ETHNOBOTANICAL AND PHARMACOLOGICAL STUDY OF *GYMNEMA SYLVESTRE*

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Summary

Gymnema sylvestre is one of the most important medicinal plants of the Asclepiadaceae family. It is used in folkloric medicine since time immemorial. Recent studies on *Gymnema sylvestre* (especially leaves) shows a number of compounds isolated, like Gymnemic acid A, B, C, D, gymnemagenol, deacyl gymnemic acid etc. that tend to possess potential medicinal properties against diabetics, obesity, cancer, inflammation, mosquito larvae, snake venom etc. This paper aims to detail the ethnobotanical and pharmacological uses of *Gymnema sylvestre* to provide better scope for performing the in-vivo experiments and their application in future.

Keywords: *Gymnema sylvestre*, ethnobotanical studies, isolated compounds, medicinal properties

Introduction

Gymnema sylvestre R.Br is a medicinal herb native to central and western India, tropical Africa and Australia. It is often called "gurmar" (destroyer of sugar), as chewing the leaves causes a loss of sweet taste [1]. Gymnemic acid, extracted from leaves and roots of *G. sylvestre* is mainly used in India and parts of Asia as a natural treatment for diabetes as it helps to lower and balance blood sugar levels [2]. In addition, it possesses antimicrobial, anti-hyper cholesterolemic [3], sweet suppressing [4] and hepatoprotective [5] activities. It also acts as feeding deterrents to caterpillar, *Prodenia eridania* [6], prevent dental caries caused by Streptococcus mutans [7] and in skin cosmetics[8]. Besides, it is also used in the treatment of asthma, eye complaints, inflammations, snake bite [9 - 10].

Nomenclature:

The word *Gymnema* is derived from the Greek words "gymnos"- "naked" and "nēma"- "thread" and the word *sylvestre* means "of the forest" in Latin. It is commonly called as "miracle fruit" despite of the part mainly used being the leaf. Other common names are described in table 1 [11- 15].

Table 1: Common names of *Gymnema sylvestre* in different languages

S.No	Common name	Language
1	*Gymnema, Periploca of the woods, cowplant and Australian cowplant*	English
2	*Meshashringi, Madhunashini, vishani*	Sanskrit
3	*Gur-mar, merasingi*	Hindi
4	*Kavali, Kalikardori, vakundi*	Marathi

5	*Dhuleti*, *mardashingi*	Gujarati
6	*Gudmari*	Oriya
7	*Podapatri*	Telugu
8	*Adigam*, *cherukurinja*	Tamil
9	*Chakkarakolli*	Malayalam
10	*Sannagerasehambu*	Kannada

Distributional range:

Table 2: Geographical distribution of *Gymnema sylvestre* [2, 12, 15]

S.No	Continent	Region	Country
1	Africa	West Tropical Africa	Benin; Ghana; Guinea; Guinea-Bissau; Mali; Mauritania; Nigeria; Senegal; Togo
		Southern Africa	Botswana; Namibia; South Africa - Cape Province, KwaZulu-Natal, Transvaal
2	Asia-temperate	China:	China - Fujian, Guangxi, Yunnan, Zhejiang
		Eastern Asia:	Japan - Ryukyu Islands; Taiwan
3	Asia-tropical	Indian Subcontinent:	India (Deccan peninsula, extending to parts of northern and western India); Sri Lanka
		Indo-China:	Thailand; Vietnam
		Malaysia:	Indonesia; Malaysia
4	Australasia	Australia:	Australia - Northern Territory, Queensland, Western Australia

Taxonomical classification:

Table 3: Taxonomical classification of *Gymnema sylvestre* [16]

Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Gentianales
Family	Asclepiadaceae
Genus	Gymnema R. Br.
Species	*sylvestre*

Morphological description:

G. sylvestre is a slow growing, large, perennial, medicinal woody climber. The leaves are opposite, usually elliptic or ovate (1.25 – 2.0 inch x 0.5-1.25 inch); flowers are small, yellow and are in axillary and lateral umbellate cymes; the follicles are terete; lanceolate and upto 3 inches in length; pedicels are long; Calyx-lobes are long, ovate, obtuse, pubescent; Corolla is pale yellow campanulate, valvate, corona single, with 5 fleshy scales. Scales adnate to throat

of corolla tube between lobes; Anther connective produced into a membranous tip, pollinia 2, erect, carpels 2, unilocular; locules many ovuled [12, 15].

