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Role of *Gymnema sylvestre* as Alternative Medicine

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Abstract

Context: *Gymnema sylvestre* R.Br, belonging to the family Asclepiadaceae, has been employed to control diabetes, obesity, atherosclerosis etc., by traditional medicinal practitioners of India for nearly two millennia. The active principals from the leaf extracts is assumed to be gymnemic acid and its derivatives which are of triterpenoids in chemical nature have the ability to renew the islet cell mass for the possible cure of diabetes.

Objective: The present review deals with botanical description, chemical constituents, and pharmacological effect of the plant using herbal and homeopathic medicine from the past to recent developments.

Methods: Scientific databases including SCOPUS, PUBMED, SCIELO, NISCAIR, and Google Scholar were used to retrieve articles and only relevant studies published in English were considered.

Results: This paper gives an overview of *G. sylvestre* from antiquity to till date. There is sufficient evidence of pharmacological and phytochemical studies to draw a definite conclusion about the efficacy of the gymnemic acid for the treatment of diabetes and obesity but, there is still inadequate literature related to other activities. The reported studies on the effect of *G. sylvestre* as homeopathic medicine are not sufficient. Therefore further studies are needed to explore the role of *G. sylvestre* in homeopathy.

Conclusion: There is still a dire need to explore the mechanism of action of *G. sylvestre*, toxicity profile and to determine its role as alternative medicine.

Keywords: Gymnema sylvestre, Diabetes, Homeopathy, Ayurveda

Introduction

The use of plants as medicine is as old as human civilization. Renewed interest of developing as well as developed countries in the natural resources has opened new horizons for the exploration of natural sources with the perspectives of safety and efficacy. Herbal drugs, in India are also used as household remedy for common ailments since time immemorial. The plant *Gymnema sylvestre* R. Br. (Asclepiadaceae) is a vine which grows in the southern part of China, including the Guangdong, Guangxi and Fujian provinces. *G. sylvestre* occurs mainly in the Deccan peninsula of western India, Tropical Africa, Vietnam, Malaysia, and Srilanka and is widely available in Japan, Germany and the USA as a health food [1]. The plant extracts are also used in folk, Ayurvedic and Homeopathic systems of medicine [2]. *G. sylvestre* is a traditional medicinal plant, with reported use as a remedy for diabetes mellitus, stomachic and diuretic problems.

Traditionally its use has been indicated in adenopathy, cough [3], asthma, biliousness, bronchosis, cardiopathy, conjunctivosis, cornea, diabetes, dysuria, fever, furunculosis, glycosuria, hemorrhoid, inflammation, leukoderma, opacities, ophthalmia, and worm [4]. The roots of Gymnema sylvestre has also been used in snake bite [5]; boil, constipation, and water retention [6]; epilepsy, pain [7]; high cholesterol, IDDM, NIDDM and obesity [8]. The extract of *G. sylvestre* plays a major role in blood glucose homeostasis through increased serum insulin level and regeneration of the endocrine pancreas [9]. Within the last 10 years, a number of Gymnema products including Gymnema capsules, Gymnema tea, Bioshape®, Diaxinol®, Body Slatto Tea®, Gymnema®, Gymnema Diet®, Sugar Off®, Glucoset™, Cinndrome X™ , and Pilisoft™ have appeared on the world market [10].

The principle of Homoeopathy has been known since the time of Hippocrates from Greece, the founder of medicine, around 450 B.C. Homoeopathy as it is practiced today was evolved by the German physician, Dr. Samuel Hahnemann (1755–1843). The word 'Homoeopathy' is derived from two Greek words, 'Homois' meaning similar and 'pathos' meaning suffering. Homoeopathy simply means treating diseases with remedies, which are capable of producing symptoms similar to the disease when taken by healthy people [11].

In *Gymnema* species a number of phytochemical constituents have been reported by several authors. Its constituents include two resins, gymnemic acids, saponins, stigmasterol, quercitol and the amino acid derivative of betaine, choline and trim ethylamine, but its main active compound is gymnemic acid, saponins and oleanane type of triterpenoid [12]. *G. sylvestre* contains oleanane type triterpene (Gymnemagenin) and gymnemic acid which itself is not pure entity, but composed of 4 components, A_1 - A_4, with gymnemic acid A_1 as the predominant one [13]. Gymnemagenin and gymnestogenin were isolated and crystallized by Stocklin in 1968, who reported the isolation of a new compound gymnemic acid A_1, which could be converted to gymnemic acid A_2 [14], but gymnemic acid A-D were reported in different forms [15]. Yoshikawa and co-workers [16,17] isolated gymnemic acids from the hot water extract of *G. sylvestre* dry leaves, which they named gymnemic acids I, II, III, IV, V, VI and VII (compound 1-7) respectively (Figure 1). In contrast, the next series of anti-sweet compounds, Gymnema saponins I, II, III, IV, and V were isolated from *G. sylvestre* [18]. Further work carried out in *G. sylvestre* led to isolate and characterization of other gymnemic acids VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII and XVIII (Compound 8-18, Figure 1) [19-22].

