PHYTO-PHARMACOLOGICAL PROFILE OF *GYMNEMA SYLVESTRE*

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Summary

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

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].

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- Trophical Africa. It is occasionally cultivated as medicinal plant[3,4]

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].

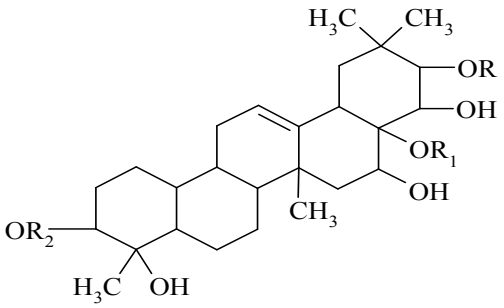
PHYTOCHEMICAL STUDIES

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%[6]. 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, (-) amyrin, stigmasterol 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* [7]. 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-Dglucopyranosyl (1→3)-beta-D-glucuronopyranoside and the potassium salt of 29-hydroxylongispinogenin 3-O-beta-Dglucopyranosyl (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* [8].

Figure: *Gymnema sylvestre*

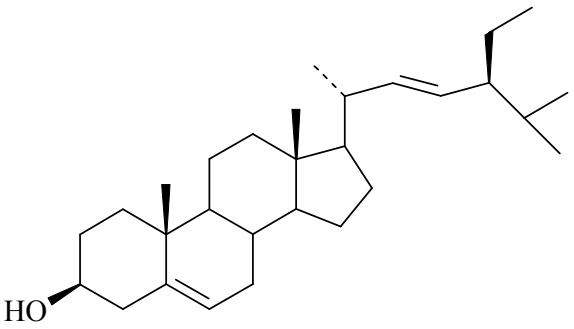
Saponins have been found to be present in the alcoholic extract of *G. sylvestre*. Besides six known gymnemic acids, four new tritepenoid saponins, gymnemasins A, B, C and D, isolated from the leaves of *G. sylvestre* were identified as 3-O-[beta-D-glucopyranosyl(1→3)-beta-D-glucuronopyranosyl]-22-O- 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 [9]. Gymnestrogenin, a new pentahydroxytriterpene from the leaves of *G. sylvestre* has been reported [10].

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[11], 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.



Gymnemic acid

	R	**R_1**	**R_2**
[1] Gymnemic acid I	Tigloyl	Acetyl	Gluconic
[2] Gymnemic acid II	Methylbutyryl	Acetyl	Gluconic
[3] Gymnemic acid III	Methylbutyryl	H	Gluconic
[4] Gymnemic acid IV	Tigloyl	H	Gluconic



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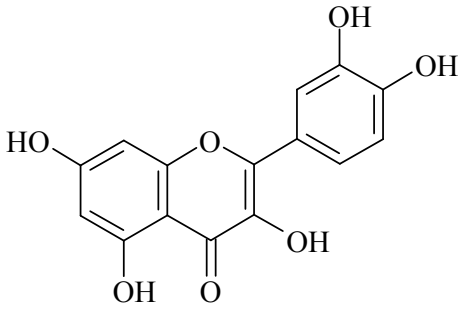
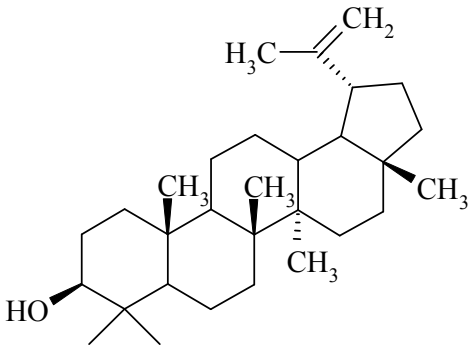
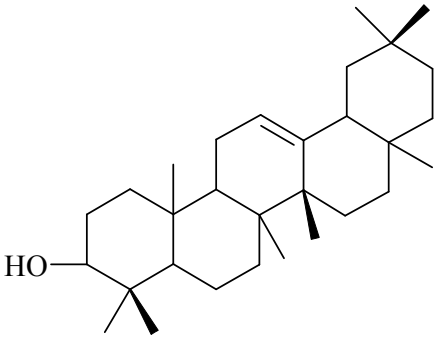


Quercetin



Lupeol



b-Amyrin

PHARMACOLOGICAL STUDIES

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].

Anti hyperglycemic 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, anthelmentic, alexipharmic, laxative, cardiotonic, 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, vaids 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 bittersweet 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 μg/ml) in rats[29]. Gurmarin at 3 μg /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. sylvestr* [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 parentral 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].

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].

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