Chemical composition:

The leaves of *G. sylvestre* contain triterpene classes of oleanane saponins (gymnemic acids, gymnemasaponins) and dammarene saponins (gymnemasides) [17 - 19]. The leaves also contain resins, albumin, chlorophyll, carbohydrates, tartaric acid, formic acid, butyric acid, anthraquinone derivatives, inositole alkaloids, organic acid (5.5%), parabin, calcium oxalate (7.3%), lignin (4.8%), and cellulose (22%) [20].

The major bioactive component, Gymnemic acid contains several acylated (tigloyl, methylbutyroyl etc.,) derivatives of deacylgymnemic acid (DAGA) which is the 3-O-β-glucuronide of gymnemagenin (3β, 16β, 21β, 22α, 23, 28-h-hexahydroxy-olean-12-ene). The presence of gymnemic acids, (+) 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 been reported in aerial parts of *G. sylvestre* [21]; [22]. 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 longiospinogenin 3-O-beta-D-glucopyranosyl (1-->3)-beta-D-glucopyranoside and the potassium salt of 29-hydroxylongispinogenin 3-O-beta-D-glucopyranosyl (1-->3)-beta-D-glucopyranoside along with sodium salt of alternoside II were isolated from an ethanol extract of the leaves of *G. sylvestre* [23]. Four new triterpenoid saponins, gymnemasins A, B, C and D isolated from the leaves of *G. sylvestre* have been identified as 3-O-[beta-D-glucopyranosyl(1-->3)-beta-D-glucopyranosyl]-22-O-tiglyol-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-glucopyranosyl-gymnemanol respectively. The aglycone, gymnemanol, a new compound, has been characterized as 3 beta-16 beta-22 alpha-23-28-pentahydroxyolean-12-ene [24]. Gymnestrogenin, a new penta hydroxytriterpene from the leaves of *G. sylvestre* has been reported [25].

Even though it is not yet clear regarding the specific constituent, the water-soluble acidic fractions are responsible for hypoglycemic actions [26]. Gymnemic acid can be a possible candidate for anti-diabetic activity. Besides, Gurmarin isolated from the *Gymnema sylvestre* leaves (GSE), act as anti-sweeteners in humans [20, 21, 27].

Folkoric uses:

Gymnema has been under the use to treat diabetes since 2,000 years. While, the other uses included as a remedy for rheumatism, cough, ulcer, jaundice, dyspepsia, constipation, eyes pain and in snakebite. It is also used as an anodyne, digestive & liver tonics, diuretic, stomachic, laxative, appetite suppressant, stimulant, anti-helminthic, cardiotonic, expectorant, antipyretic and uterine tonic[15, 28].

Studies and pre-clinical data

Anti-Diabetic activity:

Gymnema sylvestre has shown promising results as an anti-diabetic agent. Numerous animal model studies have confirmed its hypoglycemic effect [51 - 53]. The aqueous extract of GSE when administered at a dose concentration of 800mg/Kg has shown a drastic decrease ($p<0.05$) in the levels of fasting blood glucose, serum triglyceride and serum cholesterol (reduced by 46%) content in both normal and alloxan induced diabetic rats. Besides, a potent elevation in the level of serum HDL cholesterol has been observed. This increase may be

useful leading to the negative correlation between HDL-cholesterol levels and cardiovascular diseases [54].

