipid levels while concomitantly ameliorating serum protein levels (25). The administration of the ethanolic excerpt (50%) of the leaves of *Gymnema sylvestre* (GS3, 20 mg/day/rat) and the processed residue of GS3 (GS4, 20 mg/day/rat) presented a 30% boost in the total β-cells mass and also in the numbers of the islets (p <0.001) (26). The regeneration of pancreatic tissue also caused the success in the absolute management of the fasting sugar levels within 60 days in GS3 and 20 days in the GS4 group.

The alcoholic extract of *Gymnema sylvestre* stimulates the release of insulin from the HIT-T15, MIN-6, and RINm5F β-cells by increasing membrane permeability (27, 28). Trypan blue exclusion test indicated that extract increased the permeability of cells for dye due to high saponin in glycoside content. Ca^{++} sensitive component leads to the release of insulin through channel in-

dependent influx of Ca^{++} into the β-cells. Similar effects were reported by Liu et al. (29) where aqueous alcoholic extract (0.06-0.25 mg/ml conc.) secreted insulin from MIN6 β-cell line. Higher concentration (> 0.5 mg/ml) causes increased trypan blue uptake and increases β-cell Ca^{++} levels. The methanolic extract of *Gymnema sylvestre* leaf and callus also exhibits the antidiabetic activities through regeneration of β-cells (30).The green compact callus obtained through *in-vitro* culture exposed to stressful circumstances of exposure to blue light with 2, 4-D (1.5 mg/L) and KN (0.5 mg/L) also showed a significant β-cell regeneration. Sujin et al. in 2008 reported that administration of higher doses (5, 10, 15, 20/g/25 days) of *Gymnema sylvestre* did not show significant mortality but behavioral changes were observed *viz*. lethargic movements and suppression of appetite were observed upon 5 g and 20 g dose (31). *Gymnema sylvestre* is known to suppress the taste stimulus in taste buds. A compound isolated from the searing aqueous excerpt of the *Gymnema sylvestre* leaves was seen to condense the neural response of the murine chorda tympani towards sucrose and this matter was confirmed to be the peptide named Gurmarin which comprised of 35 amino acids of 4,000 Dalton molecular mass. The forestalling potential of the peptide on the sweet perception was established by exposing the tongue with above $1x10^{-6}$M of the peptide (32). The inhibitory effect of gurmarin differs among tongue regions and mouse strains (33). A study conducted on the taste perception of rats towards gurmarin revealed that the apex of the tongue is activated upon consumption mostly due to the binding of gurmarin to the receptor protein responsible for the sweet taste perception (34).

The pharmacokinetic and pharmacodynamic interaction was studied by Kamble's colleagues in diabetic rats after concomitant treatment with 400 mg/kg of *Gymnema sylvestre* extract and 0.8 mg/kg of glimepiride drug for four weeks (35). The results revealed a beneficial pharmacodynamic interaction with a significant increase in anti-hyperglycemic activities with no major alterations in the pharmacokinetic parameters. The chitosan nanoparticle with *Gymnema sylvestre* extract was also evaluated against rats induced with streptozotocin and was found to decrease the fasting glucose level and glycosylated hemoglobin at the dose of 100 mg/kg body weight of the rats (36).

