

Recent Updates in Research on *Gymnema sylvestre*

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ABSTRACT

Gymnema sylvestrae (GS) is a large woody climbing plant that is available in dry forests of India and China. It is also proven for other activities like anti-hemolytic, anti-bacterial and anti-cancer. Present review covers recent updates in research on this plant typically during last 10 years. Also, its characterization and extraction, structure activity relationship, *in-vitro* pharmacology, *in-vivo* pharmacology, pharmacodynamics, clinical pharmacology and clinical efficacy, safety and toxicity is discussed in details. Detailed review of available literature on GS indicates it is promising plant for treatment of Type 2 Diabetes Mellitus. GS acts only in presence of pancreas as it acts by stimulation of β cells of langerhans. However, it has also shown hepatotoxic property.

Key words: *Gymnema sylvestre*, Diabetes, Pharmacology, Gymnemangenin, Gymnemic acid.

INTRODUCTION

Gymnema sylvestrae (GS) commonly known as Gurmar is widely used for its anti-diabetic activity. It is used as folklore medicine in India for various conditions. It is used in ayurvedic formulations such as *Mahavisagarbha Taila*, *Ayaskrti*, *Nyagrodhadi Churna*, *Mrtasanji Vani Sura*.^[1] These formulations are used in conditions like inflammation, eye diseases, asthma, dental caries and diabetes. GS is also used in the form of a simple tea brew, tea bags, beverages and confectioneries^[2] or in health supplements.^[3] This plant recently came into spotlight being part of drug IME 9 which is formulated by Central Council for Research in Ayurvedic Sciences marketed by Kudos Laboratories. Another drug containing GS is BGR-34 launched by Council for Scientific Industrial Research (CSIR) marketed by Aimil Pharmaceuticals Pvt. Ltd. as an anti-diabetic Ayurveda based formulation.

Present review includes update in research on GS, typically during last ten years. Characterization and extraction, structure activity relationship, *in-vitro* pharmacology, *in-vivo* pharmacology, pharmacodynamics, clinical pharmacology and clinical efficacy, safety and toxicity of GS is discussed in details.

Review methodology

Articles published on research in GS published during 2011 to 2021 were studied. However, few research articles published after 2000 were included in the study since they were important to highlight particular research. Comprehensive and systematic data mining was done emphasizing pharmacological activity of GS. Original articles and papers available

on Pubmed, SCOPUS, Science Direct, Clinicaltrials.org and Pubmed central databases were studied in detail along with their citations and cross references. Research articles were searched using keywords viz. pharmacological activity of GS, toxicity studies of GS, Chemical constituents of GS, Anti-bacterial, anti-diabetic and anti-cancer activities of GS.

Distribution and Folklore claims

GS is a low growing perennial medicinal woody climber which is found in central and peninsular India and Africa.^[4] It is widely distributed in East Africa to Saudi Arabia, India, Sri Lanka, Vietnam and Southern China, as well as Japan (Ryukyu Islands), the Philippines, Malaysia, Indonesia and Australia. In addition, it occurs throughout most of West Africa and extends to Ethiopia and South Africa. In India, Genetic variation in GS has been studied in various parts of India like Western Ghats of Maharashtra^[5] Kerala^[6] in central India,^[7] Andhra Pradesh and Telangana.^[8]

GS have been used as folklore medicine in various part of India. Following table describes an account of its claims Table 1.

Characterization and Extraction

GS belongs to the family *Asclepiadaceae*. The leaves have a pleasant and aromatic odor.