The anti-diabetic active constituents have been identified majorly as gymnemic acids and their glycosides. The isolated saponin, 21 beta-O-benzoylsitakisogenin 3-O-beta-D-glucopyranosyl (1-->3)-beta-D-glucuronopyranoside and the sodium salt of alternoside II have exhibited anti-sweet activity [18, 23, 29, 36]. Crystalline compounds, gymnemagenin and gymnestrogenin have been isolated from GSE [30]. The major constituents, 3-β-glucuronides of different acetylated gymnemagenins, gymnemic acid a complex mixture of about 9 closely related acidic glycosides[20];[27];[21]. Gurmarin has shown to suppress responses of the chorda tympani nerve to sweet substances in C57BL mice [31]. GS_3 and GS_4, obtained from the aqueous extract of GSE, have shown to double the number of islet and *beta* cells in STZ treated rats. These compounds tend to attain blood glucose homeostasis by increasing serum insulin levels through repair/regeneration of the endocrine pancreas [32]. GS4 has shown significant results in patients with Type 2 diabetics. The GS_4 administration, have shown a substantial reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins. Five of the 22 diabetic patients have discontinued their conventional drug and maintained their blood glucose homeostasis with GS_4 alone. The raised insulin levels in the serum of the patients supports that *beta* cells may have regenerated/repaired [55]. Another compound Dihydroxy gymnemic triacetate, isolated from GSE when administered with a dosage of 20mg have shown to possess hypoglycemic activity in STZ induced diabetic rats [33]. *Gymnema* also inhibits the peripheral utilization of glucose by somatotropin and corticotrophin, also inhibiting epinephrine-induced hyperglycemia [56 - 57]. The aqueous extract of GSE has shown to rise the survival time of diabetic rats. It has reduced the hyperglycemia in moderately diabetic rats and the effect of the drug persisted more than a two months' period after its discontinuation [58].

Table 3: The table briefly illustrates the list of compounds isolated from the respective part of *Gymnema sylvestre* with its activity

S.No	Activity	Part used	Compound isolated	Reference
1	*Anti-diabetic*	Leaves	Gymnemic acids and their glycosides	[18, 23, 29]
			Saponin (21 beta-O-benzoylsitakisogenin 3-O-beta-D-glucopyranosyl(1-->3)-beta-D-glucuronopyranoside)	
			Sodium salt of alternoside II	
			3-β-glucuronides of different acetylated gymnemagenins	[20, 21, 27
			Gymnestrogenin	[30]
			Gurmarin	[31]
			GS_3 and GS_4	[32]
			Dihydroxy gymnemic triacetate	[33]
2	*Hypolipidemic*	Leaves	Gymnemate	[34]
			Gymnemic acids	[35]
3	*Anti-obesity*	Leaves	Gymnemic acid	
			Gymnemate	[34]
4	*Anti-cancer*	Leaves	Gymnemagenin	[36]
			Deacyl Gymnemic acid	
			Gymnemagenol	[37]

5	*Anti-larvicidal*	Leaves	Gymnemagenol	[38]
6	*Anti-microbial*	Roots	Pure saponin fractions	[39]
7	*Anti-oxidant*	Leaves	Gymnemic acids	[40]
8	*Anti-viral*	Leaves	Gymnemic acid A, B, C and D	[41]
			Gymnemagenol	[42]
9	*Anti-allergic*	Leaves	Purified pectic substances	[43]
10	*Muscle relaxant*	Leaves	Gymnemic acids	[44]
11	*Snake venom antidote*	Roots	Gymnemic acid	[9 - 10]
12	*Anti-caries/ antieurodontic*	Leaves	Gymnemic acid	[7, 45].
13	*Anti-parasitic*	Leaves	Gymnemagenol	[46]
14	*Inhibition of palatal taste response*	Leaves	Gymnemic acid	[47]
			Gurmarin	[48 - 50]

Inhibitory effect on palatal taste response:

GSE have shown to affect the palatal taste response. The sweetness threshold of the human tongue has shown an elevation from 0.01 M to 1 M when fed with 5mM of gymnemic acid [47]. About (40–50%) suppression of taste responses to sugars and saccharin sodium has been observed from the greater superficial petrosal (GSP) nerve, innervating palatal taste buds in rats, on administration of Gurmarin (10 μg/ml) [48]. It has selectively decreased the Chorda Tympani (CT) nerve responses to sweet sensations in rats[49];[59] and C57BL mice [50]. This compound is thought to act by binding to the sweet taste receptor protein [60]. The sensitivity for gurmarin probably depends on the size of sweet-responsive fibres [61]. It is assumed to alter the dpa locus in mice which probably controls the sweet-taste receptors [62]. This sweet-taste suppressing activity of Gurmarin can be reduced significantly by beta-cyclodextrin (beta-CD) [63] or anti-gurmarin serum [59].