Phytochemistry and Bioactive components having anti-diabetic property

The principle component of *Gymnema sylvestre* is gymnemic acid, a complex mixture of at least 17 different saponins (37) mostly oleanane (38) and dammarene classes (39). The longispinogenin 3-O-β-D-glucuronopyranoside, 3-O-β-D-glucopyranosyl (1-6)-β-D-glucopyranosyloleanolic acid 28-O- β-D-glucopyranosyl ester,21β-benzoylsitakisogenin3-O-β-D-glucuronopyranoside 3-O-β-D-xylopyranosyl (1-6)-β-D-glucopyranosyl (1-6)-β-D-glucopyranosyl oleanolic acid 28-O-β -D-glucopyranosyl ester, oleanolic acid 3-O-β-D-xylopyranosyl(1-6)-β-D-glucopyranosyl(1-6)-β-D-glucopyranoside and 3-O-β-D-glucopyranosyl (1-6)-β-D-glucopyranosyl oleanolic acid 28-β -D-glucopyranosyl (1-6)-β-D-glucopyranosyl ester are the oleanane-triterpene glycosides. These have been unraveled by hydrolysis followed by spectrophotometric analysis. Correspondingly, 7 other novel dammarane-style saponins, extracted from the leaf excerpt of *Gymnema sylvestre*, these are the gymnemasides I-VII. The same category saponins that were known earlier are gypenoside XXVIII, XXXVII, LV, LX11 and LXIII.

The saponin components responsible for the anti-hyperglycemic effect of *Gymnema sylvestre* are gymnemosides and gymnemic acid (40). The consumption of glucose by muscles is prevented by the triterpene glycosides fraction of the plant (41, 42). The inhibitory effects of triterpene glycosides and various gymnemosides from *Gymnema sylvestre* were found to inhibit glucose uptake in rat (43). A novel compound named dihydroxy gymnemic triacetate isolated from acetone extract reduced the blood sugar level by 65% and glycosylated hemoglobin by 39.56% and an increased in plasma insulin level by 63% at 20 mg/kg dose (44). The administration of gymnemic acid IV lowered the sugar level (13.5 mg/kg body weight) to 60%, which was similar to the efficiency of glibenclamide (14.8 mg/kg body weight) (45). Recently, the crystallographic analysis of gymnemagenin indicated its good gelling with the target protein's crystallographic constitution (dipeptidyl peptidases, aldose reductase, glucokinase, fructose 1,6-bisphosphate, cytochrome 450, 11β-hydroxysteroid dehydrogenase, tyrosine

phosphatases, protein kinase B, glutamine fructose-6-phosphate amidotransferase, Insulin receptor substrate, Glucose transporter, AMP-activated protein kinase, cholesteryl ester transfer protein) having a key responsibility in the carbohydrate regulation (46).

Antihyperlipidemic activity

Diabetes mellitus is often associated with disturbances in lipid metabolism regulating in levels of lipoproteins (47). The lipoprotein abnormalities cause insulin resistance through different factors which may alleviate lipoprotein lipase (LPL) and peroxisome-proliferator activated receptor (PPAR) gamma, on contrary by elevating acyl-CoA synthetase and transporter of microsomal triglyceride. The administration of 25-100 mg/kg dose of the leaf extract of *Gymnema sylvestre* showed a tectonic decline in the lipid profile in a dose reliant approach when administered orally for two weeks in experimental rats. The extract (at 100 mg/kg) of *Gymnema sylvestre* lowers the serum triglyceride, total cholesterol and atherosclerotic property which was almost comparable to a standard lipid-lowering agent (48).

The hypolipidemic activity of higher dose of aqueous leaf extract (up to 800 mg/kg body weight for 30 days) was examined by Mall et al. in alloxan induced diabetic rats (49). The reduction was examined at all doses (400,600 and 800 mg/kg body weight) but the highest concentration was substantial compared to all observed days. While the administration of the excerpt indicated a consequential diminution in the serum lipids and the fasting blood glucose level, it has also shown proof of desirable increase in the serum high-density lipoprotein (HDL)-cholesterol. Similar considerable dwindle in the other lipid parameters and a significant increase (p <0.05) in HDL level was obtained by Rachh et al. in 2010 when hydroalcoholic leaf extract (200 mg/kg body weight) of the plant was administered in the diet of high cholesterol-fed (2% cholesterol + 1 % sodium cholate + 2% coconut oil) rats (12).

