

Phcog Rev.: Review Article

Systemic review: Pharmacognosy, phytochemistry, pharmacology and clinical applications of *Gymnema sylvestre* R Br.

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ABSTRACT

Gymnema sylvestre R Br. (Gurmar) is a tropical vine whose leaves are considered antidiabetic in Ayurvedic medicine. It has been commonly used for the diabetes and as a diuretic in Indian proprietary medicines. This review attempts to encompass the available literature on *Gymnema sylvestre* with respect to its pharmacognostic characters, traditional uses, chemical constituents and summary of its various pharmacological activities and clinical effects. Other aspects such as toxicology and precautions are also discussed.

KEYWORDS- *Gymnema sylvestre* R Br., pharmacology, clinical application, chemistry

INTRODUCTION

Medicinal plants, which form the backbone of traditional medicine, have in the last few decades been the subject for very intense pharmacological studies; this has been brought about by the acknowledgement of the value of medicinal plants as potential sources of new compounds of therapeutics value and as sources of lead compounds in the drug development. In developing countries, it is estimated that about 80% of the population rely on traditional medicine for their primary health care. There arises a need therefore to screen medicinal plants for bioactive compounds as a basis for further pharmacological studies.

Gymnema sylvestre is an Indian herb reported in Ayurveda, the ancient Hindi medicine system of India. It consists of the dried leaflets of *G. sylvestre* R Br. Family: Asclepiadaceae; Synonyms: Meshasringi (meaning "ram's horn") in Sanskrit; Parpatrah in Duk, Shir-kurunja in Tamil, Chhotadudhilata in Bengali, Gurmar in Marathi. The word "Gymnema" is said to be derived from a Hindu word "Gurmar", "destroyer of sugar." When Gurmar is chewed, it interferes with the ability to taste sweetness. This explains its primary application for diabetes (1).



Fig.1 Photograph of *Gymnema sylvestre*

GEOGRAPHICAL DISTRIBUTION

G. sylvestre is a perennial, woody climbing plant that grows in the tropical forests of central and southern India (2). It is

distributed through out India, in a dry forest up to 600-meter height. It is found in Banda, Konkan, Western Ghats, Deccan extending to the part of the northern and western India, Ceylon- Tropical Africa. It is occasionally cultivated as medicinal plant (3, 4).

GENERAL APPEARANCE

The plant is large; more or less pubescent, woody and climber. The leaves of *G. sylvestre* are opposite usually elliptic or ovate (1.25 -2.0inx 0.5-1.25in). Flowers are small, yellow in colour with umbellate cymes, follicles terete, lanceolate up to 3 inch in length. The macroscopic and microscopic characters of the leaves have been described. The lamina is ovate, elliptic or ovate-lanceolate, with both surfaces pubescent. The colour of the leaves is green. The odor is characteristic and taste is slightly bitter and astringent (4, 5).

MICROSCOPIC CHARACTERISTICS

Microscopically *G. sylvestre* is observed that hairs are non-glandular and profusely present all over the surface. In leaves there are five vascular bundles. These are fan shaped in the center flanked on either side by two small bundles. The midrib has a ventral bulge. In the lamina, rosette crystals of calcium oxalate are present. In the spongy parenchyma, idoblasts are present (6).

POWDER PLANT MATERIAL

The powdered plant material is slight yellowish green in colour showing vascular bundles. Rosette crystals of calcium oxalate are present in lamina. It also shows presence of spongy parenchyma, a fan shaped vascular bundle (5).

IDENTIFICATION TESTS

General identity tests (5) for the extract of the *G. sylvestre* hydro-alcoholic extract are as follows:

The dilute solution suppresses the sweet taste buds.

It gives copious foam when shaken with water. On addition of the dilute acid, it forms a voluminous precipitate.

PURITY TEST

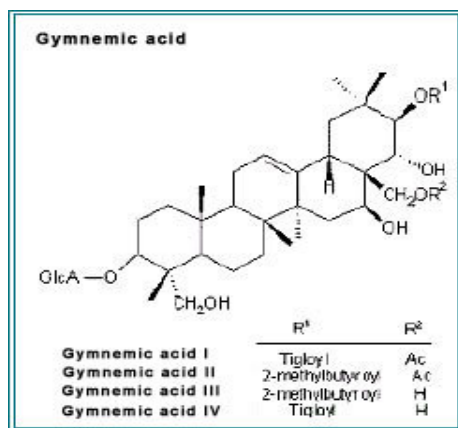
The following qualitative characteristics are described for the purity test of *G. sylvestre* (6);

- Total ash: Not more than 12 %
- Maximum Moisture: Not more than 6%
- Heavy metals: Not more than 40 PPM in the leaves or the leaves extract and 10 PPM in the final dosage form.