Hypolipidemic activity:

Gymnema sylvestre possesses a substantial hypolipidaemic activity. GSE have shown anti-atherosclerotic potential, a condition where an artery wall thickens as a result of the accumulation of fatty materials such as cholesterol. The GSE activity was nearly similar to that of a standard lipid lowering agent—clofibrate [3]. In vivo studies have been conducted mainly on rats for testing the activity. Significant decrease in the fat digestibility has been observed when the GSE extract was orally administrated to rats fed on high fat diet and to those on normal fat diet. I.e. decrease in the total cholesterol and triglyceride levels in serum and increase in the excretion of neutral sterols and acid steroids into faeces. Besides, it has improved serum cholesterol and triglyceride levels by influencing their lipid metabolism [34]. *Gymnema* leaves extract (GSx) has been observed to reduce the increased serum triglyceride (TG), total cholesterol (TC), very low-density lipoprotein (VLDL)-and low-density lipoprotein (LDL)-cholesterol levels when orally administered to experimentally induced hyperlipidaemic rats for 2 weeks [3]. Gymnemate extracted from GSE has been found to decrease the total cholesterol by about 1/3 in Otsuka Long-Evans Tokushima Fatty (OLETF) rats (a genetic multifactor syndrome model which exhibit progressive overweight, hyperlipidemia and hyperglycemia) and the LDL+VLDL (Low-Density and Very-Low-Density Lipoprotein) cholesterol has decreased by about half. While, the proportion of High-Density Lipoprotein (HDL) cholesterol to the total cholesterol was increased [34]. GSx has shown to suppress the accumulation of liver lipids to the same extent as chitosan in rats on

high fat diet. The intra peritoneal fat and fat drop vacuoles on the epithelium of renal tubules have scattered by administration of the GSE extract. While, the administration of the extract in normal fat diet rats have decreased the plasma triglyceride levels [34]. SHR (Spontaneously Hypersensitive Rats) consuming GSE have shown a decrease in their circulating cholesterol concentrations [64].

Experiments for testing the Hypolipidaemic activity of GSE have also been conducted on human volunteers where a group of volunteers have been administered a combination of GSx (400 mg, providing 100 mg gymnemic acid), calcium potassium salt of (–)-hydroxycitric (HCA-SX) acid and niacin-bound chromium (NBC). The group has shown a reduction in total cholesterol, LDL and triglyceride levels by 9.1%, 17.9% and 18.1%, respectively in moderately obese human volunteers. While, HDL and serotonin levels have increased by 20.7% and 50%, respectively. Serum leptin levels have decreased by 40.5% and have enhanced excretion of urinary fat metabolites by 146-281% [35]. High dose of gymnemic acids isolated from GSE have found to increase the fecal excretion of neutral steroids and bile acids especially those of cholesterol and cholic acid (CA)-derived bile acids [65].

Anti-obesity agent:

Obesity is a well-established risk factor for cardiovascular disease, diabetes, hyperlipidemia, hypertension, osteoarthritis, and stroke. *Gymnema sylvestre* promotes weight loss may be through its ability to reduce cravings for sweets and control blood sugar levels. Supplementation with gymnemate extracted from GSE is a novel therapeutic tool for weight management. It has been checked on Otsuka Long-Evans Tokushima Fatty (OLETF) rats which have shown a decrease in food and water intake by 1/3 and 2/3 respectively, along with a body weight reduction of 57.2± 6.4 and 75.5± 6.3 g during 1 and 2 weeks respectively [66]. GSx has found to suppress body weight gain in rats fed on high fat diet to the same level as chitosan [34]. The efficiency of GSx on body weight, body mass index (BMI) and appetite were monitored moderately obese human volunteers. The group administered with a combination of HCA-SX (hydroxycitric acid), NBC (niacin-bound chromium) and GSx (400 mg, providing 100 mg gymnemic acid) has shown a reduction in body weight and BMI by 7.8% and 7.9%, respectively. Besides, the food intake has reduced by 14.1% [35]. Studies have been conducted to determine the weight-loss effects of Calorie-Careâ„¢, a dietary supplement containing *Gymnema sylvestre* in addition to glucomannan, chitosan, fenugreek, and vitamin C. The novel combination has resulted in significant body weight and fat loss in obese adults [67].