Gymnema sylvestre when mixed with chitosan and ascorbic acid (1:10:2), possesses protective effects against hypercholesterolemia. Significant decrease in serum triglyceride (35.87%), total cholesterol (43.89%), LDL (54.00%), and atherogenic index (AI) (41.47%), was observed at dose of 4.68 g/kg diet (50). Leaf extract consumption in rats was also seen to reduce the noticeable digestion of fat and kick off the emission of neutral sterols and acidic steroids (51). A novel dihydroxy gymnemic triacetate caused a reduction in total cholesterol, triglyceride, LDL by 54%, 55%, and 40% respectively and simultaneously increase in HDL level was 38% observed (44).

Anti-Obese Activity

Abdominal fat deposition is yet another pivotal criterion branded as the harbinger of diabetes. The increase in adipocytes lessens the quantity of insulin receptors on cells that are targets of insulin in our body. This substantially diminishes the requisite amount of insulin to be present in the circulation and potentially reduces its metabolic functions. An alarming 40-80 percentile of diabetics have been reported to be obese. The adipocytes secrete resistin hormone, a 12.5 kDa cysteine-rich protein (52). Studies in murine models have implicated that the prevalence of resistin in the blood circulation accentuates insulin resistance development. Recent *in vivo* and *in vitro* investigations have shown that resistin sways glucose metabolism. In murine models, the inclusion of resistin patently amplifies the creation of glucose from the liver and thus drops the hepatic insulin exploit (53). Pravenec and co-workers (2003) have shown that genetically modified rats which secrete more resistin than required have glucose intolerance and disrupted skeletal muscle glucose metabolism (54).

Gymnema sylvestre is shown to have very useful properties for the management of both obesity and diabetes. Administration of a supplement comprising of *Gymnema sylvestre* with glucomannan, fenugreek, vitamin C and chitosan to a patient with body mass index 30 kg/m^2 or more resulted in significant reduction in their weight and also the overall fat percentage.

Administration of gymnemic acid increased the fecal excretion of steroids and cholesterol (55). Weight gain was eventfully curbed in rats treated with the extract (56). The hexane extract of *Gymnema sylvestre* leaves (150 mg/kg and 250 mg/kg body weight) significantly (p<0.001) reduced increased body weight in Sprague dawley rats (13). A separate study was undertaken to analyze the effect of a new extract of an immensely bio-available, calcium-potassium salt of (–)-hydroxycitric acid for weight loss. The same ex-

cerpt was also used along with a niacin-bound chromium compound and with *Gymnema sylvestre* extract achieved weight loss in mildly fat individuals. Weight loss was analyzed by evaluating body weight fluctuations, body mass index, appetite, serum triglyceride, total cholesterol, HDL, LDL, leptin and serotonin concentrations, the elimination of urinary fat metabolites was also noted (57). *Gymnema sylvestre* extract endorses weight loss as it trims down sweet cravings and thus manages the blood sugar concentrations.

Anti-Oxidant Activity

Oxidative stress is produced under diabetic conditions which are responsible for the development of secondary complications. Reactive oxygen species (ROS) are produced under such conditions through glycation reaction which occurs in various tissues and plays a deleterious role in the diabetic secondary complications (58). The insinuation of oxidative stress in worsening diabetes has been proved by further generation of free radicals, non-enzymatic protein glycosylation, glucose auto-oxidation, alterations of antioxidant enzymes and increase in lipid peroxidation (59).

Antioxidants are effective in reducing diabetic complications. Numerous researchers have professed the healing of insulin resistance in type 2 diabetics and cardiovascular disease patients after the administration of antioxidants such as vitamin C, glutathione and vitamin E. The alcoholic extract of *Gymnema sylvestre* has been seen to restrict the 1, 1-Diphenyl-2-picryl-hydrazyl (DPPH) and clear up superoxide and hydrogen peroxide. This ability to reduce radicals has also been exhibited in the ferric reducing prototype wherein the antioxidant capability was 17.54 mg/g expressed in terms of ascorbic acid (14). A noteworthy decline (19.27%) (p<0.05) in the plasma alanine aminotransferase potentiality was obtained by administration of a mixture (4.68 g/kg diet) of chitosan, vitamin C and *Gymnema sylvestre* (10:2:1) (50).

