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Phytochemical and Pharmacological Review of *Gymnema Sylvestre*

Sakshi Kotwal, K. G. Bhutkar, Dr. S. R. Chaudhari
KJ's Educational Institute , Trinity college of Pharmacy, Pune
Sr. No. 25 & 27, A/P. Pisoli, Bopdev Ghat Road, Next to Yewalewadi, Pune 411 048

Abstract:- Gymnema 'gurmar' is a widely used herb in the Ayurvedic system of medicine. *G. sylvestre R. Br* (Asclepiadaceae) is large woody climber that is distributed in dry forests of India extending southern and northern regions. The herb is associated with many pharmacological activities due to the presence of bioactive constituents 'triterpene saponins'. Gymnemic acid is the principle phyto constituent mainly associated with anti-diabetic and anti-sweet activity. Researchers found several other bioactiveconstituentswhich gives pharmacological activitiesbased on their phytochemical nature.The present review provides an overview of phyto chemicals that are responsible for a broad range of therapeutic effects including anti-diabetic, anti-hyper lipidaemic, anti-obesity, anti-sweet, anti-oxidant, anti-microbial, anti-inflammatory, immune modulatory and cytotoxic activity. The herbal extracts of gymnema are used in various dietary supplements to support blood sugar levels, body weight, blood cholesterol and triglyceride levels as well as to reduce sugar cravings. The anti-sweet activity of herb is due to its triterpene saponins gymnemic acids, gymnemasponins and a polypeptide known as 'gurmarin'. This review explores traditional application of 'gudmar' in the modern medication considering its pharmacognostic, phytochemical, pharmacological and pharmaceutical aspects.

Keywords:- *Ayurvedic, Anti-Diabetic, Gymnemic Acid, Triglyceride, Saponins.*

I. INTRODUCTION

A. Drug

Gymnema sylvestre, also known as "gurmar," is a renowned Ayurvedic herb known for its sugar-destroyer properties (1). It is a plant in the Asclepiadaceae family,used for traditional therapy and as a dietary supplement due to its numerous therapeutic benefits.The antidiabetic properties of gymnema were confirmed after the successful isolation and purification of the active ingredient gymnemic acid from the leaves(2). Thus, its important therapeutic effects includes diabetes mellitus treatment, arthritis, anemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, microbial infections, indigestion, and anti-inflammatory properties. Its extract is used in dietary supplements to reduce body weight, cholesterol, and triglyceride levels, offering high potential for modern dietary and pharmacological applications(1,3). Gymnemic acid, a key active component in *Gymnema sylvestre*, can suppress sweetness by blocking tongue sugar receptors, reducing sugar cravings(4). Various herbal preparations of *G. sylvestre* are currently used in nutritional supplements, beverages, tea bags, health tablets, confectionaries, etc(5).

B. Biological Source

Gymnema consist of leaves of perennial woody climberplant known as *Gymnema sylvestre* belongs to family Asclepiadaceae(6).

C. Geographical distribution

Gymnema sylvestre is widely distributed in many countries. It is native to East Africa, Saudi Arabia, Vietnam, Sri Lanka, South China, Japan, Philippines, Malaysia, Indonesia, Australia and in dry forests throughout India(7).In India, it is distributed in dry forests up to 600 m height. Also, it has been reported to found in tropical forests of central and western India(5).It is also present in Banda, Konkan, Western Ghats and Deccan, extending to the southern and northern regions of India(8).

D. Morphology

- Macroscopic characteristics :
- Colour : Green
- Odour : Pleasant and aromatic odour
- Taste : Tasteless(6)