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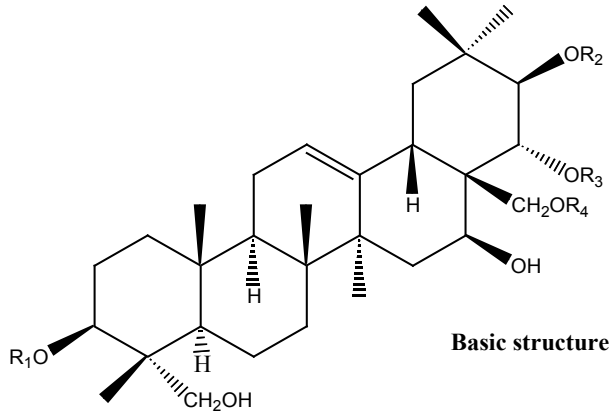
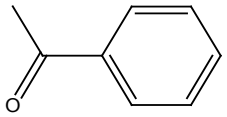
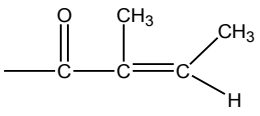


Basic structure of Gymnemic acids

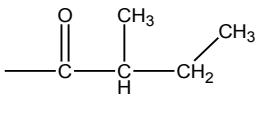
Compound	R_1	R_2	R_3	R_4
1	Gluconic acid	Tigloyl	H	Acetyl
2	Gluconic acid	2-methyl butyloyl	H	Acetyl
3	Gluconic acid	2-methyl butyloyl	H	H
4	Gluconic acid	Tigloyl	H	H
5	Gluconic acid	Tigloyl	Tigloyl	H
6	Gluonicacid-3-glucose	Tigloyl	H	H
7	H	H	H	H
8	Gluonicacid-3-(2-oxo-glucose)	2-methyl butyloyl	H	H
9	Gluonicacid-3-(2-oxo-glucose)	Tigloyl	H	H
10	Gluconic acid	H	H	H
11	Gluconic acid	Tigloyl	H	Tigloyl
12	Gluonicacid-3-glucose	Tigloyl	H	H
13	Gluconic acid	H	H	2-methyl butyloyl
14	Gluconic acid	H	H	Tigloyl
15	H	2-methyl butyloyl	Tigloyl	H
16	Tigloyl	H	H	H
17	H	Benzyl	H	H
18	H	H	H	Benzyl



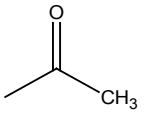
Benzyl group



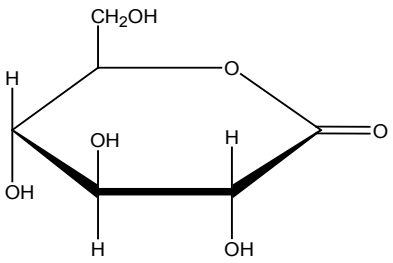
Tigloyl



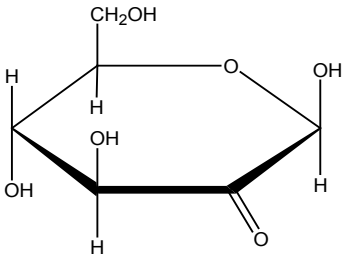
2-methyl butyloyl



Acetyl group



Gluconic acid



2-oxo glucose

Figure 1: Structures of Gymnemic acid I-XVIII (1-18).

Ye et al. [1] isolated six new oleanane saponins along with two known oleonolic acids (Figure 2), 28-*O*- β-D-glucopyranosyl ester and oleanolic acid 3-*O*- β-D-glucopyranosyl (1→6) - β-D -glucopyranoside. New Oleanane saponins were characterized as longispinogenin 3-O-β-D-glucuronopyranoside (19), 21β- benzoylsitakisogenin 3-O-β-D-glucuronopyranoside (20), 3-O-β-D-glucopyranosyl[1→6]-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester (21), 3-O-β-D-xylopyranosyl[1→6]-β-D-glucopyranosyl[1→6]-β-D-glucopyranoside (22), 3-O-β-D- xylopyranosyl [1→6]-β-D-glucopyranosyl[1→6]-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester (23) and 3-O-β-D-glucopyranosyl[1→6]-β-D-glucopyranosyl oleanolic acid 28-β-D-glucopyranosyl[1→6]-β-D-glucopyranosyl ester(24). Ye et al. [23] further isolated new saponins which were identified as 21-β-O-benzoylsitakisogenin 3-O-beta-D-glucopyranosyl(1→3)- β -D-glucuronopyranoside (25), the potassium salt of longispinogenin 3-O- β -D-glucopyranosyl (1→3)- β -D-gluc-

