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Review Article

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.

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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, i*n-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 studies 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 stresse.[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 oleane 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. sylvestre* 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-glucuronyl oleanane-type moiety might exert stimulatory effects on glucose uptake. Glycosylation of glucoronic 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]

Table 1: Statewide folklore claims and traditional knowledge of *Gymnema sylvestre* (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]
		In Jashpur District, this plant is used for vomiting/ ulcers, and dyscentry.[11]
3	Karnataka	In Gulbarga district of Karnataka, its roots are used as anti-diabetic.[12]
4	Kerala	Leaves of GS are crushed with water and its juice is taken before meal in Kerala as a remedy to diabetes. [13]
5	Tamil Nadu	Leaves of GS are ground with pepper, garlic and pinch of common salt to cure ephemeral fever in animals
		Leaf juice is used to cure opacity of cornea.[14]
6	Uttar Pradesh	Fresh leaf paste is applied on eyelid twice daily to cure cataract in Jhansi district of Uttar Pradesh.[15]
7	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

In-vitro Pharmacology

In-vitro cytotoxicity of gymnemagenol was reported in HeLa and Vero cell lines at IC_{50} 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 sylvestrae* 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 EC_{50} value 3.10, 3.75 and 2.68 µg/ml for NBT reduction, nitrite release and lympho-proliferation, respectively.[24]

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]

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. Gymnemangin 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 exihibit hepatoprotective activity.[17] GS also significantly lowers cholesterol which indicates

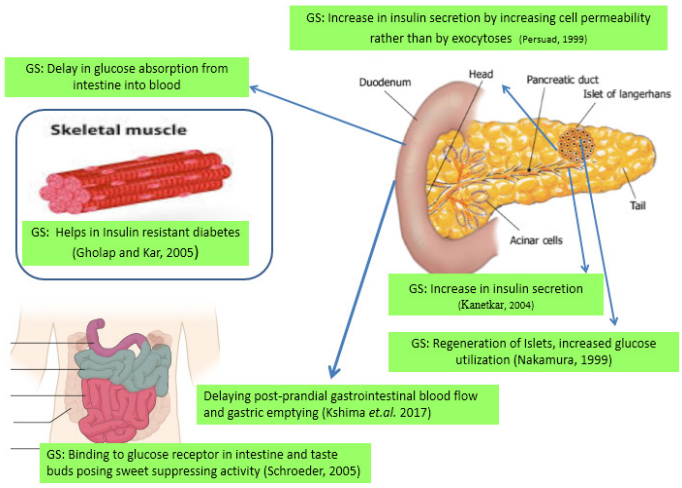

Figure 1: Mechanism of action of GS.

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; **IC_{50}:** Inhibitory concentration 50; **NO:** Nitric Oxide; **ROS:** Reactive Oxygen Species; **EC_{50}:** Effective Concentration 50; **DGA:** Deacylgymnemic acid; **NBT:** Nitro-Blue Tetrazolium.