Anti-cancer activity:

The alcoholic extract of GSE is a potent anti-cancer agent on A549 (Human lung adenocarcinoma epithelial cell line, Giard et al, 1972) cell lines and MCF7 (Human breast carcinoma, Soule et al, 1973) cell lines [36]. The alcohol extract (95%), Gymnemagenin and deacyl Gymnemic acid were tested for cytotoxic activity on MCF7 cell lines by MTT assay. The compound deacyl Gymnemic acid has shown significant and good cytotoxic activity compared to standard drug Etoposide and its cytotoxic activity is proportional with the dosage. While, moderate activity has been shown by Gymnemagenin. The deacyl Gymnemic acid when subjected to Annexin V assay has shown that the % of Annexin V positive cells treated with deacyl Gymnemic acid is 53.3 % and 64.8 % at 5 µg and 10 µg respectively indicating the potential cytotoxic activity of deacyl Gymnemic acid [68]. Another compound Gymnemagenol, isolated from GSE have shown to possess anticancer-cytotoxic activity against HeLa cells (Human cervical carcinoma) under *in vitro* conditions. This cytotoxic activity depends on the concentration of gymnemagenol and time

with maximum inhibition of 73% at concentration of 50µg/ml at 96 hrs. But, this compound does not show cytotoxic activity on Vero cells [37]. Besides, the alcohol extract of GSE has shown to inhibit intestinal breast cancer resistance protein (BCRP) [69]. BCRP inhibition enhances the systemic availability of orally administered drugs like topotecan, irinotecan, nitrofurantoin, and sulfasalazine by increasing their absorption in the body [69 - 70]. In this way, GSE possess potent medicinal value in the cancer treatment.

Anti-inflammatory activity:

The aqueous extract of *Gymnema sylvestre* leaves (GSE) has been studied for *in vivo* anti-inflammatory activity using the carrageenin-induced paw oedema in rats with doses ranging from 200, 300 and 500 mg/kg. The 300 mg/kg dose has shown a decrease in the paw oedema volume by 48.5% as compared to the standard drug, Phenybutazone (57.6%) within 4 hours after administration[71].Besides, the doses of 200 mg/kg and 300 mg/kg produced significant reduction in granuloma weight, when compared to control group [15, 71]. By elevating the liver enzymes like γ-glutamyl transpeptidase (γ-GT) and Superoxide dismutase (SOD), GSE has shown a protective mechanism against the release of slow-reacting substances and free radicals. It did not inhibit granuloma formation and related biochemical indices, such as hydroxyproline and collagen. GSE is less gastrotoxic anti-inflammatory agent as even in high doses, it did not affect the integrity of the gastric mucosa when compared with other non-steroidal anti-inflammatory agents [72].

Anti-larvicidal activity:

Aqueous extract of GSE have been shown to be significantly effective in controlling *Culex* larvae. 44, 58, 76, 83 and 89% mortality of *Culex quinquefasciatus* larvae has been observed with the concentrations of 1,2,3,4 and 5 ppm respectively after 24 hours on testing with the aqueous extract of GSE [73]. The effects of purified gymnemagenol compound against *Anopheles subpictus* and *Culex quinquefasfciatus*, with varying time periods results have shown larval mortality of 28%, 69%, 100% and 31%, 63%, 100% at 6, 12 and 24 h respectively. While, its effects at different concentrations on the percentage mortality were 100, 86, 67, 36, 21 and 100, 78, 59, 38 and 19 observed in the concentrations of 1,000, 500, 250, 125 and 62.75 ppm against the fourth-instar larvae of *A. subpitcus* and *C. quinquefasciatus*, respectively. The crude GSE extract has shown a potential larvicidal activity with highest mortality in the concentration of 1,000 ppm against the larvae of A. subpictus (LC (50) = 166.28 ppm, r (2) = 0.807) and against the larvae of C. quinquefasciatus (LC (50) = 186.55 ppm, r (2) = 0.884), respectively [38].