Immunomodulatory Activities

Several components of the immune system face discrepancies when inflicted with type 2 diabetes which lead to inflammation and glucose abnormalities. The cytokines are produced when the macrophages enter the adipocytes; these cytokines specifically cause the neighboring liver, muscle or fat cells to become insulin resistant. Several markers of inflammation such as C-reactive protein, fibrinogen, the interleukins and tumor necrosis factor-α (60) get elevated in diabetes.

The extracts of *Gymnema sylvestre* restricted the histamine release *in vitro* (21). The leaf extract had significantly elevated the neutrophil chemotaxis that consequentially elevated neutrophils reduction of Nitro Blue Tetrazolium dye to form formazan thus ascertaining intracellular carnage aspect and a total increase in metabolic activity of phagocytosing neutrophils. This is perhaps due to the presence of tannins present in *Gymenma* leaves which have anti-inflammatory and immunomodulatory attributes (16). The methanolic extract of *Gymnema sylvestre* leaves showed a potential effect at 100μg/ml in nitric oxide and ROS generation in macrophage and 20μg/ml in lymphocyte proliferation leading to stimulation of myeloid and lymphoid elements of the immune system and thereby restoring the innate immunity (61).

Wound Healing Activity

Diabetes exponentially reduces the wound healing capacity of the body, hence the recurrence of a severe, never-healing infection from a simple wound is always a major threat (18). In one of the recent studies, Carbopol gel was prepared from the hydroalcoholic extracts of *Gymnema sylvestre* and *Tageteserecta Linn.* to determine its wound healing activity in albino mice (62). In both, the models, a prominent decrease in the time required for the occurrence of epithelial tissues was evidently noticed and the combined gel exhibited hastening of the wound healing process. The hydro alcoholic extracts could possibly accentuate wound healing as they have antioxidant potential and the phytoconstituent (flavonoids) prevalent in it that fastens the process of wound healing.

Clinical Studies and Trials on Humans

Gymnema sylvestre is shown to be an effective antidiabetic agent in the clinical trials. The insulinotropic activity of *Gymnema sylvestre* was observed in adult human subjects (25-40 year age group) by administering the 2 g/day in two doses (25). A water based excerpt

of *Gymnema sylvestre* leaves when administered at a dosage of 2 gm thrice daily to 10 normal individuals over a period of ten days and in 6 diabetics for fifteen days potentially lowered the fasting and oral glucose tolerance test (OGTT) glucose intensity barring the OGTT in the normal cluster (63). Quotidian administration of 400 mg leaf excerpt of *Gymnema sylvestre* twice has been observed to diminish the glycosylated hemoglobin (HbA1C) concentration in diabetics (64).

The universal applicability of the *Gymnema sylvestre* in diabetes with either type 1 or type 2 has been established by various studies. In one of the studies, the efficacy of quotidian consumption of 400 mg GS4 was examined on 22 type 2 diabetes patients (65). *Gymnema sylvestre* was seen to radically shrank plasma glucose (p<0.001), HbA1c (p<0.001), and glycosylated plasma protein (GPP) levels during the 18–20-month of valuation time. In another individual study, the efficacy of the *Gymnema sylvestre* excerpt on 27 type 1 diabetics was investigated for 6–30 months (66). It was observed that *Gymnema sylvestre* drastically diminished the GPP levels in the initial six to eight months, and then reduced serum amylase (p<0.001) within 16–18 months. As compared with insulin therapy (n=37), *Gymnema sylvestre* appreciably boosted serum C-peptide concentration in 16–18 months' time (p<0.001). The outcome of the administration of the leaf powder of *Gymnema sylvestre* on plasma glucose concentration of 20 type 2 diabetic women aged between 40-60 years living in Udaipur, Rajasthan was studied by Paliwal et al. in 2009 (67). Everyday 6 gm of *Gymnema sylvestre* leaf powder was given to the subjects in three divided doses and dietary survey using 24 hours recall method was also adopted. Results of intervention revealed that the powder effectively worked on reducing sugar levels with no undesirable side effects, hence it is an effective remedy and a therapeutic agent in lowering sugar level.