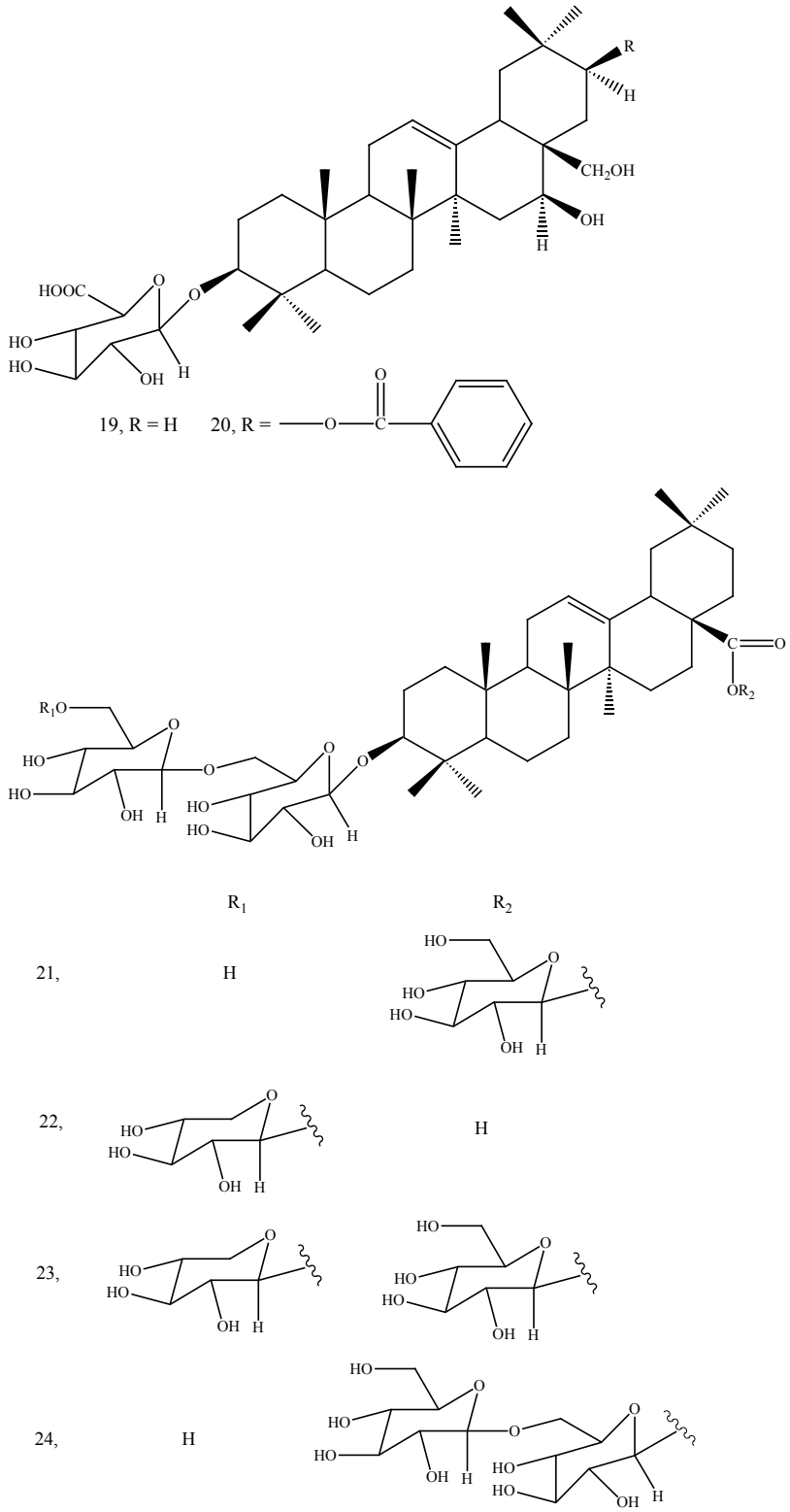
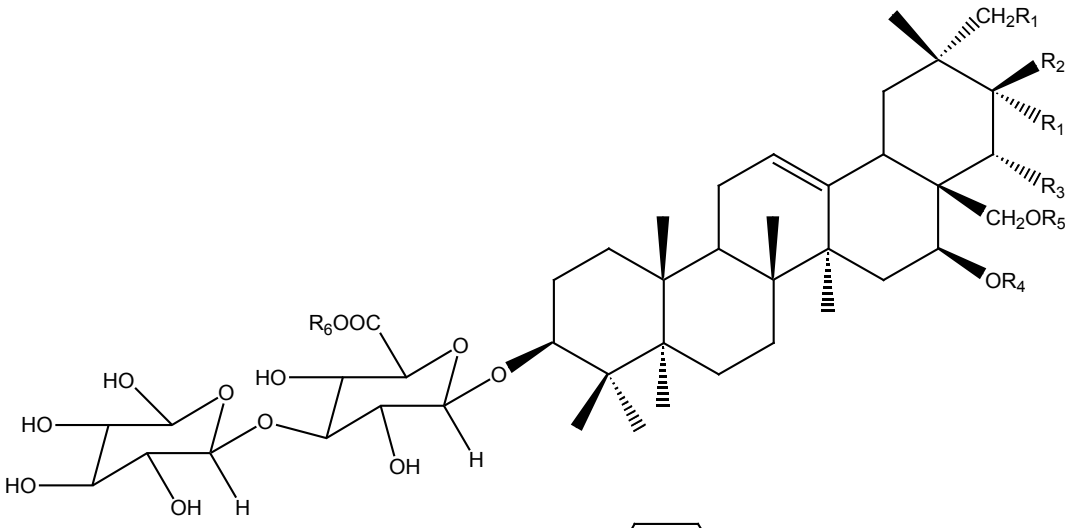