REFERENCES

1. Anonymous. The ayurvedic formulary of India. The Ayurvedic Formul India. 2003:1-110.
2. Tiwari P, Mishra BN, Sangwan NS. Phytochemical and pharmacological properties of *Gymnema sylvestre*: an important medicinal plant. BioMed Res Int. 2014;2014:830285. doi: 10.1155/2014/830285, PMID 24511547.
3. Paliwal R, Kathori S, Upadhyay B. Effect of gurmar (*Gymnema sylvestre*) powder intervention on the blood glucose levels among diabetics. Stud Ethno-Medicine. 2009;3(2):133-5. doi: 10.1080/09735070.2009.11886350.
4. Thakur GS, Sharma R, Sanodiya BS, Pandey M, Prasad GBKS, Bisen PS. *Gymnema sylvestre*: an alternative therapeutic agent for management of diabetes. J Appl Pharm Sci. 2012;2(12):1-6.
5. Shahnawaz M, Zanan RL, Wakte KV, Mathure SV, Kad TD, Deokule SS, Nadaf AB. Genetic diversity assessment of *Gymnema sylvestre* (Retz.) R. Br. ex Sm. populations from Western Ghats of Maharashtra, India. Genet Resour Crop Evol. 2012;59(1):125-34. doi: 10.1007/s10722-011-9757-7.
6. Nair S, Keshavachandran R. Molecular diversity in chakkarakolli (*Gymnema sylvestre* R. Br.) assessed through isozyme and RAPD analysis. Trop Agric. 2006;44(September 2004):31-6.
7. Verma AK, Dhawan SS, Singh S, Bharati KA, Jyotsana. Genetic and chemical profiling of *Gymnema sylvestre* accessions from Central India: its implication for quality control and therapeutic potential of plant. Pharmacogn Mag. 2016;12(Suppl 4):S407-13. doi: 10.4103/0973-1296.191443, PMID 27761067.
8. Prashanti M. Evaluation of genetic diversity studies in *Gymnema sylvestre* assessed through RAPD markers. Int J Pure App Biosci. 2017;5(5):740-8. doi: 10.18782/2320-7051.5620.
9. Reddy KN, Trimurthulu G, Reddy CS. Medicinal plants used by ethnic people of Medak district, Andhra Pradesh. Indian J Tradit Knowl. 2010;9(1):184-90.
10. Jain J, Kumane S, Bhattacharya S. Medicinal flora of Madhya Pradesh and Chattisgarh – a review. Indian J Tradit Knowl. 2006;05(2):237-42.
11. Journal I. Pharmacy G. Int J Green Pharm Iraq. 2010;4(3):223-6.
12. Ghatapanadi SR, Johnson N, Rajasab AH. Documentation of folk knowledge on medicinal plants of Gulbarga district. Karnataka; 2011. p. 10(April):349-53.
13. Jayakumar G, Ajithabai MD, Sreedevi S, Viswanathan PK, Remeshkumar B. Ethnobotanical survey of the plants used in the treatment of diabetes. Indian J Tradit Knowl. 2010;9(1):100-4.
14. Kiruba S, Jeeva S, Dhas S. Enumeration of ethnoveterinary plants of Cape Comorin, Tamil nadu. Indian J Tradit Knowl. 2006;05(4):576-8.
15. Nigam G, Sharma NK. Ethnoveterinary plants of Jhansi district, Uttar Pradesh. Indian J Tradit Knowl. 2010;9(4):664-7.
16. Dixit AK, Sudurshan M. Review of flora of anti-diabetic plants of Puducherry ut. Int J Appl Biol Pharm Technol. 2011;4:455-62.
17. Srividya aR, Varma SK, Dhanapal SP, Vadivelan R, Vijayan P. in vitro and in vivo Evaluation of Hepatoprotective Activity of *Gymnema sylvestre* ABSTRACT :. 2010;2(4):768-73.
18. Khramov VA, Spasov AA, Samokhina MP. Chemical composition of dry extracts of *Gymnema sylvestre* leaves. Pharm Chem J. 2008;42(1):29-31. doi: 10.1007/s11094-008-0051-8.
19. Verbruggen N, Hermans C. Proline accumulation in plants: a review. Amino Acids. 2008;35(4):753-9. doi: 10.1007/s00726-008-0061-6, PMID 18379856.
20. Nikhat SR. Road K. Extraction and characterization of gymnemagenin in. *Gymnema sylvestre* Leaves. Int J Pharm Sci Res. 2017;8(8):3503-7.
21. Devi K, Jain N. o f Phytom A va lidated H PLC met thod for estimation e n of

