Gymnema sylvestre for Diabetics

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ABSTRACT. *Gymnema sylvestre* R.Br., a medicinal plant that is indigenous to India, grows wild in the tropical forests of central, western and southern parts of India and in the tropical areas of Africa, Australia, and China. The plant is listed in the Indian pharmaceutical codex and is popular in Indian systems of traditional medicine, such as Sidha, Unani, and Ayurveda, where the plant leaves are used to treat type II (adult-onset) diabetes (Madhumeha). Due to a lack of successful agrotechniques, however, the plant has become vulnerable and therefore, the different varieties and populations growing in various phytogeographical regions merit attention of the research community. This article elucidates the botany, biochemistry, pharmacology, and medicinal uses of the plant and suggests a strategy for conservation of the species while emphasizing the need for further research.

KEYWORDS. Anti-sweet, diabetes, gurmar, gymnemic acid, medicinal plant, traditional medicine

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INTRODUCTION

Gymnema sylvestre R.Br., a climbing shrub indigenous to India, is referred to as *Gurmar* (the sugar killer) in ancient texts. The leaves of this plant, which are consumed orally for treatment of diabetes in Ayurvedic medicine (25,30,44), are also known to lower serum cholesterol and triglycerides (48). An extract of the plant (gymnemic acid) lowers blood sugar, similar to sulfonylureas, by stimulating release of the endogenous insulin stores (49). The gymnemic acid also blocks glucose receptors in the small intestine (9). A paste of the leaves is useful in eye complaints and mycosis of toes (52), and the roots and leaves are used as a remedy for snakebite (44,57).

Despite growing wild, the species, now regarded as a vulnerable plant in Madhya Pradesh and Southern India (63), has been identified and prioritized by the National Medicinal Plant Board, Government of India, for promotion of cultivation. Yet, only negligible efforts have gone into developing proper agrotechniques for the cultivation. The vulnerability of the species emphasizes the need of investigating the genetic diversity in different phytogeographical locations before the plant becomes extinct.

Systematics

The genus *Gymnema* belongs to the Class Dicotyledonae and the family Asclepiadaceae. Of a total of 25 species in this genus, 11 species, including *sylvestre* R.Br., have been reported in India (35). *G. sylvestre* is known as "Periploca of the Woods" in English and "Waldschlinge" in German. In India, the plant is called *Gudmar* in Hindi, *Mesashringi* in Sanskrit, *Kadhasige* in Kannada, *Madhunashini* or *Cakkrakkol* in Malayalam, *Sirukurunkay* or *Sakkaraikkolli* in Tamil, *Podapatra* in Telugu, *Meshashringi* in Bengali, *Mardashringi* in Gujarati, and *Kalikardori* in Marathi (35).

Geographical Distribution

Gymnema sylvestre, which originated in Indian, has a natural occurrence in the tropical forests of Central India, Western Ghats, and Southern India and in the southern part of China, tropical Africa, Malaysia, and Sri Lanka. In Central India, the plant is most frequent in Satpura Valley, Pachmari, Amarkantak, and Chhindwara; in the Mandala forest and Hoshangabad division of Madhya Pradesh; and in the Bundelkhand region of Uttar Pradesh. The plant grows best in areas with a high to average rainfall (63).

Morphology and Anatomy

As a woody and highly branched climbing vine, *Gymnema sylvestre* can reach and run over the top of high trees. Young stems and branches are pubescent. The leaf (3–6 cm × 2–3 cm) has a 1- to 2-cm long petiole and a leaf blade that is ovate elliptical, or ovate lanceolate, acute or shortly acuminate, and more or less pubescent on surfaces. Venation is transverse and reticulate with a marginal vein (35).

