GYMNEMA SYLVESTRE R. : A REVIEW

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Summary

Gymnema sylvestre R. is regarded as one of the plants with potent antidiabetic properties. This plant is also used for controlling obesity. The active constituents of the plant are a group of acids termed as gymnemic acids. This review attempts to encompass the available literature on *Gymnema sylvestre* R with respect to its pharmacognostic characters, traditional uses, chemical constituents and summary of its various pharmacological activities and clinical effects.

KEY WORDS: *Gymnema sylvestre* R., antidiabetic, obesity, Gymnemic acids,

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Introduction

Gymnema sylvestre R. 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]

***Gymnema sylvestre* R.**

GEOGRAPHICAL DISTRIBUTION

G. sylvestre is a perennial, woody climbing plant that grows in the tropical forests of central and southern India. 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 [2,3] .

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 [2, 4].

MICROSCOPIC CHARACTERISTICS

Microscopically *G. sylvestre* is observed that hairs are nonglandular 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 [5].

IDENTIFICATION TESTS

General identity tests for 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 [4].

PURITY TEST

The following qualitative characteristics are described for the purity test of *G. sylvestre*

Total ash: Not more than 12 %

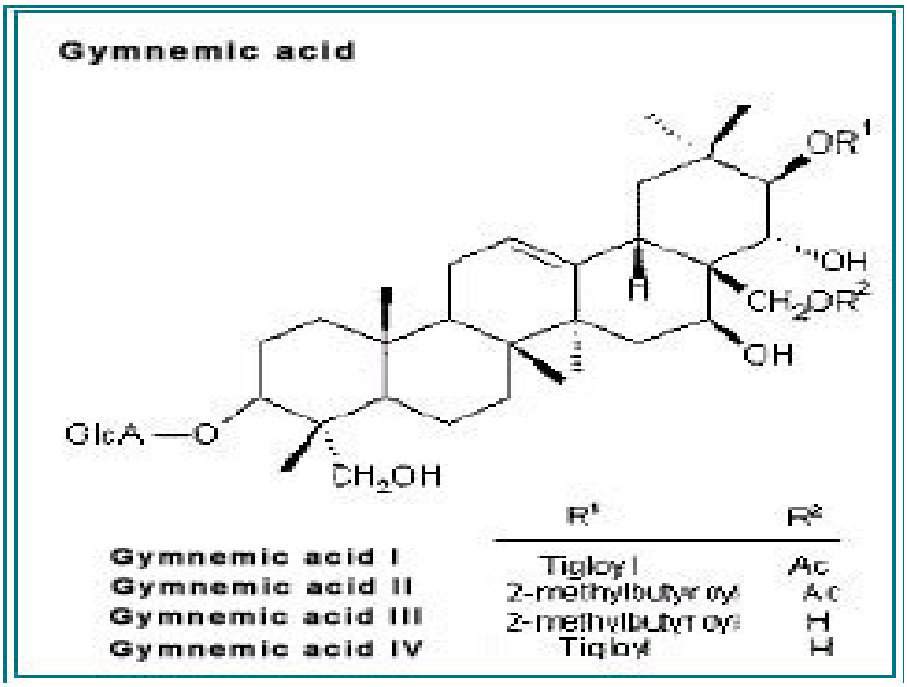
Maximum Moisture: Not more than 6%

Heavy metals: Not more than 40 PPM in the leaves or the leaves extract and 10 PPM in the final dosage form [5] .

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% [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, 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* [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]. 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-Dglucuronopyranosyl- 22-O-tigloyl-gymnemanol and 3-O-beta-Dglucuronopyranosyl-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].



Mechanism of Action of Gymnemic Acids

Gymnemic acid formulations have also been found useful against obesity, according to recent reports [11]. This is attributed to the ability of gymnemic acids to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. These molecules fill the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food, thereby curbing the sugar craving. Similarly, Gymnemic acid molecules fill the receptor location in the absorptive external layers of the

intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood sugar level [12]. *G. sylvestre* leaves have been found to cause hypoglycemia in laboratory animals and have found a use in herbal medicine to help treat adult onset diabetes mellitus (NIDDM). When Gymnema leaf extract is administered to a diabetic patient, there is stimulation of the pancreas by virtue of which there is an increase in insulin release [13]. These compounds have also been found to increase fecal excretion of cholesterol, but further studies to prove clinical significance in treating hypercholesterolemia (high serum cholesterol) are required. Other uses for Gymnema leaf extract are its ability to act as a laxative, diuretic and cough suppressant. These other actions would be considered adverse reactions when Gymnema is used for its glucose lowering effect in diabetes. Gymnema leaf extract, notably the peptide 'Gurmarin', has been found to interfere with the ability of the taste buds on the tongue to taste sweet and bitter. Gymnemic acid has a similar effect. It is believed that by inhibiting the sweet taste sensation, people taking it will limit their intake of sweet foods and this activity may be partially responsible for its hypoglycemic effect [14].

There are some possible mechanisms by which the leaves and especially Gymnemic acids from *G. sylvestre* exert its hypoglycemic effects are: 1) it increases secretion of insulin, 2) it promotes regeneration of islet cells, 3) it increases utilization of glucose: it is shown to increase the activities of enzymes responsible for utilization of glucose by insulin dependant pathways, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase, and 4) it causes inhibition of glucose absorption from intestine. The gymnemic acid components are believed to block the absorption of glucose in the small intestine, the exact action being unknown. It could be involve one or more mechanisms[14].

PHARMACOLOGICAL ACTIONS

ANTIOBESITY EFFECT

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

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 a traditional system 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 lexipharmic, 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 [20]. 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 [2].

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 [21]. 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 [22, 23]. 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 [24]. The hypoglycemic activity of this indigenous drug in normal and diabetic persons was demonstrated by Khare et al [25]. 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 [26].

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 [27]**.** Gurmarin also showed its suppressive effect on the neural responses to sweet taste stimuli in the rats [28]**.** Gymnemic acid is a powerful suppressor of sweet taste in humans and chimpanzees but lacks this ability in non-primates and lower primates. This is possible due to inhibitory effect of the gymnemic acid to glucose [29]**.** 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 [30]**.** Gurmarin at 3 μg /ml suppressed sucrose responses in C57BL mice but not BALB mice [31]. 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. [32]. 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 [33]. Effect of *G. sylvestre* on blood glucose, cholesterol and triglycerides levels in normoglycaemic and alloxan diabetic rabbits has been proved [34]. Powdered leaves of *G. sylvestre* when fed for 10 days in protected rats, fall of blood glucose level was observed [35]. *G. sylvestre* extract suppressed neural responses to mixture of monosodium glutamate and disodium inosine monophosphate in rats T [36]. 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 [37]. 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 [38]. *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 [39]. *G. sylvestre* (120 mg/kg/day) did not improve insulin resistance in diabetic rats [40]. 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 [41]. Aqueous extract of *G. sylvestre* have been possess hypoglycemic activity [42]. In vitro, the inhibitory effects of DPPH radicals and LDL oxidation were found with aqueous extract of *G. sylvestre* [43]. Hypoglycemic and life-prolonging properties of *G. sylvestre* leaf extract in diabetic rats have been proved by the literature [44]. Liver glycogen content in glucose fed rats was lowered by administration showed significant serum cholesterol lowering effects [45]. 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 [46]. 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 [47].

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