The leaves contain pentriacontane, phytin, d-quercitol, gymnemic acids which are anti-sweet agents.^[17] Interestingly, leaves don't contain amino acid Proline which is generally present in the leaves^[18] However, Proline accumulates in various biotic

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and abiotic stress.^[19] Leaves also contain Gymnemagenin (Mol. wt. 506.70) an aglycone of Gymnemic acid (Mol.wt. 809.00). Hence, the amount of Gymnemic acid can be calculated based on the quantity of Gymnemagenin which can be estimated by HPLC with Limit of Detection 1 µg/ml.^[20] The other validated method for quantification of Gymnemic acid is by quantifying Deacyl Gymnemic acid in which Limit of Detection was 6.5 µg/ml.^[21]

However, for studying anti-diabetic activity, which is mainly attributed to Gymnemic acid,^[22] leaves are the best source as maximum concentration is found in shoot tips (54.29 mg-g-1 DW) and least in seeds (1.31mg-g-1 DW) (2).^[23] Singh *et al.* (2015)^[24] reported leaf contain 2.4% of Gymnemic acid (W/W). Other active components are a group of Gymnemic acids with a b-glucuronic acid at C-3 and a hydroxyl substitution at C-23 on an oleanane triterpene-type aglycone.^[25] There are around 10 kinds of Gymnemic acid and related compounds which are tedious to isolate.^[26] Di Fabio *et al.* 2014^[27] have reviewed triterpenoids oxidized at C-23 isolated from GS and characterized 53 compounds and 46 biological properties of these compounds

Out of various extraction methods studied, ultrasound-assisted extraction process of GS causes fourfold increase in insulin secretion in RIN5MF cell lines. This method of extraction is time-saving and prevents excessive degradation of the target analytes.^[28] Hydrodistillation of *G. sylvestris* fresh leaves is also a reported method of extraction of oils from GS leaves with 0.2% yield.^[29] Extraction with 90% methanol by Hooper's method gives the maximum yield of Gymnemic acid from GS leaves.^[30]

Structure activity relationship

Since GS mainly studied in India, it is different from its Vietnamese variety. Detailed microscopic and macroscopic differences are reported.^[31] Nine previously undescribed compounds were isolated (Table 2). A detailed analysis of the Structure-Activity Relationships (SARs) of all the isolates indicated that the 3-b-glucuronol oleanane-type moiety might

Table 1: Statewide folklore claims and traditional knowledge of *Gymnema sylvestris* (GS) in India.

S. N.	Name of the state	Folklore claim
1	Andhra Pradesh	In Medak district of Andhra Pradesh, leaf powder is given for gastric trouble and in diabetes; leaf juice is used as eye drops ^[9]
2	Chhattisgarh	Whole plant for anti-inflammatory and anti-asthmatic activity and leaves as diuretic ^[10]
3	Karnataka	In Jashpur District, this plant is used for vomiting/ ulcers, and dysentery. ^[11]
4	Kerala	In Gulbarga district of Karnataka, its roots are used as anti-diabetic. ^[12]
5	Tamil Nadu	Leaves of GS are crushed with water and its juice is taken before meal in Kerala as a remedy to diabetes. ^[13]
6	Uttar Pradesh	Leaves of GS are ground with pepper, garlic and pinch of common salt to cure ephemeral fever in animals
7	Pondicherry	Leaf juice is used to cure opacity of cornea. ^[14]
8	Uttar Pradesh	Fresh leaf paste is applied on eyelid twice daily to cure cataract in Jhansi district of Uttar Pradesh. ^[15]
9	Pondicherry	Dried leaf powder (2-3g) is given with water. Seven fresh leaves are prescribed daily in the morning for 15 days for diabetes. ^[16]

Table 2: Compounds found in Vietnamese variety of GS which was not previously described in Indian variety.