E. Botanical description

G. sylvestre is a perennial, woody climber belonging to family Asclepiadaceaewhich is also called as the "milk weed" family.The genus has other 40 species, some important of which includes *G. sylvestre, G. montanum, G. yunnanense, and G. inodorum*have medicinal properties(9,10).The tree that grows in the dry forests of south-central India and other parts of Asia.It's shrub has young stems and branches(3). Stems are cylindrical, branched, hard, twining, with terete internodes. Leaves are ovate or elliptical, simple, acute or acuminate, 1to 2cm long, smooth above, rounded base, densely velvety beneath, and ciliate along margins, especially on nerves(1,3). Stems are 0.7-17 cm long, while leaves are 2.5-6 cm long(1). The plant has 1.3 cm long, flat seeds.Seeds are sown from November to December and harvested from September to February.The flowers are small, yellow, and cymes in axillary and lateral umbels(11).The follicles are round and lance-shaped up to 3 inches long. The sepals are long, ovate, blunt, and pubescent. The corolla is pale yellow and bell-shaped, with one corolla and five fleshy scales. Scales grow between the leaves on the neck of the corolla tube(8). Flowering occurs

from August to March. Propagation is difficult due to seed viability, so root or terminal cuttings are used(3).

F. Taxonomical classification

Table 1: Taxonomy of *Gymnema sylvestre*

Kingdom	**Plantae**
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Gentianales
Family	Apocynaceae
Sub-family	Asclepiadaceae
Genus	*Gymnema*
Species	*sylvestre R. Br*.

G. Chemical composition

Researchers have been reported that the bioactive components present in plant were found to be mixture of phytomolecules including gymnemic acids, gymnemosides, gurmarin, gymnema saponins, gymnemanol,*β*-amyrinrelated glycosides, anthraquinones, flavones, lupeol, stigmasterol(12,13).

Table 2: Chemical Composition

Sr. No.	**Chemical constituent**	**Activity**	**Reference**
1.	Gymnemic acid I,II,III,IV	Anti-sweet, glucose uptake inhibition	(14,15)
	Gymnemic acid V,VI	Anti-sweet	(16)
	Gymnemic acid VII,VIII,IX	Anti-sweet absent	(14)
	Gymnemic acid X,XI,XII,XIII	Anti-sweet	(17)
	Gymnemic acid XIV,XV,XVI,XVII,XVIII	Anti-sweet	(18)
2.	Gymnemic acid A1,A2,A3,A4 (Gymnemagenin/3β,16β,21β,22α,23,28-hexahydroxyolean-12-ene)	Anti-diabetic, Anti-viral	(1,19)
3.	Gymnemanol/3β,16β,22α,23,28-pentahydroxyolean-12-en	Glucose uptake inhibition	(20)
4.	Gymnemoside I,II,III,IV,V,VI,VII	Biolarvicidal	(21)
5.	Gurmarin	Sugar suppression	(1,22)
6.	Gymnemasin A,B,C,D	Glucose uptake inhibition	(23)
7.	Gymnemasaponin I,II,III,IV,V	Biolarvicidal	(20,21)
8.	Gymnestrogenin/3β,16β,21β,23,28-Pentahydroxyolean-12-ene	Anti-inflammatory	(20,24)
9.	Gymnemagenol	Cytotoxic, anti-cancer	(20)

Table 3: Essential oils present in leaves are

Sr.No.	**Chemical constituent**	**Activity**	**Reference**
1.	1,8-Cineole,Octanol, β-Elemene, Acetophenone, Germacrene A, p-Guaiacol, Dodecanol, Eugenol, m-Ethyl phenol, Tetradecanol, Pentadecanol, Tetracosane, Pentacosane, 8,11,14-Ecosatrienoic acid, Methyl-11,14-eicosadienoate, Pentadecanoic acid	Anti-oxidant, anti-microbial	(25)
2.	Phytol, Pentacosane, 10-Heneicosene (c, t), 3-Eicosene, (E) -and 2-Methyl-Z-2-docosane.	Anti-microbial	(26)
3.	Gymnemagenol 3β, 16β, 28, 29-tetrahydroxyolean- 12-ene	Biolarvicidal	(27)

Table 4: Bark and Stem

Sr.No.	**Chemical constituent**	**Glycation protein inhibition Activity**	**Reference**
1.	3-O-β- D-glucuronopyranosyl-3β, 16β, 22α, 28β-tetrahydroxy-olean-12-ene 28-O-α-L-rhamnopyranoside	Less potent	(28)
2.	22α-hydroxy-longispinogenin3-O-β-D-glu- curonopyranosyl-28-O-α-L-rhamnopynoside	Less potent	(28)
3.	conduritol A	Less potent	(29)
4.	stigmasterol	More potent	(30,31)
5.	lupeol	More potent	(32)
6.	stigmasterol-3-O-β-D-glucoside	More potent	(33)