Flowering occurs during August to March with blossoms nearly sessile or pedunculate on densely pubescent peduncles shorter than the petioles, producing successive umbels or whorls of yellow flowers. Pedicels are 0.5 to 1.5 cm long. Bracts are minute, ovate-oblong, and hairy. The calyx is divided to the base or nearly so with segments 2 mm long and that can be oblong, obtuse, and ciliolate; the corolla is yellow, companulate, valvate, corona single with five fleshy scales, adnate to the throat of the corolla tube between lobes; anther connective changes into a membranous tip with two erect pollinia, two unilocular carpels with many ovuled lobules, and solitary follicles that can be 8 cm long by 0.7 cm in diameter and have a rigid, straight, or slightly curved lanceolate shape. Seeds, which are glabrous and brown, are 1.3 cm long, narrowly ovoid-oblong, and flat with a thin marginal wing (13,35).

The petiole, which has a more or less plano-convex outline in transverse section, has a profuse abundance of non-glandular epidermal hairs, consisting of normally three to seven, but occasionally nine or more, thick-walled cells. A cross section of the petiole shows a single-layered epidermis, a wide collenchymatous cortex with parenchyma, and five small vascular bundles on the inner side. A fan-shaped bundle in the petiole center is flanked on either side by two small bundles. The central vascular bundle is composed of one or two xylem elements and a few phloem cells. Other bundles lying close to the central bundle are not completely surrounded by phloem (4).

The midrib has a ventral bulge that becomes less prominent toward the apical region. The epidermis consists of a single layer of cells covered externally with a prominent cuticle. The cells of the upper epidermis are larger than those of the lower epidermis. Some of the epidermal cells, especially on the veins and leaf margins, elongate to form hairs of a non-glandular type, resembling those on the petiole. The base of the hair normally develops from several epidermal cells but sometimes only by the enlargement of a single epidermal cell (4). Beneath the epidermis is a wide zone of cortex composed of four to five layers of collenchyma and a

wide zone of parenchyma. Rosette crystals of calcium oxalate are present in the cortical cells, mostly in the parenchyma. The vascular bundle, which is large and fan-shaped, is bicollateral, having phloem on both the upper and the lower sides of xylem. The cambium layer occurs between xylem and the lower phloem.

The cross-section of the lamina shows a dorsi-ventral structure with mesophyll differentiated into palisade and spongy tissues. The cells of the upper epidermis are somewhat tubular and covered externally by a prominent cuticle. The cells of the lower epidermis are small, with a thin cuticle. Non-glandular hairs are present on both epidermises. Stomata, present only on the lower surface and surrounded by subsidiary cells, are of the rubiaceous type with the long axes parallel to the stomatal pore. The mesophyll in the lamina is composed of a single layer of columnar palisade parenchyma cells and five to seven layers of spongy parenchyma cells. Rosette crystals of calcium oxalate are present in the idioblasts of the spongy parenchyma. A number of large or small veins in the parenchyma generally run parallel to the lamina axis but at times cut across transversely. The large veins are similar to the midrib and possess phloem on both sides in the bundle, while the smaller veins have phloem only on the lower side and the very small veins are without any phloem element (4).

Cultivation and Micropropagation

Although sparsely cultivated, *G. sylvestre* can grow in a variety of soils but prefers a well-drained red loamy soil or a medium black soil. The plant grows in dry areas and does not tolerate water logging. Areas with tropical/subtropical climate and receiving a well-distributed high or average rainfall are congenial for the luxuriant growth. Seeds are normally sown in a nursery during January and February and transplanted to the field after 3 to 4 months of growth, preferably in June or July. Irrigation is essential immediately and after fertilizer application. The irrigation frequency can be increased during summer. Fruiting occurs in November and December (4,13,35,63,67).

While *G. sylvestre* can be propagated through seeds, the period of seed viability is very short. No alternative mode of propagation was available for propagating and conserving genetic stock until recently. Reddy et al. (1998) have developed a tissue culture technique for rapid multiplication of the desirable clones (53). Micropropagation by axillary bud proliferation has been most successful (36).