No.	Name/Code	Formula	Chemical name
01.	Gymnemoside ND1	C ₄₂ H ₆₆ O ₁₆	3 β -16 β -28-trihydroxyolean-12-en-29-oic acid or myrtillogenic acid
02.	Gymnemoside ND2	C ₄₂ H ₆₆ O ₁₆	1,3β,16β,28-trihydroxyolean-12-en-29-oic acid 3-0- β -D-galactopyranosyl(1-3)-0-β -D-glucuronopyranoside
03.	Gymnemoside ND3	C ₄₂ H ₆₈ O ₁₅	Sitakisogenin 3-0- β -D-glucuronopyranosyl (1-3)-0- β -D-glucuronopyranoside
04.	Gymnemoside ND4	C ₄₂ H ₆₈ O ₁₃	3 β,16β-dihydroxyolean-12-en-3-0- β -D-glucuronopyranosyl(1-3)-0-β -D- glucuronopyranoside
05.	Gymnemoside ND5	C ₄₂ H ₆₈ O ₁₅	29-0-(β -D-glucopyranosyl) gymnemagenol 3-0- β -d-glucuronopyranoside
06.	Gymnemoside ND6	C ₃₆ H ₅₈ O ₁₀	Sitakisogenin 3-0-β-d-glucuronopyranoside
07.	Gymnemoside ND7	C ₃₆ H ₅₈ O ₁₀	Gymnemagenol-3-0-β-D-glucuronopyranoside
08.	Gymnemoside ND8	C ₄₃ H ₆₂ O ₁₂	28-benzoyl-22α-hydroxygymnemagenol-3-0-β-D-glucuronopyranoside
09.	Gymnemoside ND9	C ₃₆ H ₅₄ O ₁₁	3-0-β-D-glucuronopyranosyl-3β,16β,28-trihydroxyolean-12-en-29,22β-olide
10.	Gymnemoside ND10	-	29-hydroxylongispinogenin 3-0-D-glucopyranosyl(1-3)-D- glucuronopyranoside
11.	Gymnemoside ND11	-	Longispinogenin 3-0-D-glucopyranosyl(1-3)-D glucuronopyranoside
12.	Gymnemoside ND12	-	Alternoside XII
13.	Gymnemoside ND13	-	Gymnemic acid A

exert stimulatory effects on glucose uptake. Glycosylation of glucuronic acid reduces the activity, oxidation of alcohol functional group at C-29 to a carboxylic acid decreases the activity but esterification of the same recovered the activity. Compared with insulin, compounds 7-9 showed the most potent stimulatory activities.^[31]

In-vitro Pharmacology

In-vitro cytotoxicity of gymnemagenol was reported in HeLa and Vero cell lines at IC₅₀ value 37 µg/ml^[32] but Gymnemic Acid Fraction of GS

leaves did not confer any Cytotoxicity and showed better glucose uptake potential in comparison to standard drug Metformin in L-6 cell line.^[33]

In vitro antibacterial activity

The antimicrobial activity of the leaf extracts of GS might be attributed to the presence of phytochemicals i.e. flavonoids, terpenoids, amino acids, glycosides, tannins, amino acids and carbohydrates.^[34] The protective effect of GS observed is attributed to its effect on mucus production, increase in nucleic acid and NP-SH levels, which appears to be mediated through its free radical scavenging ability and/or possible cytoprotective properties.^[35]

In-vivo Pharmacology

In-vivo anti-diabetic activity

Various diabetes models and their response to *Gymnema sylvestre* treatment are described in Table 3.

GS has been studied widely for its anti-diabetic potential. Its anti-diabetic activity was studied in the streptozotocin-induced diabetic rat model and alloxan-induced diabetic rat model. GS increased insulin secretion which led to a decrease of cholestrogenesis and fatty acid synthesis along with hyperglycemia. Similar results were described by other researchers.^[36,37] Its hypoglycemic activity was comparable to Glibenclamide.^[38]

The anti-diabetic activity of GS lies mainly in leaf extract.^[39-41] Leaf and callus extracts of GS stimulate regeneration of β cells *in-vivo* and *in-vitro*, respectively.^[42] Various other parts like wood bark and whole plant were also studied for the anti-diabetic activity. All possible mechanisms involved in anti-diabetic activity are studied and reported; viz. Increase in insulin secretion,^[43,44] delay in glucose absorption from intestine into blood due to presence of alpha-glucosidase;^[45] suppressing the desire for high sugar sweet food,^[46] regeneration of Islets, increased

glucose utilization;^[26] binding to glucose receptor in intestine and taste buds posing sweet suppressing activity. It was previously considered that Gurmarin peptide presumably blocks sucrose receptors of the tongue.^[47] However, researchers have recently established that GS does not block only sweet receptors on the taste buds of the mouth. It has the same inhibitory activity on sodium-dependent glucose transporter 1 (SGLT1) which was observed in *Xenopus laevis* oocytes microinjected with cRNA for SGLT1. SGLT1 is found in high levels in brush-border membranes of intestinal epithelial cells.^[48] Along with anti-sweet activity GS delays postprandial gastrointestinal blood flow and gastric emptying.^[49] GS also increases insulin secretion^[43] possibly due to calcium influx and protein kinase activation.^[50]