The polyherbal formulation made from *Gymnema sylvestre* (GSPF kwath; mixture of 10 herbs) exerted a significant curtailment of blood glucose (23.5 % and 26.7% for fasting and postprandial glucose level, respectively) and glycosylated hemoglobin (11.7%). 6 months of GSPF therapy reduce the serum cholesterol (14.4%), triglycerides (21.7%), LDL (26.8%) and VLDL (21.7%) levels. A marked increase was also recorded in the biochemical marker for oxidative stress (68). In another study, the short-term supplementation of G-400, a polyherbal formulation (1000mg/day for 8 weeks) was used to attenuate the hyperglycemia and hyperlipidemia in the patients (69). Yadav et al. reviewed the preventive and therapeutic aspects of *Gymnema sylvestre* as a potential herbal drug in type 2 diabetes (70).

Other Therapeutic Activates of *Gymnema sylvestre*

The *Gymnema sylvestre* has proved to possess several other therapeutic activities. Various parts of the plant though pungent act as a tonic for liver, vomiting causative, promote the production of urine, refrigerant, astringent, heal, treatment of anomalies in liver and spleen, gas, acidity, constipation, jaundice, helminthiasis and abnormal menstruation.

Antimicrobial Activity

In vitro, antibiotic activity of *Gymnema sylvestre* extracted with petroleum ether then with chloroform and lastly with a mixture of water: Ethanol (1:1) was effective to inhibit *Bacillus subtilis*, *Staphylococcus aureus* but not *Escherichia coli* (71). The hexane extract of *Gymnema sylvestre* also showed maximum inhibition against *Serratia marcescens* (MTCC 86) (72). The ethanol-based excerpt of the leaves of *Gymnema sylvestre* have exhibited microbicidal potential against *Bacillus pumilis*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and but was ineffective in case of *Proteus vulgaris* and *Escherichia coli* (17). The bioactive molecule, Gymnemic acid is also used as an antifungal agent as it inhibits the *Candida albican* from yeast to hyphal transition which is a key virulence factor (73).

Anticancer Activity

The efficacy of chloroform, ethyl acetate and alcoholic extracts of *Gymnema sylvestre* were tested on A549 (human lung cancer) cell lines and MCF7 (human breast cancer) cell lines *in vitro* by MTT Assay (74). At 50 and 100 µg/ml concentration, the extracts positively affect the MCF 7 cell lines while the activity was dose-dependent with similar IC_{50} values their efficacy on the A549 cells was trivial. However, the effectiveness of chloroform and ethyl acetate excerpts was better when compared to that of the alcoholic extract

on the A549 cell lines. The anticancer activity may be due to the gymnemic acids. The cytotoxic activity of isolated saponin, gymnemagol from leaves was tested on HeLa cells and reported to be a good cytotoxic agent (63%) (75). The green synthesis of silver and gold nanoparticle from *Gymnema sylvestre* showed cytotoxic activity against Hep2 cells with the IC_{50} value of 121 µg/ml for sliver nanoparticle and 38% inhibition for gold nanoparticle at a concentration of 250 µg/ml. However, silver nanoparticles of *Gymnema sylvestre* proved much better for their antiproliferative effects in Hep2 cells which were mediated through induction of apoptosis (76). The gold nanoparticle of *Gymnema sylvestre* was also synthesized by Arunchalam et al. (15) evaluated against HT29 and Vero cell lines at different concentration. It was observed that the gold nanoparticles were more sensitive toward human cancer cell line (HT29) as compared to Vero cell line.