7.	22α-hydroxy-longispinogenin-3-O-β-D- glucopyranosyl-(1→3)-β-D-glucuronopyranosyl-28-O-α-L- rhamnopyranoside	Less potent	(34)
8.	oleanolic acid-3-O-β-D- glucopyranosyl-(1→6)-β-D-glucopyranoside	Less potent	(35,36)

Table 5: Roots

Sr. No.	Chemical constituent	Activity	Reference
1.	Gymnemic acid A and B	Antimicrobial	(37)
2.	Gymnemagenin	Anti-diabetic, anti-obesity, anti-viral	(37)

H. Mechanism of action of Gymnemic Acid

Gymnemic acid is the main component of gymnema and is a mixture of at least 17 saponins(38).Gymnemic acids have been proven to have anti-diabetic, anti-lipidemic, and anti-inflammatory activities.Phytochemical constituents decreases the absorption of glucose into the blood(13). The gymnemic acid molecule has been found to have same atomic arrangement as that of the glucose molecule(5). Gymnemic acids therefore fill the receptors in the taste buds and prevent the activation of sugar molecules present in the food we consume. In addition, the acid fills the receptors in the absorptive outer layer of the intestine,preventing the intestine from absorbing glucose. This results in lowering the blood sugar level(23). Additionally, this acid has been shown to stimulate the pancreas to produce insulin. Insulin is necessary for blood sugar control and treatment of adult-onset diabetes(39).The acid also increases the excretion of cholesterol in the stool and can have laxative, antitussive, and diuretic effects. Gymnemic acids have been shown to interfere with the tongue's taste buds' ability to perceive sweet and bitter tastes. Researchers believe that the acid's ability to inhibit sweet taste means that it also inhibits glucose absorption. However, reserarcher's have not proven this yet(40).

There are several possible mechanisms by which the leaves and especially the oleanane type triterpene saponins i.e gymnemic acids of *G. sylvestre* exert their hypoglycemic effects:

- By increasing insulin secretion
- By promoting regeneration of islet cells
- By increasing glucose utilization: It has been shown to increase the activity of enzymes responsible for glucose utilization through the insulin-dependent pathway,increase phosphorylase activity, decrease gluconeogenic enzymes and sorbitol dehydrogenase and
- It also inhibits the absorption of glucose from the intestine. It's exact effects are unknown, this may involve one or more mechanisms(41).

II. PHARMACOLOGICAL ACTIVITIES

A. Anti-diabetic activity

The studies have concluded that there are number of pathways by which *G. sylvestre* exerts its anti-diabetic effect. Some of these effects may be similar to that produced by the oral hypoglycemic drugs, while some may be unique(42). According to experimental studies various constituents in the *G. sylvestre* are responsible for decreasing the glucose uptake from small intestine(43). Experimental studies, for instance, have also demonstrated progress in synthesis of glycogen, gluconeogenesis, glycolysis, glucose uptake and reversal of plasma protein and hemoglobinglycosylation(44). *G. sylvestre* may also stimulate insulin release from the islets of Langerhans in pancrease and thereby enhancing glycemic control(45). Gymnema extract have inhibitory effects on the activity of α-amylase (enzyme involved in the hydrolysis of glucosides to glucose) which confirms its antidiabetic potential(46,47). G. sylvestre produces proteins which forms complex after interaction with dipeptidyl peptidase. Thus, inhibits the activity of dipeptidyl peptidase enzyme which regulates activities of glucose-dependent insulinotropic polypeptide(48,49).