Gymnemic acids as de eacyl emic acid in variou us extract ts and for rmulations s of *Gymnema sylvestre*. Int J Phytomed. 2014;6:165-9.
22. Wang Y 1, Corinna Dawid, Gabor Kottra, Hannelore Daniel TH. Gymnemic Acids Inhibit Sodium-Dependent Glucose Transporter 1. J Agric Food Chem. 2014;25((62)):5925–31.
23. Manohar SH, Naik PM, Praveen N, Murthy HN. Distribution of gymnemic acid in various organs of *Gymnema sylvestre*. J For Res. 2009;20(3):268-70. doi: 10.1007/s11676-009-0046-7.
24. Singh VK, Dwivedi P, Chaudhary BR, Singh R. Immunomodulatory effect of *Gymnema sylvestre* (R.Br.) leaf extract: an in vitro study in rat model. PLOS ONE. 2015;10(10):1-15. doi: 10.1371/journal.pone.0139631.
25. Pothuraju R, Sharma RK, Chagalamarri J, Jangra S, Kumar Kavadi P. A systematic review of *Gymnema sylvestre* in obesity and diabetes management. J Sci Food Agric. 2014;94(5):834-40. doi: 10.1002/jsfa.6458, PMID 24166097.
26. Nakamura Y, Tsumura Y, Tonogai Y, Shibata T. Fecal steroid excretion is increased in rats by oral administration of gymnemic acids contained in *Gymnema sylvestre* Leaves. J Nutr. 1999;129(6):1214-22. doi: 10.1093/jn/129.6.1214, PMID 10356090.
27. Di Fabio GD, Romanucci V, De Marco A, Zarrelli A. Triterpenoids from *Gymnema sylvestre* and their pharmacological activities. Molecules. 2014;19(8):10956-81. doi: 10.3390/molecules190810956, PMID 25072200.
28. Sheoran S, Panda BP, Admane PS, Panda AK, Wajid S. Ultrasound-assisted extraction of gymnemic acids from *Gymnema sylvestre* leaves and its effect on insulin-producing RINm-5F β cell lines. Phytochem Anal. 2015;26(2):97-104. doi: 10.1002/pca.2540, PMID 25469471.
29. Naik DG, Dandge CN, Rupanar SV. Chemical examination and evaluation of antioxidant and antimicrobial activities of essential oil from *Gymnema sylvestre* R. Br. Leaves. J Essent Oil Res. 2011;23(3):12-9. doi: 10.1080/10412905.2011.9700451.
30. KRISHNA RB, REDDY SRR. Harika, Javangula, Swapna D, REDDY KJ. Isolation and characterization of gymnemic acid from *Gymnema Sylvestre* R.BR. IN CONTROL OF DIABETES. Int J Life Sci Pharm Res. 2012;2(1):1-9.
31. Pham HTT, Hoang MC, Ha TKQ, Dang LH, Tran VO, Nguyen TBT, Lee CH, Oh WK. Discrimination of different geographic varieties of *Gymnema sylvestre*, an anti-sweet plant used for the treatment of type 2 diabetes. Phytochemistry. 2018;150:12-22. doi: 10.1016/j.phytochem.2018.02.013, PMID 29529525.
32. Khanna V, Kannabiran K. Anticancer-cytotoxic activity of saponins isolated from the leaves of *Gymnema sylvestre* and Eclipta prostrata on HeLa cells. Int J Green Pharm. 2009;3(3):227-9.
33. Nirmala S, Ravichandiran V, Vijayalakshmi A. *In vitro* cytotoxicity and glucose uptake activity of gymnemic acid fraction of *Gymnema Sylvestre* Leaves. 2016; 4 (2):1104-9.
34. David BC, Sudarsanam G. Antimicrobial activity of *Gymnema sylvestre* (Asclepiadaceae). J Acute Dis. 2013;2(3):222-5. doi: 10.1016/S2221-6189(13)60131-6.
35. Al-Rejaie SS, Abuohashish HM, Ahmed MM, Aleisa AM, Alkhamees O. Possible biochemical effects following inhibition of ethanol-induced gastric mucosa damage by *Gymnema sylvestre* in male Wistar albino rats. Pharm Biol. 2012;50(12):1542-50. doi: 10.3109/13880209.2012.694894, PMID 22978267.
36. Mall GK, Mishra PK, Prakash V. Antidiabetic and hypolipidemic activity of *Gymnema sylvestre* in alloxan induced diabetic rats. Glob J Biotechnol Biochem. 2009;4(1):37-42.
37. El Shafey AAM, El-Ezabi MM, Seliem MME, Ouda HHM, Ibrahim DS. Effect of *Gymnema sylvestre* R. Br. leaves extract on certain physiological parameters of diabetic rats. J King Saud Univ Sci. 2013;25(2):135-41. doi: 10.1016/j.jksus.2012.11.001.