Anti-microbial activity:

Studies on crude ethanolic GSE extract have shown to possess significant antibacterial activity against *Bacillus pumilis*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [74]. Potential activity has been shown by hydro alcoholic (Water-Ethanol 1:1) GSE extract against gram positive bacteria viz: *Bacillus subtilis*, *Staphylococcus aureus* even at minimum concentrations of 50µg/ml [75]. Aqueous extract has shown a moderate activity against three pathogenic *Salmonella* species like *Salmonella typhi, S. typhimurium* and *S.paratyphi* [76]. The pure saponin fractions of 10,000 mg/l were found to be effective against gram negative bacterial pathogens (*Pseudomonas aeruginosa*, *E. coli, Salmonella typhi, K. pneumoniae, Proteus mirablis* & *Staphylococcus aureus)* and the fungal pathogens (*Aspergillus fumigatus*, *Aspergillus niger* & *Aspergillus flavus)* making them equally potent as commercially available antibiotics like Chloramphenicol (con 25mg/disc). Minimum Inhibitory Concentration (MIC) studies have shown that *Proteus mirablis* is more susceptible even at less concentration (600 mg/l) of saponin [39].

Anti-oxidant activity:
GSE extracts rich in gymnemic acids have examined for its antioxidant activities. The IC(50) values for DPPH scavenging assays, superoxide radical scavenging assays, inhibition of in vitro lipid peroxidation assays, and protein carbonyl formation assay were 238, 140, 99.46, and 28.03 µg/mL, respectively[40]. The antioxidant activity shown by 55% v/v alcoholic extract of GSE may be due to presence of Flavonoids, Phenols, Tannis and Triterpenoids found in the preliminary phytochemical screening [77]. In vivo studies have shown that upon pre-treatment with GSE, the radiation (8 Gy)-induced augmentation in the levels of lipid peroxidation and depletion in glutathione and protein levels in mice brain have enhanced significantly. This radioprotective efficacy of GSE may be due to its antioxidant properties [40]. Some poly herbal ayuvedic formulations like Hyponidd and Dihar containing GSE have shown antioxidant activity by increasing superoxide dismutase (SOD), glutathione (GSH) and catalase levels in rats [78 - 79].

Anti-viral activity:
The GSE extracts have shown to possess potent anti-viral activity against Influenza virus and Grouper Nervous Necrosis Virus (GNNV). Gymnemic acid A, B, C and D obtained from the ethyl acetate extract of GSE after chromatography have been tested for anti-viral activity against influenza virus in mice. Gymnemic acid A (75 mg/kg/day) has shown the maximum activity and moderate inhibition was shown by Gymnemic acid B. While, Gymnemic acid C and D have not found to effect the growth of influenza virus [41]. The compound Gymnemagenol isolated from GSE has been tested for anti-viral activity against GNNV, a fish nodavirus which infects SIGE (Sahul Indian Grouper Eye) cell lines. The activity of gymnemagenol is effective against GNNV because, even at low concentrations of 20 µg mL^{-1}, it inhibited the proliferation of GNNV to 53% at the end of the 6th day and the viable SIGE cells have been reduced to 47% as observed by MTT assay [38].

Anti-allergic activity:
Gymnema preparations have shown to possess anti-allergic activity [45]. In-vivo activities of the pectic substances, purified from GSE have shown to inhibit histamine release from isolated rat peritoneal mast cells, which has been induced by the antigen. The inhibition of organic compounds like histamine, triggering responses to foreign particles shows that these pectic substances have anti-allergic activities [43].