PHYTOCHEMISTRY/ MAJOR CHEMICAL CONSTITUENTS

The *G. sylvestre* leaves contain resins, albumin, chlorophyll, carbohydrates, tartaric acid, formic acid, butyric acid, anthraquinone derivatives, inositol alkaloids, organic acid 5.5%, parabin, calcium oxalate, 7.3%; lignin, 4.8%; cellulose, 22% (7). The organic acid-glycoside possesses antisaccharine properties and it is called gymnemic acid. It is a complex mixture of closely related acidic glycosides. The major active component is 'gymnemic acid'. The presence of gymnemic acid, (+) quercitol, lupeol, (-) amyirin, stigma sterol etc. have been reported from *G. sylvestre*. A new flavonol glycoside namely kaempferol 3-O-beta-D-glucopyranosyl-(1-->4)-alpha-L-rhamnopyranosyl-(1-->6)-beta-D-galactopyranoside has also found in aerial parts of *G. sylvestre* (8). Three new oleanane-type triterpene glycosides i.e. beta-O-benzoylsitakisogenin 3-O-beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranoside, the potassium salt of longispinogenin 3-O-beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranoside and the potassium salt of 29-hydroxylongispinogenin 3-O-beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranoside along with the sodium salt of alternoside II were isolated from an ethanol extract of the leaves of *G. sylvestre* (9).

Saponins have been found to be present in the alcoholic extract of *G. sylvestre*. Besides six known gymnemic acids, four new triterpenoid saponins, gymnemasins A, B, C and D, isolated from the leaves of *G. sylvestre* were identified as 3-O-[beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranosyl]-22-O-tigloyl-gymnemanol, 3-O-[beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranosyl]-gymnemanol, 3-O-beta-D-glucuronopyranosyl-22-O-tigloyl-gymnemanol and 3-O-beta-D-glucuronopyranosyl-gymnemanol respectively. The aglycone, gymnemanol, which is a new compound, was characterized as 3 beta-16 beta-22-alpha-23-28-pentahydroxyolean-12-ene (10). Gymnestrogenin, a new pentahydroxytriterpene from the leaves of *G. sylvestre* has been reported (11).



CHEMICAL EVALUATION

Several methods were tried for the isolation and characterization of the *G. sylvestre* plant and to know better

about its phytochemistry and pharmacology. Among the various methods the gravimetric method (6), HPTLC method (12, 13) and HPLC method (14) were under consideration for the analysis of the gymnemic acid from the *G. sylvestre* extract. The gravimetric method is applicable for the crude total gymnemic acid estimation. The HPLC method is useful for the estimation of deacylgymnemic acid from the extract and HPTLC method is useful for the standardization of *G. sylvestre* with reference to gymnemogenin from the extract.

PHARMACOLOGICAL ACTIONS

Antiobesity study/ Weight control

A standardized *G. sylvestre* extract (GSE) in combination with niacin-bound chromium (NBC) and hydroxycitric acid (HCA-SX) has been evaluated for antiobesity activity by monitoring changes in body weight, body mass index (BMI), appetite, lipid profiles, serum leptin and excretion of urinary fat metabolites. A randomized, double blind, placebo-controlled human study was conducted in Elluru, India for 8 weeks in 60 moderately obese subjects (ages 21-50, BMI >26 kg/m). All subjects received a 2000 kcal diet/day and participated in supervised walking. At the end of 8 weeks, body weight and BMI decreased by 5-6% in all subjects. Food intake, total cholesterol, low-density lipoproteins, triglycerides and serum leptin levels were significantly reduced while high-density lipoprotein levels and excretion of urinary fat metabolites increased. This study showed that the combination of GSE and HCA-SX, NBC can serve as an effective and safe weight-loss formula that can facilitate a reduction in excess body weight and BMI, while promoting healthy blood lipid levels (15).

Antimicrobial activity of leaf extracts

In an *in vitro* study, the ethanolic extract of *G. sylvestre* leaves showed an antimicrobial activity against *Bacillus pumilis*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and inactivity against *Proteus vulgaris* and *Escherichia coli* (16).