B. Anti-sweet activity

G. sylvestre shows its action on sweet receptors which results in modulation of taste.Also, the herbal extracts have been reported for suppressing the neural responses to a mixture of disodium inosine monophosphate and monosodium glutamate, and sucrose(43). It has been reveal that the bioactive constituent gymnemic acid can block perception for sweet taste completely(50). A temporary suppression has been seen towards the sensitivity to sweet and bitter substances after chewing leaves of gymnema for about 1-2 min(51). This suppression response has found to be selective towards different sweeteners including fructose, saccharin, sucrose and cyclamate. The sweet taste caused by water after citric acid is what drives 50% of this action(52). The presence of ester group in gymnemic acid may be responsible for exhibiting anti-sweet activity. Eluting Gymnemic acid A1 with ethanol reduced the sweetness of cyclamate, d-amino acids, sucrose, sodium saccharin, BeCl2, and Pb(OAc)2. Also,sodium glutamate was transformed to a taste similar to that of sodiun chloride(53). The taste modifying protein present in gymnema called as 'Gurmarin' is the another bioactive constituent consisting 35 residual polypeptides. It gives action by acting on large superficial petrosal nerve which innervates palatal taste buds and suppresses the taste resopnse to sugars(54). Gurmarin contains hydrophobic groups that may act with receptor proteins and suppress the response to fructose, glucose and sucrose(55).

C. Anti-hyper lipidaemic Activity

The studies using all the extracts significantly showed improvements in fecal excretion of total bile acids, neutral steroids except CA-related bile acids which is correlated with gymnemageninfecal levels. This study was conducted by using rats to find out the function of gymnemic acids in steroidal fecal excretion(56). In another study which was

conducted for three weeks revealed a decrease in the ability of fat digestion and an increase in excretion of neutral and acidic sterols in rats administering leaves extract of gymnema. This study also showed a significant decrease in triglycerides and total serum cholesterol. After ten weeks, rats treated with leaves extract showed reduction in plasma triglycerides, but no significant difference seen in total plasma cholesterol levels(57). In addition, inhibition of oleic acid absorption due to gymnemic acid was observed in another study carried out by using intestinal perfusion method(58).Experimentally induced hyperlipidaemic rats when orally administered with leaves extract at a dosage of 25-100 mg/kg for about two weeks showed reduction in serum triglyceride (TG), total cholesterol (TC),low density lipoprotein (LDL), very low density lipoprotein (VLDL) in a dose dependent manner(59).

D. Anti-obese activity

The fecal excretion of steroids and cholesterol was found to be increased after administration of *G. sylvestre* leaves extract. Thus, weight gain ultimately controlled in the rats. The hexane extract of leaves when tested in Sprague dawley rats at dosage of 150 mg/kg and 250 mg/kg body weight showed significant reduction ($p<0.001$) in increased body weight. The parameters including appetite, total cholesterol, serum triglyceride, LDL, HDL, serotonin and leptin concentrations, fluctuations in body weight, body mass index and fat metabolites excretion were noted to analyse weight loss. As the extract supports weight loss and trims down sweet cravings, plays role in managing blood sugar concentrations(60). Another study on the anti-obesity effect of *Gymnema sylvestre* extract showed decrease in body weight gain as well as in hemodynamic parameters such as systolic, diastolic heart rate, mean blood pressure, organs and visceral fat pad weights. Hence, this study was useful as an initial evidence for revealing that obesity can be controlled by using water soluble fraction of *G. sylvestre* extract(12).

E. Anti-oxidant activity

The antioxidant activity of*G. sylvestre* extract was confirmed after inhibition of DPPH, scavenging of hydrogen peroxide, super oxide radical scavenging as well as determination of ferric reducing power which may be due to presence of four important secondary metabolites including flavonoids, tannins, phenols and triterpenoids. The leaves extract was analysed spectrophotometrically and total antioxidant capacity was found to be 17.54 mg/gm expressed as ascorbic acid(61). The bioactive constituents such as gymnemic acids, gymnemagenin and other triterpenoids are mainly antioxidants but also shows antidiabetic activity. So, based on the presence of these bio components it has been revealed that *G. sylvestre* is one of the important medicinal herb with antioxidants and antidiabetic potential(7). The plant also contains cinnamic acid, ascorbic acid, butyric acid and tartaric acid which may act as secondary major antioxidants(62).

F. Immunomodulatory Activity

Methanolic leaf extract of *G. sylvestre* is known for its immunomodulatory activities and it is an important plant of indigenous system of Indian medicine. A wide range of biological and therapeutic activities, including immunomodulatory activity are due to the phytochemicals present in gymnema(63). A significant decrease in the primary and secondary antibody titer as well as inhibition in increase of CD3 and CD19 lymphocytes and cytokines, IL-2, IL-4 was supported in one study. These results conclude that methanolic leaf extract of *G. sylvestre* shows significant immunosuppresive activity(64).