Muscle relaxant activity:
In vivo studies of aqueous extract of GSE containing Gymnemic acids have shown muscle relaxant properties. The extracts have relaxed the rat intestinal circular muscles, which has been contracted by high potassium ions. The inhibition of 45mM KCl-induced contraction in a dose dependent manner and a reduction in the spontaneous contraction of the muscles has been observed. The muscle relaxant activity of aqueous extract of GSE may due to action of Nitric Oxide (NO) and Endothelium-Derived Hyperpolarizing Factor (EDHF) [44].

Snake venom antidote activity:
Antidote activity has been shown by the root extracts of *Gymnema sylvestre* against against snakebites [49, 80]. This activity may be due to alkaloids detected in the phytochemical screening [81]. The ATPase, an enzyme which catalyzes the hydrolysis of ATP to ADP, forms the toxic component of venom. The potassium salt of gymnemic acid, which is a triterpenoid glycoside isolated from *Gymnema sylvestre* inhibits ATPase in *Naja Naja* (Indian

cobra) venom [9, 10, 82] and Vipera russelli (viper) venom [10]. Inhibition occurs due to competitive binding between gymnemate and ATP [9, 10].

Anti-caries/ antieurodontic effect:
Gymnema sylvestre has been reported for its antieurodontic effect. It is used as cariostatic food. Purified Gymnemic acid obtained from GSE has shown activity against dental caries by preventing the decomposition of sugar and production of glucan by *Streptococcus mutans* [45]; [7].

Anti-parasitic activity:
The methanol extract of GSE has shown an IC (50) of 24 µg/mL against the CQ resistant INDO strain of *P. falciparum* [83]. Gymnema sylvestre has shown potential Lesihmanicidal property Gymnemagenol, a saponin isolated from GSE has shown leishmanicidal activity with an IC_{50} value of 965μg/ml and has reduced the parasitic population by 52% [46].

Side effects

Gymnema sylvestre has been regarded as safe when taken in recommended doses. Short term uses of low doses may have unnoticeable side effects [84**]**. Extremely high doses have the potential to induce hypoglycemia (abnormally low blood sugar levels. Symptoms of weakness, confusion, fatigue, shakiness, experience excessive sweating and lose control of muscles may occur. *Gymnema*, when taken in an empty stomach may cause gastrointestinal distress including abdominal cramping, nausea and vomiting. Studies on spontaneously hypersensitive rats (SHR) consuming *Gymnema sylvestre* has shown neither decrease nor increase in the systolic blood pressure [64].

Toxicity:
52-weeks study in wistar rats, with administration of 1.00% basal powder (GSE) in the diet have not shown any toxic effects as, none of the animals died during this period[85]. *Gymnema sylvestre* has been reported to cause toxic hepatitis or Drug-Induced Liver Injury (DILI) in patients who have been treated with this herb for diabetes mellitus [86]. A study with D-400 having *Gymnema sylvestre* as one of its major components has shown no adverse effects on rats. This shows the lack of teratogenicity of the extract [87]. The plant has shown to increase the effectiveness of diabetic medications [15]. It might also show side effects if you are taking it with other herbs such as Aloe Vera, Devil's Claw [88].

Precautions:
It is better for people taking prescribed drugs and those allergic to plants in the Asclepiadaceae family, to refrain from Gymnema. Or else they should take accurate doses with proper supervision. [89].

Conclusion

Though known from time immemorial, the ethnobotanical and traditional uses of the natural compounds from plants have dragged much attention in recent years. There has been a rapid development in the isolation and characterization techniques, also in the in vivo studies using various rat and mice models against life-threatening diseases. *Gymnema sylverstre* has potent activity against Diabetes, one of the common diseases these days throughout the world. Besides, it can be simultaneously used for treating obesity, allergic, microbial and viral infections. The wide varieties of compounds isolated from this plant have extensive range of pharmacological activities which need to be researched in depth to establish their therapeutic potential. This broad range of uses and medicinal values reflects

about the idea that, in future, pharmaceutical & drug manufacturing sector mainly relies on plants to obtain lifesaving therapeutics and drugs.

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