Antihyperglycemic activity

In an animal study, Sugihara and et. al have investigated the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnemasaponin V) derived from the methanol extract of leaves of *G. sylvestre* in streptozotocin (STZ)-diabetic mice. The saponin fraction (60mg/kg) reduced blood glucose levels within 2-4h after the intraperitoneal administration. Gymnemic acid IV, not the other 4 glycosides at doses of 3.4-13.4 mg/kg reduced the blood glucose levels by 13.5- 60.0% 6h after the administration comparable to the potency of glibenclamide, and did not change the blood glucose levels of normal mice. Gymnemic acid IV at 13.4 mg/kg dose increased plasma insulin levels in STZ-diabetic mice (17).

MEDICINAL USES

Uses described in pharmacopoeias and traditional systems of medicine

Susruta describes *G. sylvestre* as a destroyer of 'Madhumeha' and urinary disorder. On account of its property to abolish the taste of sugar, it has been given the name of 'Gurmar' meaning sugar destroyer (18). It is bitter, astringent, acrid, thermogenic, anti-inflammatory, anodyne, digestive, liver tonic, emetic, diuretic, stomachic, stimulant, anthelmintic,

alexipharmic, laxative, cardiogenic, expectorant, antipyretic and uterine tonic. It is useful in inflammations, hepatosplenomegaly, dyspepsia, constipation, jaundice, haemorrhoids, strangury renal and vesical calculi, helminthiasis, cardiopathy, cough asthma, bronchitis, intermittent fever, amenorrhoea, vitiated conditions of vata, conjunctivitis and leucoderma (1, 19). The people from Nagari Hills of the North Arcot District, Bombay and Gujarat from India have the habit of chewing a few green leaves of *G. sylvestre* in the morning in order to keep their urine clear and to reduce glycosuria. In Bombay and Madras, vairs are known to recommend the leaves in the treatment of furunculosis and Madhumeha (4).

Uses described in folk medicines, supported by experimental clinical studies

G. sylvestre extract (400 mg/day) for 18-20 months was observed to reduce blood glucose in 22 non-insulin dependent diabetic patients (20). The glycosylated hemoglobin and glycosylated plasma proteins were allowed to reduce by conventional drug dosage. The sweetness perception of sucrose or aspartame was reduced by oral application of extract (21, 22). Lawless has carried out psychophysical experiments to give evidence for neural inhibition in bitter-sweet taste mixtures and found that suppression of bitter and sweet taste may be due to neural inhibition or competition rather than chemical interactions in solution of molecules at receptor sites (23). The hypoglycemic activity of this indigenous drug in normal and diabetic persons was demonstrated by Khare et al. (24). The extended release tablet of the *G. sylvestre* as a supplementary treatment in about 65 patients also showed the positive results to reduce blood glucose, glycosylated hemoglobin and glycosylated plasma proteins, thereby reducing the complications of the diabetes (25).

Uses described in folk medicines, supported by experimental animal studies

Various chemical constituents in *G. sylvestre* have difference in anti sweetening property. This is also reported in the literature that the 'Gurmarin', a 35 residue peptide with 3 disulfide bonds, suppressed the sweetness response to sucrose, but not that of glucose, fructose, saccharin or glycine in rats (26). Gurmarin also showed its suppressive effect on the neural responses to sweet taste stimuli in the rats (27). Gymnemic acid is a powerful suppressor of sweet taste in humans and chimpanzees but lacks this ability in nonprimates and lower primates. This is possible due to inhibitory effect of the gymnemic acid to glucose (28). The sweet response of sugars, sweet amino acids and saccharin were suppressed by gurmarin. At pH 4.5, with 5 μM of gurmarin gives maximal effect and this was still significant at 0.5 μM (2 $\mu\text{g/ml}$) in rats (29). Gurmarin at 3 $\mu\text{g/ml}$ suppressed sucrose responses in C57BL mice but not BALB mice (30). Chemicals of diverse structures can elicit sweet response in humans, but marked species difference in response to sweet-tasting compounds exists among mammalian species. Sweet response in certain mammals can be selectively blocked by a number of compounds, including gymnemic acid and ziziphin (31).

Apart from the antisweet property, it is reported that the *G. sylvestre* extract when given in streptozotocin treated rats, is able to double the islet number, beta cell number and glucose homeostasis (32). Effect of *G. sylvestre* on blood glucose, cholesterol and triglycerides levels in normoglycaemic and alloxan diabetic rabbits has been proved (33). Powdered leaves of *G. sylvestre* when fed for 10 days in protected rats, fall of blood glucose level was observed (34). *G. sylvestre* extract suppressed neural responses to mixture of monosodium glutamate and disodium inosine monophosphate in rats (35).