G. Antimicrobial activity

The gymnemic acids A and B are known for its antiviral activity. The maximum activity was observed against influenza virus at the concentration of 75 mg/kg body weight after andministringGymnemic acid A followed by Gymnemic acid B. But, the fractions containing other constituents lack this actions(65). Moreover, both the crude and pure saponins fractions were also analysed for antimicrobial activity. Highest activity was noted for pure extract than crude extract when compared with the activity of chloramphenicol(66). The methanolic and crude ethanolic extracts of leaves showed significant antimicrobial activity against *B. subtilis, B. pumilis, S. aureus, P. aeruginosa.* But, strongest antimicrobial activity was found due to methanolic extract. When the chloroform extracts of aerial and root parts were compared with that of the diethyl ether and acetone extracts, more activity was observed due to chloroform extracts(67,68).

H. Anti-inflammatory activity

G. sylvestre has been widely applicable as liver tonic, bitter, acrid, digestive, thermogenic and anti-inflammatory in the Ayurvedic system of medicine. The phytochemicals of tannins and saponinscategory(gymnestrogenin) are known for anti-inflammatory activity. When the aqueous extract of leaves was investigated for its anti-inflammatory activity, a significant decrease observed in paw oedema volume at concentration of300 mg/kg. A reduction in granuloma was determined at a concentration of 200 mg/kg and 300 mg/kg. This experimental study was demonstrated in rats using two methods such as carrageenan induced paw oedema and cotton pellet induced granuloma(41).

I. Anti-cancer and Cytotoxic Activity

The bioactive constituent gymnemagenol has been found to possess an anticancer activity when studied in vitro on HeLa cancer cell lines(69). The MTT cell proliferation assay was conducted for saponins. In this assay different concentrations of gymnemagenol including 5,15,25 and 50 μg/mL were taken and incubation of plates done for 48 hours. At the concentration of 37 μg/mL IC50 value was observed and after 96 hours, the cytotoxic activity improved at a concentration of 50 μg/mL. Thus, the proliferation of HeLa cancer cell line found to be inhibited. But, further inhibition was not observed under these in vitro conditions(70).

Table 6: Marketed Formulations

Gymnema sylvestre ;Supplement 500 mg 60 Veg capsules **INLIFE** 	*Gymnema sylvestre* ;Regulates glucose Herbal capsules 500 mg ;60 veg capsules  **RIFFWAY INTERNATIONAL**
Gymnema sylvestre; Food supplement 500 mg 120 tablets  **MERLION NATURALS**	*Gymnemasylvestre* 1X; Each 550 mg 50 Tablets  **BAKSON'S HOMOEOPATHY**
Cinnamon, Fenugreek and *Gymnema sylvestre* Blood sugar support;Herbal supplement 200 mg 120 capsules  **SWANSON**	*Gymnema sylvestre* ;Mother Tincture 30 ml Regulate blood sugar levels  **BAKSON'S HOMOEOPATHY**

III. CONCLUSION

G. sylvestre can be widely applicable in pharmaceutical as well as in dietary or health supplements due to its bioactive phytochemicals. Gymnemic acid is one of the important constituent which is responsible for anti-diabetic, anti-sweet, anti-hyperlipidaemic activities. As large number of people from developing countries rely on herbal remedies for treatment of various diseases, *G.sylvestre* may become an effective medicinal herb. The pharmacological activity of plant is completely dependent on the type of existing phytochemical. For example, dammarene saponins gives anti-sweet as well as anti-diabetic effect, sterols reduces cholesterol, anthraquinones exert anti-inflammatory effect, gurmarin having sweet suppressing activity. Furthermore, in future study, the isolated constituents gymnemagenol and gurmarin, needs to be evaluated in scientific manner, so that its potent pharmacological or therapeutic benefit can be widely explored. Also, we can conclude from various literature reviews that more research on gymnema must require to find out other active phytochemicals with exact mechanism of action for anti-diabetic and anti-sweet effects.

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