Anti-Arthritic Activity

The leaf extracts of *Gymnema sylvestre* is has been utilized for demonstrating the anti-arthritic activity in albino rats. The anti-arthritic action of petroleum ether extract and aqueous extract was studied in Freund's adjuvant-induced arthritis in rats (19). The presence of steroids, triterpenoids and saponin glycosides in the leaves *Gymnema sylvestre* leads to the potential anti-arthritic activity. The petroleum ether extract treated groups exhibited significantly reduced paw swelling by blocking the inflammatory cells (77).

Toxicological Evaluation of *Gymnema sylvestre*

Even in the long-term study, there was no report of any undesirable effect. However, hypoglycemia is one of the possibilities of its administration.

High doses of *Gymnema sylvestre* leaves did not exhibit any adverse effect on the gastrointestinal mucosa; hence, it poses to be a harmless gastrotoxic anti-inflammatory response compared with other anti-inflammatory agents (78). While in an acute toxicity investigation in mice a negative behavioral changes, neurologic and autonomic upshots were evident. Safety ratio (LD50/ED50) in the diabetics was sixteen while in the healthy rats it was eleven (79).

Evidence regarding the toxicity of the plant or its parts on the human has been documented rather in patients with quotidian consumption of *Gymnema sylvestre* the serum urea, uric acid, and hemoglobin levels remain normal. However, it is suggested to avoid the administration of *Gymnema sylvestre* during pregnancy. Thus, *Gymnema sylvestre* is generally safe and devoid of side effect. The administration is recommended under the clinical supervision of the healthcare professional.

Future Perspectives of Herbal Drug and its Challenges

The use of plants and their parts for the effective healing of any ailment has been the fulcrum of the investigation. It is estimated that nearly 70% of the drugs used in India are derived from plants. Its efficacy has mounted its marketability with a twelve-monthly growth of 5% and 15%. The gross global herbal market of US $ 62 billion approximately may exponentially sprout to US $ 5 trillion by 2050. Ayurveda contributes Rs. 3500 crores (US $ 813 million) annually to international market (80).

Gymnema sylvestre is a magical herb effective for combating a wide range of health conditions. Every part of the plant has been attributed with medicinal values which have been immensely exploited for the same. Various herbal products based on *Gymnema sylvestre* are formulated and sold in the market. Several brands of extracts, tablets and herbal tea are based on this herb. There are various products of *Gymnema*, *viz. Gymnema* 4G (M1320/M1325), *Gymnema sylvestre* 75, *Gymnema* tea are now regularly used in the day today life.

As with any type of herbal supplement, safety and strength of the formulation are not clinically proven. Thus, taking a note of the intake dose is imperative to minimize the risk of *Gymnema sylvestre* side effects. No established and safe methodology is available for the product eminence and effectiveness. The improvement and materialistic functionality of herbal medicine industries are largely reliant upon its accessibility to amenities and in a row concerning the isolation, refining, and advertisement the industrial potential of plants. Therefore, a systematic investigation is mandated to develop drugs based on the components of *Gymnema sylvestre*. An ef-

Illustration of the bioactive compounds isolated from different parts of *Gymnema sylvestre*