GS increases fecal steroid excretion^[26] when given orally at dose equivalent to 36.33 mg/kg. It interrupts the formation of micelles that contain cholesterol and bile acids in the gut and due to interference with absorption of cholesterol or re-absorption of bile acids. Practically it is impossible to take a dose of Gymnemic acids sufficiently high to increase fecal excretion of neutral steroids due to its bitter test.

GS leaf extract showed significant enhancement in NO and ROS generation in macrophages and the proliferation of lymphocytes in a dose-dependent manner at EC₅₀ value 3.10, 3.75 and 2.68 μ g/ml for NBT reduction, nitrite release and lympho-proliferation, respectively.^[24]

Pharmacokinetics

Aqueous extract of GS does not affect any of the Cytochrome enzymes. GS extracts shows differential effect on CYP activities in the following order of inhibitory potency: ethyl acetate > Chloroform > methanol > *n*-hexane > aqueous > DGA. This differential effect was observed against CYP1A2, 2C9 and less on CYP3A4 and 2C8.^[54]

GS causes a decrease in the bioavailability of Metformin significantly^[40] which further leads to decrease in the therapeutic dose level. Gymnemanin has beneficial pharmacodynamic interactions with Glimepiride whereas no major alterations in the pharmacokinetic parameters is reported.^[55] Mechanism of action is shown in brief in Figure 1.

Other Pharmacological activities

Leaf followed by flower and the stem exert protective effects against oxidative injury to biological macromolecules like lipids and proteins in the erythrocyte membrane.^[56] Leaves also exhibit hepatoprotective activity.^[17] GS also significantly lowers cholesterol which indicates

Table 3: Details of anti-diabetic activity study on *Gymnema sylvestre* in laboratory animals with their dose and extract type.

Sr No.	Laboratory animals / test system	Dose	Extract type / Part used	Reference
1	Streptozotocin-induced diabetic rat	200 and 400 mg/kg	GS standardized 75% dry extract	[51]
2.	Normal and streptozotocin (STZ) diabetic rats.	18 mg/kg	GS leaves extract	[37]
3.	Alloxon Induced Diabetic Rats	400, 600 and 800 mg/kg body weight	aqueous leaf extract of GS	[36]
4	STZ induced rats	@ 250 mg/kg b. Wt.	glycoside from GS leaf extract	[38]
5	Normal and Alloxan induced diabetic rats.	2 ml/kg	GS whole plant extract	[52]
6	Insulin-resistant diabetes in mice	intraperitoneally @ 13.4 mg/kg	Gymnemic acid	[53]

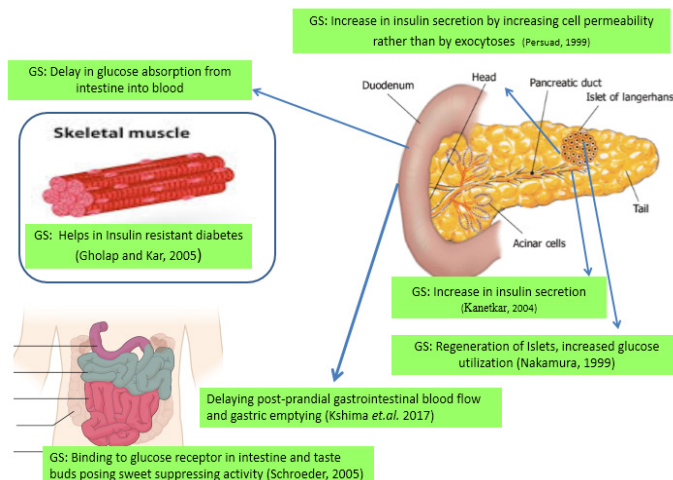


Figure 1: Mechanism of action of GS.

effect on metabolism.^[57,58] Leaf extract can restore innate immunity by increasing Macrophage reactivity and lymphocyte proliferation.^[24] GS has been recently used in various experiments to understand taste physiology.^[47]

Pharmacodynamics

Thakur *et al.* 2012 described GS as an alternative therapeutic agent for the treatment of diabetes it also increases the effectiveness of diabetic medication.^[59] The possible mechanisms by which GS exerts its hypoglycemic effects are increasing insulin secretion, regeneration of Islet cells, improved glucose utilization, decreased glucose absorption and increasing NO levels.