Phytochemistry

The active principles of *G. sylvestre* suppress the sweet taste of sucrose and the sweetness effects of sodium saccharin, cyclamate glycine, D-alanine, D-tryptophan, D- leucine, beryllium chloride, and lead acetate but do not affect the sweetness effect of chloroform (22,37,70,71). Taste response experiments have confirmed the suppression of sweet taste in houseflies (33), dogs (1), hamsters, mice and humans (17,27,40,45,72). The plant, however, produces no sweetness-suppressing effects in rabbits, pigs (27), and 22 other primate species, including orangutan, chimpanzee, and gorilla that are closely related to humans (22). In 1889, Hooper (28), the first person to isolate the active compound(s) from the leaves of *G. sylvestre*, named the mixture of substances *gymnemic acid* and reported the extract as a potassium salt in the plant. In 1959, Warren and Pfaffmann (69) were able to obtain a relatively pure sample of gymnemic acid in the form of the potassium salt.

The primary bioactive constituents of the plant include a group of oleanane-type triterpenoid saponins. These constituents contain acylated derivatives of deacylgymnemic acid, a 3-O-β-glucuronide of gymnemagenin (3β,16β,21β,22α,23,28-hexahydroxyolean-12-ene) (50,64). The structure of gymnestrogenin, another triterpene from *G. sylvestre* leaves, was proposed as 3β,16β,21β,23,28-pentahydroxyolean-12-ene (65). Both compounds, later obtained in crystalline form, have several derivatives (51). Gymnemic acid A has been reported to consist of gymnemic acids A_1, A_2, A_3, and A_4. Named gymnemagenin, this constituent is a D-glucuronide of hexahydroxy-triterpene that esterifies with acids (65).

Kurihara (37) isolated gymnemic acid A_1 and derivatives. The gymnemic acid A_1 was converted into A_2 and finally into A_3 owing to loss of one acyl group by alkaline hydrolysis. The anti-sweet activity of gymnemic acid A_1 was greatly decreased by conversion into A_2, while A_3 had no activity, suggesting that the ester group in the genin of gymnemic acid manifests the anti-sweet activity (37). Gymnemic acid A_1 was further resolved into components A_{11} and A_{12} (14), both of which are active in suppressing the sweet taste of sucrose. Glucuronic acid was found to be the sole moiety in gymnemic acid A_1 components, while gymnemic acids A_2 and A_3 possessed both glucuronic acid and galactose in their molecular structures (10). Further, Yoshikawa (75–82) et al. isolated and characterized a series of gymenmic acids (gymnemic acid I, II, III, IV, V, VI, and VII) from the hot water extract of dry leaves of *G. sylvestre*.

Study of structures and anti-sweet activity of these gymnemic acid derivatives has elucidated the importance of acyl moieties in generating the anti-sweet activity (75,76,78). Another five anti-sweet principles, named gymnemic acida VIII, IX, X, XI, and XII, were later isolated and characterized (77). Other anti-sweet compounds, gymnemasaponins III, IV, and V, isolated from *G. sylvestre*, consist of 23 hydroxylongispinogenin as the aglycone glycosylated with either one or two glucose molecules at both the 23 and 28 hydroxyl groups (42,77). The anti-sweet potency of these compounds is less than those of gymnemic acids I–VI (78). The structure of gymnemagenin has been confirmed through X-ray crystallographic analysis of 3β,23,21β,22α-di-O-isopropylidene derivatives (38). The Yoshikawa group (82) has isolated and elucidated the structure of four new antisweet saponins, namely gymnemic acids XV–XVIII, having equal anti-sweet activity (Table 1). An additional seven new Dammarane-type triterpene glycosides (gymnemosides I –VII) have also been isolated from the leaves of *G. sylvestre* and the structures elucidated (Table 2).

A novel 35-amino-acid peptide with a 4209 molecular weight isolated from *G. sylvestre* (29), named *gurmarin*, has been studied electrophysiologically on the taste responses of rat (*Rattus* sp.) chorda tympani (20,41). The inhibitory action of gurmarin is highly specific to sweet taste on the tongue (12). This effect of gurmarin on the tongue was affected considerably by pH with the most effective pH near the isoelectric point of gurmarin. Gurmarin forms a 3-D structure with a specific domain rich in hydrophobic amino-acid residues (18). The half-life of gurmarin in the blood is about 40 min and the hydrophobic, rather than the ionic interaction, plays a major role in making gurmarin properly bind to the target molecules (5,29). The complete amino acid sequence of gurmarin has been elucidated (31; Table 3).