Bioactive compounds	Part used	Extraction	Study results	Model used to induce diabetes	Beneficial role	References
Conduritol	Stem	Ethanol	Exhibited antidiabetic activity by elevating thymus, pancreas, splencia index or inhibiting the atrophy of thymus, pancreas, splencias of diabetic rat	Diabetic rats induced by alloxan	Antidiabetic activity	(81)
Dihydroxy gymnemic triacetate	Leaves	Acetone	Acquire the hypoglycemic and antihyperlipidemic activity in streptozotocin-induced diabetic rats	Streptozotocin-induced diabetic rats	Hypoglycemic and antihyperlipidemic	(44)
Gymnemic acids I-IV and gymnemasaponin V	Leaves	Methanol extract	Gymnemic acid IV treatment decrease glucose uptake and blood glucose level, Increase plasma insulin	Streptozotocin-induced diabetic mice.	Anti-obese and antihyperglycemic pro-drug.	(82)
Deacyl gymnemic acid	Leaves		Administration of deacyl gymnemic acid reduced the blood pressure and improved fasting sugar level. A decrease in HOMA-IR with fair improvement in lipid profile was observed.	High fructose diet for 20 days to induce metabolic syndrome in a rat model	Deacyl gymnemic acid alleviates the insulin resistance a rat model of metabolic syndrome.	(83)
Gymnemate (GA), a mixture of triterpene of glucuronides	Leaves	Water extract	Gymnemate treatment improved the lipid profiles, total cholesterol was decreased about 1/3, LDL, VLDL decreased about 1/2. The ratio of HDL-C to the total cholesterol was increased. The serum triglyceride was decreased to the 1/4 of OLETF control.	Genetic multifactor syndrome animal (OLETF rat)	Administration with gymnemate promoted weight loss was due to the anti-lipidemic action	(84)
Saponin rich gymnema. sylvestre	Leaves	Water extract	Lowers body weight and organ weights. Moreover, Plasma TC, TG, VLDL, LDL-C were also reduced.	High fat diet induced wistar rats	Saponin rich *Gymnema* sylvestre R.Br aqueous leaf extract can be used for obesity treatment.	(85)
Gymnemagenin and gymnemic acids	Leaves	Ethanol extract	A decrease in the blood glucose, serum TG, LDL, TC. Increase in serum insulin and antioxidant enzymes such as glutathione, catalase, and reduced glutathione was reported.	Sprague-Dawley rats	Increase in the antioxidant level and lowering lipid peroxidation	(86)
GS3, and GS4	Leaves	Alcoholic extract	Raise the serum insulin to levels closer to normal fasting levels. diabetic rat pancreas, Treatment with both GS_3, and GS_4, compound were able to double the islet number and β cell number	Streptozotocin treated rats	Probably due to repair/regeneration of the endocrine pancreas	(87)
Triterpene glycoside Glycoside	Leaves	90 % alcohol	Decrease the blood glucose ($p < 0.05$) at 2 and 4 hr after glucose load in the glucose tolerance test.	Streptozotocin induced diabetic rats	Hypoglycemic activity in control and streptozotocin induced diabetic rats.	(88)
Gymnemoside b	Leaves	Methanol extract	Gymnemoside b produced some inhibitory activity on glucose absorption after oral glucose loading in rats.	Male Wister rat	Inhibitory activity on glucose absorption	(89)

Abbreviation: HOMA-IR, (homeostatis model assessment- insulin resistance; OLETF rat, Otsuka Long Evans Tokushima Fatty; LDL, low density lipoprotein VLDL, very low density lipoprotein; HDL-C, high density lipoprotein; GS, Gymnema sylvestre

fective and safe drug can be flourished after an extensive clinical investigation which would be effective, natural, pharmacologically non-toxic and pristine.

Conclusions

Diabetes mellitus is the most common metabolic disorder affecting human beings and is characterized by chronic hyperglycemia. The prevalence of diabetes is rising and aggravating all over the world is being associated with an increase in financial burden, a decrease in quality of life, morbidity and mortality. In the past few years, *Gymnema sylvestre* has emerged as a cost-effective and potential intervention by targeting the etiological factors connected with diabetes. It functions as a blood sugar lowering agent, insulin stimulator, β-cell regenerator, facilitator of anti-obesity and an anti-inflammatory agent. It produces not only blood glucose homeostasis but also showed anti-cancerous, anti-microbial, anti-arthritic activities.

Gymnema sylvestre holds a definite promise in the management of diabetes mellitus. This review has updated the pharmacological, toxicological and clinical evaluation of this plant for treatment of diabetes and its associated abnormalities. The ethnomedical approach for diabetes using *Gymnema sylvestre* is practical, logical and economically worthwhile. But still, it requires scientific and technological validation, standardization for justification of its wide acceptability among a modern system of medicine. One can look toward to an integrated approach to future medicine using this traditional drug.

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