Gymnemic acid potently inhibits the absorption of oleic acid in intestine which is dose dependent and reversible. The extent of inhibition and the recovery progress were extremely similar to that of glucose absorption. Taurocholate did not affect the inhibitory effect of gymnemic acid on oleic acid absorption, but lowering its concentration facilitated the recovery from the inhibition. The absorption of oleic acid was not affected by other glycosides such as phloridzin, stevioside, and glycyrrhizin (36).

Gymnemoside b and gymnemic acids III, V, and VII showed a little inhibitory activity against glucose absorption, but the principal constituents, gymnemic acid I and gymnemasaponin V lack this activity in oral glucose-loaded rats (37). *G. sylvestre* at 1 g/kg attenuated the glucose response in fasted non-diabetic rats and in a 4 weeks study, improved glucose tolerance and suggested its usefulness in the treatment of certain classes of non-insulin-dependent diabetes mellitus (38).

G. sylvestre (120 mg/kg/day) did not improve insulin resistance in diabetic rats (39). Release of glucose stimulated gastric inhibitory peptide, into the portal vein was depressed by *G. sylvestre* leaf extract, gymnemic acid and phlorizin but not by cytochalasin B in rats (40).

Aqueous extract of *G. sylvestre* have been possess hypoglycemic activity (41). *In vitro*, the inhibitory effects of DPPH radicals and LDL oxidation were found with aqueous extract of *G. sylvestre* (42).

Hypoglycemic and life-prolonging properties of *G. sylvestre* leaf extract in diabetic rats have been proved by the literature (43). The administration of the dried leaf powder of *G. sylvestre* regulates the blood sugar levels in alloxan diabetic rabbits (44). Liver glycogen content in glucose fed rats was lowered by administration of *G. sylvestre* leaves (45). A study report of *G. sylvestre* showed significant serum cholesterol lowering effects (33, 43, 46, 47). Ingestion of *G. sylvestre* produced a significant lowering of cholesterol in a hypertension model, but did not lower (and even tended to increase) the raised systolic blood pressure induced by sugar feeding (47). The effect of parenteral administration of the alcoholic extract of leaves of *G. sylvestre* on the hyperglycemic response of the diabetogenic hormones, somatotropin and corticotrophin has been studied in albino rats. The somatotropin induced hyperglycemia was markedly inhibited by the extract in a dose of 200 mg/kg intramuscularly. The inhibition of the corticotrophin-induced hyperglycemia was also observed with the extract (48). A laboratory animal study also investigated the effects of *G.*

sylvestre constituents on fecal steroid excretion, with the results reporting that a high dose of gymnemic acids increases fecal cholesterol and cholic acid-derived bile acid excretion (49).

When *G. sylvestre* extract orally administered once a day to rats fed with high fat diet or normal fat diet for 3 weeks, improved serum cholesterol and triglyceride levels through influence over a wide range of lipid metabolism (50). But in case of long term administration of high fat diet for 10 weeks, *G. sylvestre* extract suppressed body weight gain and accumulation of liver lipids whereas in normal fat diet for 10 weeks, plasma triglyceride levels decreased. In addition, long-term administration of the extract did not show any influence on plasma total cholesterol, hematological and blood chemical parameters (51).

The feeding of powdered leaves of *G. sylvestre* in the diet of rats for 10 days prior and 15 days after *i.v.* beryllium nitrate significantly protected the animals from the full fall of blood glucose seen in rats receiving beryllium nitrate alone. The feeding of the leaves for 25 days to normal rats did not alter blood glucose significantly (52).

Gholap and Kar (53) in their study showed that administration of the *G. sylvestre* extract either alone or in combination decreased the serum glucose concentration in dexamethasone induced hyperglycemic animals. Further it is suggested that it is not effective in thyroid hormone mediated type II diabetes but for steroid induced diabetes. *G. sylvestre* extract exhibit hypoglycemic effect in male mice without altering the serum cortisol concentration and it appears that it is mediated through their cortisol inhibiting potency (54).