38. Verma N, Shakya VK, Saxena RC. Antidiabetic activity of glycoside isolated from *Gymnema sylvestre* in streptozotocin induced diabetic rats. Asian J Chem. 2008;20(7):5033-6.
39. Zuñiga LY, González-Ortiz M, Martínez-Abundis E. Effect of *Gymnema sylvestre* administration on metabolic syndrome, insulin sensitivity, and insulin secretion. J Med Food. 2017;20(8):750-4. doi: 10.1089/jmf.2017.0001, PMID 28459647.
40. Dhande SR. DVL and SPB. Effect of *Gymnema sylvestre* on the pharmacokinetics of sitagliptin phosphate in type II diabetes mellitus. Int J Pharm Sci Res. 2017;8(3):1160-7.
41. Yogalakshmi K, Vaidehi J, Ramakotti P. Hypoglycemic effect of *Gymnema sylvestre* leaf extract on normal and streptozotocin induced diabetic rats. Int J ChemTech Res. 2014;6(12):5146-50.
42. Ahmed AB, Rao AS, Rao MV. *In vitro* callus and *in vivo* leaf extract of *Gymnema sylvestre* stimulate β-cells regeneration and anti-diabetic activity in Wistar rats. Phytomedicine. 2010;17(13):1033-9. doi: 10.1016/j.phymed.2010.03.019, PMID 20537514.
43. Kanetkar PV, Laddha KS, Kamat MY. Gymnemic acids: a molecular perspective of its action on carbohydrate metabolism. Poster Present 16th ICFOST Meet Organ by CFTRI DFRL. Mysore, India; 2004..
44. Persaud SJ, Al-Majed H, Raman A, Jones PM. *Gymnema sylvestre* stimulates insulin release *in vitro* by increased membrane permeability. J Endocrinol. 1999;163(2):207-12. doi: 10.1677/joe.0.1630207, PMID 10556769.
45. Chen G, Guo M. Rapid screening for α-glucosidase inhibitors from *Gymnema sylvestre* by affinity ultrafiltration-hplc-ms. Front Pharmacol. 2017;8:228. doi: 10.3389/fphar.2017.00228, PMID 28496409.
46. Turner S, Diako C, Kruger R, Wong M, Wood W, Rutherfurd-Markwick K, Ali A. Consuming *Gymnema sylvestre* reduces the desire for high-sugar sweet foods. Nutrients. 2020;12(4):1-14. doi: 10.3390/nu12041046, PMID 32290122.
47. Schroeder JA, Flannery-Schroeder E. Use of the herb *Gymnema sylvestre* to illustrate the principles of gustatory sensation: an undergraduate neuroscience laboratory exercise. J Undergrad Neurosci Educ. 2005;3(2):A59-62. PMID 23493970.
48. Wang Y, Dawid C, Kottra G, Daniel H, Hofmann T. Gymnemic acids inhibit sodium-dependent glucose transporter 1. J Agric Food Chem. 2014;62(25):5925-31. doi: 10.1021/jf501766u, PMID 24856809.
49. Kashima H, Eguchi K, Miyamoto K, Fujimoto M, Endo MY, Aso-Someya N, Kobayashi T, Hayashi N, Fukuba Y. Suppression of oral sweet taste sensation with *Gymnema sylvestre* affects postprandial gastrointestinal blood flow and gastric emptying in humans. Chem Senses. 2017;42(4):295-302. doi: 10.1093/chemse/bjw126, PMID 28431091.
50. Liu B, Docherty R, Amiel S, Persaud SJ, Jones PM. ??of Langerhans; 2012. p. 1-10.
51. Aralelimath VR, Bhise SB. Anti-diabetic effects of Gymnema Sylvester extract on streptozotocin induced diabetic rats and possible β-cell protective and regenerative evaluations. Dig J Nanomater Biostructures. 2012;7(1):135-42.
52. Sathya S, Kokilavani R, Gurusamy K. Hypoglycemic effect of *Gymnema sylvestre* (retz.,) R.Br leaf in normal and alloxan induced diabetic rats. Anc Sci Life. 2008;28(2):12-4. PMID .
53. Gholap S, Kar A. Gymnemic Acids from *Gymnema sylvestre* . Potentially Regulates Dexamethasone-Induced Hyperglycemia in Mice. Pharm Biol. 2005;43(2):192-5. doi: 10.1080/13880200590919564.
54. Rammohan B, Samit K, Chinmoy D, Arup S, Amit K, Ratul S, Sanmoy K, Dipan A, Tuhinadri S. Human Cytochrome P450 Enzyme Modulation by *Gymnema sylvestre*: A Predictive Safety Evaluation by LC-MS/MS. Pharmacogn Mag. 2016 July;12(Suppl 4):S389-94. doi: 10.4103/0973-1296.191441, PMID 27761064.