Newly isolated and characterized triterpene gymnemosides (-a, -b, -c, -d, -e and -f) have been studied for their inhibitory effect on increased levels of serum glucose in oral glucose-loaded rats (80,81; see Table 4). More recently, six oleanane-type triterpene glycosides have been isolated and characterized (73,74; Table 5).

Gymnema leaves also contain hentriacontane, glucoside pentatriacontane, chlorophylls a and b, xanthophylls, carotene, phytin resins, tartaric acid, formic acid, butyric acid, inositol, and anthraquinone derivatives. Flavonol glycosides, kaempferol, and quercetin have been isolated from the aerial parts of the plant. Gymnemasins A, B, C and D have been isolated from the leaves and leaves have tested positive for alkaloids (54,66).

TABLE 1. Anti-sweetness potency of sweetness inhibitors isolated from *Gymnema sylvestre*

Compound	Chemical name	Anti-sweetness potency	Ref.
Gymnemic acid I	3-O-β-D-glucuronopyranosyl-21-O-tigloyl-28-O-acetyl gymnemagenin	1	35
Gymnemic acid II	3-O-β-D-glucuronopyranosyl-21-[S(+)-2-methyl-butyloyl]-28-O-acetyl gymnemagenin	1	35
Gymnemic acid III	3-O-β-D-glucuronopyranosyl-21-[S(+)-2-methyl-butyloyl]-28-O- gymnemagenin	0.50	35
Gymnemic acid IV	3-O-β-D-glucuronopyranosyl-21-O-tigloyl gymnemagenin	0.25	35
Gymnemic acid V	3-O-β-D-glucuronopyranosyl-21, 22-bis-O-tigloyl gymnemagenin	0.50	36
Gymnemic acid VI	3-O-β-D-glucuronopyranosyl (1→3)-β-D -glucuronopyranosy-21-O- tigloyl gymnemagenin	0.50	36
Gymnemic acid VII	3-O-β-D-glucuronopyranosyl gymnastrogenin	Absent	36
Gymnemic acid VIII	3-O-β-D-glucuronopyranosyl-28-O-25-methyl butyroyl gymnemagenin	Absent	38
Gymnemic acid IX	3-O-β-D-glucuronopyranosyl-28-O-tigloyl gymnemagenin	Absent	38
Gymnemic acid X	3-O-β-D-glucuronopyranosyl-21-O-acetyl-28-O-gymnemagenin	0.50	38
Gymnemic acid XI	3-O-β-D-glucuronopyranosyl-21,28-bis-O-tigloyl gymnemagenin	1	38
Gymnemic acid XII	3-O-β-D-glucuronopyranosyl(1→3)-O-β-D-glucuronopyranosyl-21-O-tigloyl-28-O-acetyl gymnemagenin	1	38
Gymnemic acid XIII	3-O-β-D-glucuronopyranosyl-28-O-[S(+) -2-methyl-butyloyl] gymnemagenin	0.50	40
Gymnemic acid XIV	3-O-β-D-glucuronopyranosyl-28-O- tigloyl gymnemagenin	0.50	40
Gymnemic acid XV	3-O-β-D-glucuronopyranosyl-21-O-2-methyl butyryl-22-O-2-methyl crotonoyl gymnemagenin	1	41
Gymnemic acid XVI	3-O-β-D-glucuronopyranosyl-16,22-O-bis-2-methyl crotonoyl gymnemagenin	1	41
Gymnemic acid XVII	3-O-β-D-glucuronopyranosyl-21-O-benzoyl gymnemagenin	1	41
Gymnemic acid XVIII	3-O-β-D-glucuronopyranosyl-28-O-benzoyl gymnemagenin	1	41

TABLE 2. Dammarane-type triterpene glycosides isolated from the leaves of *Gymnema sylvestre*