In Complications

Diabecon (an herbal drug used for diabetes containing *G. sylvestre* as principal constituent) aqueous extract showed potential inhibitory activity with an IC₅₀ value of 10 µg/ml against rat lens aldose reductase (AR). Incubation of goat lens with supraphysiological concentrations of glucose (100 mM) led to the loss of lens transparency associated with increased AR activity, decreased soluble protein and increased protein carbonyls and glycation. Interestingly Diabecon aqueous extract inhibited Aldose Reductase activity in lens incubated with 100 mM glucose. It also decreased protein carbonyls, prevented the loss of beta (L)-crystallin against 100 mM of glucose. It has also suggested that most of these effects are mainly due to *G. sylvestre*, one of the constituent herbs of Diabecon (55).

PHARMACOLOGY

Suppression of bitter and sweet taste by *G. sylvestre* extract may be due to neural inhibition or competition rather than chemical interactions in solution of molecules at receptor sites (23).

The leaves stimulate the cardiovascular system and increase the urine secretion and activate the uterus. Leaves cause hypoglycemia in experimental animals, after the administration either by mouth or injection. This has been explained on the assumption that the drug acts indirectly through stimulation in insulin secretion of the pancreas, as it has no direct effect on carbohydrate metabolism. The

presence of anthraquinone derivatives accounts for its laxative action (4).

The *G. sylvestre* has the insulin stimulation activity and hence probably it is useful in controlling diabetes mellitus. Oral administration of the *G. sylvestre* corrected the hypoglycemia in moderately diabetic rats and result continued for more than two months after discontinuing *G. sylvestre* (55). In another study with diabetic rabbits as compared to untreated diabetic animal, *G. sylvestre* produced not only blood glucose homeostasis but also increased the activities of the enzymes involved in the utilization of glucose by insulin dependent pathways: it controlled phosphorylase levels, gluconeogenic enzymes and sorbitol dehydrogenase. The uptake and incorporation of [14C] glucose into the glycogen and proteins were increased in the liver, kidney and muscle. The pathological changes in the liver also reversed (44).

G. sylvestre showed that it doubles the islet number and beta cell number and glucose homeostasis in streptozotocin treated rats (32).

Toxicity Study

A 52-weeks study of oral-repeated dose toxicity of *G. sylvestre* leaf extract in both genders of Wistar rats proved that there was no toxic effect at 504 mg/kg/day for male and 563 mg/kg/day for female as mean daily intake. A 52-week dietary toxicity study of *G. sylvestre* leaf extract in both genders of Wistar rats showed that there was no toxic effect in rats at up to 1.00% in the diet. The no-observable-effect level was 504 & 563 mg/kg/day for male & female rats respectively (56).

Other precautions

As the safety of the *G. sylvestre* is still not established in the nursing and pregnant women or the people with severe liver or kidney disorder the drug should be taken under medical supervision and it is advisable to monitor the blood glucose levels frequently (25).

Dosage forms

The *G. sylvestre* is available in crude plant material, powder; extract paste or solid in a standardized form. It is packed in well-closed polyethylene bags or HDPE drums protected from the light and moisture. The plant material is also made available in the form of combination with other herbal medicines in capsule or tablet form of various strengths (57).

Dosage & Administration

The dosage used in Ayurvedic medicine ranges from 6 to 60 g of dry or powdered leaf per day as an infusion (58, 59, 60). The adult dosage for *G. sylvestre* liquid extract is 25 to 75 ml per week. Some cases of diabetes will respond quickly but best results come after 6 to 12 months of continuous use. *G. sylvestre* is conveniently prescribed in tablet form, in this case 8 to 12 g per day of leaf equivalent is recommended. Since they are enterically-coated, tablets should be taken whole and not crushed (61).

For sweet-craving and sweet taste depression 1 to 2 ml per day of liquid extract should be applied in divided doses directly to the tongue by dropper and rinsed off after one minute. This can be done at 2- to 3-hours intervals (61).

Currently available medical and scientific literature indicates that the dietary supplement should be standardized to 25%

gymnemic acids per dose and most common dose is standardized extract of 250 mg twice a day.

SUGGESTED COMBINATIONS

G. sylvestre combines well with fenugreek, goat's rue or neem leaves for diabetes, and with globe artichoke or blue flag for weight loss. For hypercholesterolaemia consider combinations of *G. sylvestre* with turmeric, hawthorn, Silybum, globe artichoke or garlic (61).

ADVERSE REACTIONS

As with all saponin-containing herbs, oral use may cause irritation of the gastric mucous membranes and reflux. To avoid the likelihood of these side effects, enteric-coated tablets are advised (61).

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