55. Kamble B, Gupta A, Moothedath I, Khatal L, Janrao S, Jadhav A, Duraiswamy B. Effects of *Gymnema sylvestre* extract on the pharmacokinetics and pharmacodynamics of glimepiride in streptozotocin induced diabetic rats. Chem Biol Interact. 2016 February;245:30-8. doi: 10.1016/j.cbi.2015.12.008, PMID 26721197.
56. James O, Alewo IM. In vitro antihemolytic activity of *Gymnema Sylvestre* extracts against hydrogen peroxide (H2O2) induced haemolysis in human erythrocytes. Am J Phytomed Clin Ther. 2014;2(7):861-9.
57. Higematsu NS, Sano RA, Himosaka MS, Kazaki MO. Effect of administration with the extract of *Gymnema sylvestre* R. Br. 2001;24(June):713-7.
58. Preuss HG, Jarrell ST, Scheckenbach R, Lieberman S, Anderson RA. Comparative effects of chromium, vanadium and *Gymnema Sylvestre* on sugar-induced blood pressure elevations in SHR. J Am Coll Nutr. April 1998;17(2):116-23. doi: 10.1080/07315724.1998.10718736, PMID 9550454.
59. Vijai L. SMB. Antifilarial activity of *Gymnema Sylvestre* R. Br leaves against Brugia malayi. Biomed J Scitech Res. 2018;7(3).
60. Khan KA, Dobani S, Shareef MA. Molecular docking and preclinical studies of *Gymnema sylvestre* on endothelial nitric oxide synthase in Type-2 diabetes-related complications. J Young Pharm. 2014;6(4):25-32. doi: 10.5530/jyp.2014.4.5.
61. Rathore PK, Arathy V, Attimarad VS, Kumar P, Roy S RS. *In-silico* analysis of gymnemagenin from *Gymnema sylvestre* (Retz.) R.Br. with targets related to diabetes. J Theor Biol. 2016;391:95-101. doi: 10.1016/j.jtbi.2015.12.004, PMID 26711684.
62. Joffe DJ. SHF. Effect of extended release. *Gymnema Sylvestre* Leaf Extract (beta fast GXR) alone or in combination with oral hypoglycemics or insulin regimens for Type 1 and Type 2 diabetes. Diabetes control Newsl 2001. Vol. 1(76).
63. Kumar SN, Mani UV, Mani I. An open label study on the supplementation of *Gymnema sylvestre* in type 2 diabetics. J Diet Suppl. 2010:273-82. doi: 10.3109/19390211.2010.505901, PMID 22432517; (Sep;7(3)).
64. Devi K, Jain N. Clinical evaluation of the anti-sweet effects of *Gymnema sylvestre* extract developed into a dispersable oral tablet. J Herb Med. 2015;5(4):184-9. doi: 10.1016/j.hermed.2015.09.005.
65. Nahas R, Moher M. Complementary and alternative medicine for the treatment of type 2 diabetes. Can Fam Physician. 2009;55(6):591-6. PMID 19509199.
66. Shiyovich A, Sztarkier I, Nesher L. Toxic hepatitis induced by *Gymnema sylvestre*, a natural remedy for type 2 diabetes mellitus. Am J Med Sci. 2010;340(6):514-7. doi: 10.1097/MAJ.0b013e3181f41168, PMID 20856101.
67. NesherLior ASISL Nesher. Toxic Hepatitis Induced by *Gymnema sylvestre*, a Natural Remedy for Type 2 Diabetes Mellitus. Am J Med Sci;3(40 (6)):514-:514-7.
68. Ogawa Y, Sekita K, Umemura T, Saito M, Ono A, Kawasaki Y, Uchida O, Matsushima Y, Inoue T, Kanno J. *Gymnema sylvestre* Leaf Extract: A 52-week Dietary Toxicity Study in Wistar rats. Shokuhin Eiseigaku Zasshi. 2004;45(1):8-18. doi: 10.3358/shokueishi.45.8, PMID 15168555.

69. Al-Romaiyan A, Liu B, Persaud S, Jones P. A novel *Gymnema sylvestre* extract protects pancreatic beta-cells from cytokine-induced apoptosis. Phytother Res. 2020;34(1):161-72. doi: 10.1002/ptr.6512, PMID 31515869.
70. Liu B, Asare-Anane H, Al-Romaiyan A, Huang GC, Amiel SA, Jones PM, Persaud SJ. Characterisation of the insulinotropic activity of an aqueous extract of *Gymnema sylvestre* in mouse β-cells and human islets of Langerhans. Cell Physiol Biochem. 2009;23(1-3):125-32. doi: 10.1159/000204101, PMID 19255507.

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