GS extract might help in increasing NO levels in diabetic patients and can help avoid diabetic vascular complications that occur as a result of decreased NO levels due to glucose overload and oxidative stress.^[60]

In-silico technique was used to understand and predict the drug likeliness of Gymnemagenin, one of the key constituents of GS against 15 proteins having a key role in carbohydrate metabolism. Gymnemagenin was found to dock well with crystallographic structures of 7 out of the 15 selected targets and was found even better than the two known clinically used anti-diabetic compounds i.e. repaglinide, and sitagliptin taken in the study for comparison.^[61]

Clinical Pharmacology and Clinical Efficacy

The *Gymnema sylvestre* supplementation lowered the 2-hr post-prandial plasma glucose concentrations, by 13% (207 vs. 180 mg/dl) and lowered HbA1c from 8.8% to 8.2% (0.6% Decrease) in a clinical trial.^[62] Few clinicians reported effective dose to be @ 500 mg/day for three months.^[63] It can be used as an oral dispersible tablet to control sweet-craving thus controlling the diabetes and obesity problems^[64] and also as an diet supplementation.^[63] There are contradicting clinical findings concerning insulin secretions. Zuñiga *et al.* 2017^[39] reported no significant alteration in insulin secretion in clinical subjects due to GS treatment.

All these evidences available are preliminary and micro-vascular or macro-vascular effects are not addressed well.^[65]

Safety and Toxicity

High doses may lead to side effects including hypoglycemia, weakness, shakiness, excessive sweating, and muscular dystrophy.^[2] Gymnemic acid may be hepatotoxic at the higher dose in mice.^[53] This is supported by only one reported clinical case of toxic hepatitis induced by GS in a 60 year old patient.^[66,67] In rats treated with GS the no-observable-effect level is 1.00% GS, i.e., 504 mg/kg/day for male and 563 mg/kg/day for female as mean daily intake, for 52 weeks is reported.^[68] Although it is considered safe, reports on post market surveillance are lacking.

CONCLUSION

GS is well known anti-diabetic plant, which acts only in presence of pancreas.^[69,70] Anti-diabetic activity of GS lies mainly in leaf and is comparable to Metformin and Glimepiride. Apart from anti-diabetic activity, GS has shown anti-hemolytic, anti-microbial, anti-cancer activities too but the mechanisms are not well explored as that of anti-diabetic activity. Data on anti-diabetic activity is available but its effect on cardiovascular system is not well studied in pre-clinical and clinical aspect. GS may not be safe to the liver. Hence, the use in such patients is warranted.

Detailed review of available literature on *Gymnema sylvestre* indicates it is promising plant for treatment of Type 2 Diabetes Mellitus. GS acts only in presence of pancreas as it acts by stimulation of β cells of Langerhans.^[69,70] It also shows anti-diabetic activity at lesser concentration. This

review also suggests that, anti-diabetic activity of GS mainly lies in the leaves. This plant can yield best using ultrasound-assisted extraction process which leads to increase in its activity to four folds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

GS: *Gymnema sylvestre*; **DW:** Distilled Water; **W/W:** Weight by Weight; **CYP:** Cytochrome; **HPLC:** High Performance Liquid Chromatography; **IC₅₀:** Inhibitory concentration 50; **NO:** Nitric Oxide; **ROS:** Reactive Oxygen Species; **EC₅₀:** Effective Concentration 50; **DGA:** Deacylgymnemic acid; **NBT:** Nitro-Blue Tetrazolium.

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