Compound	Chemical name[1]
Gymnemoside-I	3,20-di-O-β-D-glucopyranoside of 19-oxo-3β, 20-dihydroxydammar-24-ene
Gymnemoside-II	3-O-β-sophorosyl-20-O-β-glucopyranoside of 19-oxo-3β, 20-dihydroxydammar-24-ene
Gymnemoside-III	3-O-β-glucopyranosyl(1→2)-α-L-arabinopyranosyl-20-O-β-D-glucopyranoside of 19-oxo-3β, 20-dihydroxydammar-24-ene
Gymnemoside-IV	3-O-β-glucopyranosyl-20-O-β-primevaroside of 19-oxo-3β, 20-dihydroxydammar-24-ene
Gymnemoside-V	3-O-β-sophorosyl-20-O-β-primeveroside of 19-oxo-3β, 20-dihydroxydammar-24-ene.
Gymnemoside-VI	3-O-β-rutinoside of 2α, 3β, 12β, 20S, 25-pentahydroxydammar-23-ene.
Gymnemoside-VII	20-O-β-primeveroside of 25-hydroperoxy, 2α, 3β, 12β, 20S-tetrahydroxydammar-23-ene.

[1]Murakami, N., T. Murakami, M. Kadoga, H. Matsuda, J. Yamahara, and M. Yoshikawa. 1996. New hypoglycemic constituents in "gynmemic acid" from *Gymnema sylvestre. Chem. Pharm. Bull*. 44(2):467–471.

TABLE 3. Amino acid sequence of gurmarin

Gurmarin
The anti-sweet peptide from *Gymnema sylvestre* (<Glu = pyroglutamic-acid residue) < ^{1}Glu- Gln- Cys- Val- ^{5}Lys- Lys- Asp- Glu- Leu- ^{10}Cys- Ile- Pro-Tyr- Tyr- ^{15}Leu- Asp- Cys- Cys- Glu- ^{20}Pro- Leu- Glu- Cys- Lys-^{25}Lys- Val- Asn- Trp- Trp- ^{30}Asp- His- Lys- Cys- Ile- ^{35}Gly.

Medicinal and Traditional Uses

In traditional medicine, the leaves of *G. sylvestre* are used for treatment of diabetes, and the flowers and bark are given in diseases caused by phlegm. Root bark is very useful in treating piles, and an external application of root paste is useful in treatment of insect bites (35).

Sushruta, an ancient work on Indian medicine, describes Gurmar (*G. sylvestre*) as a destroyer of madhumeha (glycosuria) and other urinary disorders (43), activities believed to be due to *G. sylvestre*'s neutralizing excess sugar in the body. *G. sylvestre* is reported to be a bitter acrid,

TABLE 4. Triterpene glycosides isolated from the leaves of *Gymnema sylvestre*

Compound	Chemical name[1,2]	Reported activities
Gymnemoside - a	21-O-tigloyl-22-O-acetyl gymnemagenin-3-O-β-glucopyranosiduronic acid	Dose not inhibit increase in serum glucose level
Gymnemoside - b	16-O-acetyl-2-tigloyl gymnemagenin-3-O-β-D-glucopyranosiduronic acid	Slightly inhibits increase in serum glucose level
Gymnemoside - c	21-O-benzoyl-28-O-gymnemagenin-3-O-β-D-glucopyranosiduronic acid	Does not inhibit glucose uptake in rat's small intestine
Gymnemoside - d	23-O-[β-D-xylopyranosyl (1→6)-β-D-glucopyranosyl] gymnestrogenins	Does not inhibit glucose uptake in rat's small intestine
Gymnemoside - e	23-O-[β-D-xylopyranosyl (1→6)-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl] -28-O-[β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl] 23-hydroxylongispinogenin	Does not inhibit glucose uptake in rat's small intestine
Gymnemoside - f	23-O-[β-D-xylopyranosyl (1→6)-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl-28-O-[β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl] 3β,16β,23,28-tetrahydroxyolean-18-ene	Inhibits glucose uptake in small intestine.

[1]Data regarding gymnemoside -a and -b from Rao, G.S., and J.E. Sinsheimer. 1968. Structure of gymnemagenin. *Chem. Commun. (London)* 1:1681–1682.
[2]Data regarding gymnemoside -c through -f from Rao, G.S., and J.E. Sinsheimer. 1971. Constituents from *Gymnema sylvestre* leaves: VIII. Isolation, chemistry and derivatives of gymnemegenin and gymnestrogenin. *J. Pharm. Sci*. 60:190–193.

astringent, thermogenic, anti-inflammatory, anodyne, digestive, liver tonic, emetic, diuretic, stomachic, stimulant, anthelmenthics, laxative, cardiotonic, expectorant, antipyretic, and uterine tonic. The plant is thought useful in treatment of dyspepsia, constipation, jaundice, hemorrhoids, renal and vesical calculi, cardiopathy, asthma, bronchitis, amenorrhoea, conjunctivitis, leucoderma, and Parkinsonism (2,13).

In India, the Sahariya tribe of Madhya Pradesh use *G. sylvestre* to treat asthma, corneal opacity in humans and animals, and Parkinsonism (2). The Junglee Irulas of Nilgiri hills chew green leaves in the morning to ensure clear urine (13). Leaves are used by the Kol tribe of Chhattisgarh and ethnic communities of Rajasthan, Godavari district (Andhra Pradesh),

TABLE 5. Oleanane saponins isolated from the leaves of *Gymnema sylvestre*

Compound	Chemical name
Oleanane Saponin - 1	Longispinogenin-3-O-β-D-glucuronopyranoside
Oleanane Saponin - 2	21β-benzoylsitakisogenin 3-O-β-D-glucuronopyranoside
Oleanane Saponin - 3	3-O-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester
Oleanane Saponin - 4	Oleanolic acid-3-O-β-xylopyranosyl (1→6)-β-D-glucopyranosyl (1→6)-β-D-glucopyranoside
Oleanane Saponin - 5	3-O-β-D-xylopyranosyl (1→6)-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester
Oleanane Saponin - 6	3-O-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyl ester

Kandla (Maharashtra), and the Nayaks of Karnataka for treating gastric troubles, diabetes, glycosuria, urinary complaints, and eye problems (68).

Writings from different Indian systems of medicine reveal that *G. sylvestre* is considered an alexipharmic, anodyne, anthelmintic, antipyretic astringent, bitter, cardiotonic, digestive, diuretic, laxative, stimulant, stomachic, and uterine tonic and is used to treat amenorrhea, asthma, bronchitis, conjunctivitis, constipation, cough dyspepsia, hemorrhoids, hepato-plenomegaly, intermittent fever, jaundice, and leucoderma. The leaves of the plant are useful in treating diabetes, and a paste of leaves is used to remove inflammation. The bark from the plant roots is useful as an emetic, expectorant, and analgesic for body ache, and juice from the root has been acclaimed as a useful treatment for snakebite by Bhav Prakash Nighantu (55). *Gymnema* can cure phlegm, piles, colic pain, dropsy, eye troubles, cardiac, and respiratory diseases. The fruit is bitter, thermogenic, and used in treatment of diseases caused by phlegm or vata (wind) (56). In Nighantu Ratnakaram, *Gymnema* is mentioned as useful in removing cough and toxicants and in treating eye troubles (11). In Siddha and Unani systems of medicine, the *Gymnema* leaves are used as an ingredient of different anti-diabetic formulations (4).

Constituents and Actions

Gymnemic acid (gymnenin; saponin) lowers blood sugar by stimulating release of endogenous insulin stores (52) and by blocking glucose receptors (49). In normal rats, cell permeability for insulin is increased by

gymnemic acid (46) and, in hypertensive rats, cholesterol is lowered (9,60,61). Gurmarin diminishes the ability of the tongue to taste sweet substances for 15 minutes to 24 hours (71).

Efficacy Against Diabetes

Type-1 diabetes (IDDM: insulin-dependent diabetes mellitus) is an autoimmune disease that occurs owing to destruction of β-cells of the pancreas, resulting in insulin deficiency. The patients with type-1 diabetes depend for survival on a continuous supply of insulin from outside. Type-2 diabetes mellitus is the world's fastest growing metabolic disease and covers about 90% of the diabetic population (3). This causes insulin resistance and obesity and may lead to a decrease in receptor concentration, kinase activity, concentration and phosphorylation of IRS-1 (insulin receptor substrate), and IRS-2, PIK activity, glucose-transporter translocation and activity of intracellular enzymes (6). This is polygenic and involves polymorphism in multiple genes encoding the protein involved in insulin signaling, insulin secretion, and intermediary metabolism (15).

Oral administration of *G. sylvestre* reduces urine glucose in diabetic patients (21) and inhibits the adrenohypophyseal activity (25) as well as hyperglycaemic response of epinephrine, known for being mediated through phosphorylase and the gluconeogenetic activity (26). The hypoglycemic activity of the plant in normal diabetic persons is well documented (34,62). Shanrnugasundaram et al. (57) observed that activity of insulin-dependent enzymes like hexokinase, glycogen synthetase, glyceraldehydes 3-phospahte dehydrogenase, and glucose 6-phosphate dehydrogenase was lowered in the diabetic tissues in rabbits, whereas in the case of insulin-independent enzymes like glycogen phosphorylase, gluconeogenic enzymes, glucose 6-phosphatase, fructose 1,6- diphosphatase, and sorbitol dehydrogenase of polyol pathway, the activity was grossly increased in untreated diabetics and reversed during the administration of *G. sylvestre* (57).

Treatment with *G. sylvestre* leaves helped maintain blood glucose in the beryllium nitrate–treated rats with disturbed carbohydrate metabolism leading to liver damage (24) and inhibited hexokinase activity in liver (23). The treatment also brought about blood glucose and serum-insulin homeostasis in alloxan-induced diabetes in rats (39), rabbits, and dogs (47). This could be due to regeneration or repair of β cells in islets of Langerhans. Water-soluble extract of *G. sylvestre* (GS4) did not enhance insulin release in normal rats under normoglycemic (blood sugar 100 mg/dl)

conditions but enhanced hormone release in diabetic islets. The residual pancreatic function was essential for the antidiabetic activity (32).

When administered to IDDM patients on insulin therapy, the extract (GS4) reduced the insulin requirements by lowering the fasting blood glucose, glycosylated hemoglobin, and glycosylated plasma protein levels, while serum lipids returned to near normal. GS_4 therapy appeared to enhance endogenous insulin, possibly through regeneration of the residual beta cells in the IDDM patients (58).

In type II diabetes (non-IDDM), GS4 treatment for 18 to 20 months significantly reduced plasma lipids (cholesterol, triglycerides, phospholipids, and free fatty acids) (59). In contrast, anti-hyperglycemic drugs, sulfonylureas and biguanides, regulate the blood glucose homeostasis by stimulating pancreatic secretion of insulin (16) and inhibiting gluconeogenesis, respectively (8). Both of these drugs have considerable side effects, such as elevated level of plasmacholesterol, triglycerides, and free fatty acids, and the efficacy on lipid metabolism decreases over time. Long-term administration (10 weeks) of *Gymnema* extract in rats of a high-fat-diet group suppressed the body-weight gain and reduced the accumulation of liver lipids and interaperitoneal fat and the plasma triglycerides level (60,61).

In a recent study of the antihyperglycemia and antihypolipidionic effects of *Gymnema* leaves in non-diabetic and alloxan-diabetic rats, however, no antidiabetic and antihyperlipidemic effects was observed (19). The difference in response between a study that finds no antihyperglycemia and antihypolipidionic effect from *Gymnema* and those of others that do could be caused by the use of a mixture of glycosides (GS4 and gymnemic acid) by other investigators. Apparently, *G. sylvestre*, will require further experimental and clinical trials before a recommendation to be used in the treatment of diabetes (19).

Toxicity and Side Effects

Extracts of *G. sylvestre* shoots have shown antibacterial, antifungal, antiprotozoal, antiviral, and hypoglycemic activity. The LD_{50} of ethanol and water extracts of *G. sylvestre* administered intraperitoneally in mice was 375 mg kg^{-1} (7).

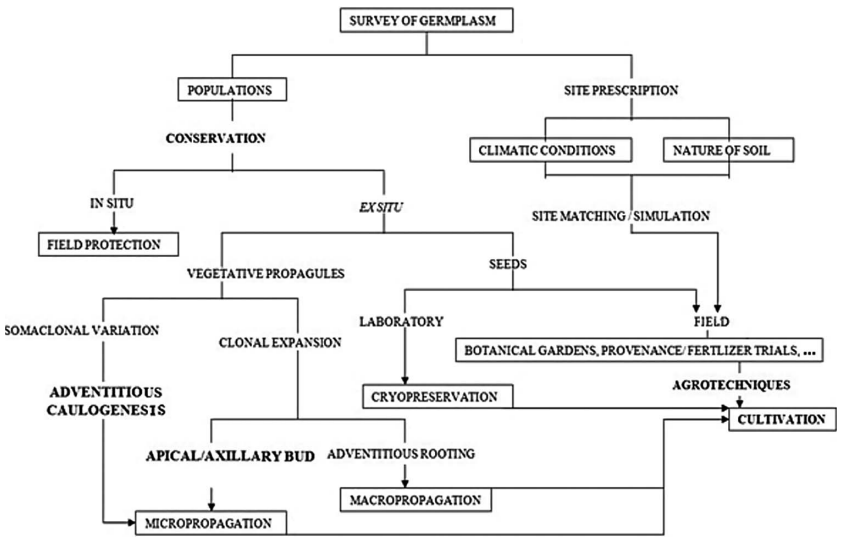
Taken in an empty stomach, gymnema can cause a mild gastrointestinal upset. Extremely high doses may induce hypoglycemia in susceptible individuals (82). Alteration to a dosage of insulin or other antidiabetic medications, including antidepressants and salicylates, can enhance the antidiabetic efficacy, whereas certain stimulants like *Ephedra* sp. may reduce the effectiveness.

CONSERVATION STRATEGY

Conservation strategy for *G. sylvestre* needs to include a comprehensive survey of diverse natural populations in locations (Patalkot, Pachmari, Chhindwara, Mandla, Satna, and Gwalior of Madhya Pradesh, in India) in which the plant is threatened with extinction followed by a physiomophological and molecular characterization of these populations for active components (gymnemic acid). The climatic conditions, edaphic factors, and ecological associations for sites in which the plant grows should be recorded and simulated for *ex situ* conservation. The gene pool of the species, however, may also be conserved *in situ* for development of genetic variations and expansion of genetic base that otherwise may be eroded owing to over-exploitation for commercial medicinal preparations. The available seeds of different populations need to be collected and conserved for future use (Figure 1).

Wild populations may serve as source material for any future breeding program for genetic improvement and development of superior cultivars of *G. sylvestre*. As an interim measure, screened germplasm that proves superior may be clonally multiplied for large-scale production of improved

FIGURE 1. Germplasm conservation/cultivation strategy for *Gymnema sylvestre*.



planting stock, using macro- and micropropagation procedures, for use in cultivation that would ease pressure on existing natural populations of *Gymnema*. Available clonal propagation procedures and field cultivation practices, however, need to be improved and scaled up for commercial use. The development of tissue culture protocols for adventitious caulogenesis/ embryogenesis will help in utilizing somaclonal variations and in undertaking genetic transformations commensurate with tolerance toward abiotic and biotic stress and adaptation to marginal and wastelands.

CONCLUSIONS

Gymnema sylvestre enjoys a unique position among the sweetness-modifying materials of natural origin. Yet, owing to unsustainable collection from natural habitats and continuous deforestation of habitats, *G. sylvestre*, which has no established varieties or lines, has become vulnerable to extinction. Agrotechniques for promoting cultivation of *G. sylvestre* are currently unavailable.

The efficacy of *G. sylvestre* extracts needs verification through continued experimentation and clinical trials on human populations. Transition mechanisms of *G sylvestre* extract in blood and modes of metabolic action on carbohydrates and lipids need to be studied. Studying the genetic diversity in different populations of the species and the genetic control of active constituents in the plant may help in planning the conservation strategies. Different chemotypes growing at different phytogeographical locations must be screened and correlated with efficacy as a drug. A comprehensive knowledge on the extent of variability within the existing populations of *G. sylvestre* will help in developing strategies for conservation of the species.

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