Figure 2: Structures of Oleanane saponins 19-24.

uronopyranoside (26) and its aglycon gymnemagenol, was characterized as 3 β,16 β,28, 29-tetrahydroxyolean-12-ene (27) (Figure 3) were isolated from an ethanol extract of the leaves of *G. sylvestre* [23]. Two new oleanane-type triterpenoid saponins (Figure 4), gymnemoside-W_1 (28) and W_2 (29) [24] and the flavonoid triglyceride (Figure 5), kaempferol 3-O-β-D-glucopyranosyl-(1→4)-alpha-L-rhamnopyranosyl-(1→6)-β-D-galactopyranoside (30) were also isolated from *G. sylvestre* [25]. Oleanane type triterpenoid saponin (Figure 5), dihydroxy gymne-



25. $R_1 = R_3 = R_4 = R_5 = R_6 = H$; $R_2 = O$ —CO—

26. $R_1 = R_2 = R_3 = R_4 = R_5 = H$; $R_6 = K+$

27. $R_1 = OH$; $R_2 = R_3 = R_4 = R_5 = H$; $R_6 = K^+$

Figure 3: Structures of saponins 25-27.

mic triacetate (31) was derived from the acetone extract of *G. sylvestre* [26]. Liu et al. [27] isolated a new triterpenoid saponin, the sodium salt of 22α-hydroxyl-longispinogenin 3-*O*-β-D-glucuronopyranosyl-28-*O*-α-L-rhamnop yranoside.

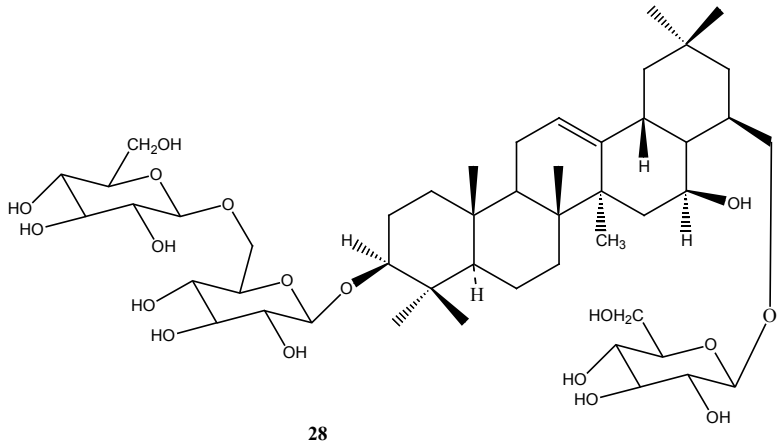
Keeping in view extensive traditional uses of *G. sylvestre* a comprehensive search of the literature was conducted to identify the best available evidence on *G. sylvestre*. Scientific databases including SCOPUS, PUBMED, SCIELO, NISCAIR, and Google Scholar were used to retrieve articles and only relevant studies published in English were considered. The search included (i) the reported animal studies on the pharmacological effect of *G. sylvestre* (ii) randomized clinical trials on *G. sylvestre* using herbal and homeopathic preparations.

Role of *Gymnema sylvestre* in ayurveda supported by experimental and clinical studies

Plants and plant-derived products are part of health care system since ancient human civilizations. The need of new chemical entities for health care is explored and served through the plant sources. Evolution of Ayurveda and plant-based remedies for health care through day-to-day life experiences is a part of cultural heritage of India. The World Health Organization (WHO) estimates that about 80% of the population living in the developing countries relies on traditional medicine for their primary health care needs [28]. In almost all the traditional systems of medicine, the medicinal plants play a major role and constitute their backbone. Indian Materia Medica includes about 2000 drugs of natural origin almost all of which are derived from different traditional systems and folklore practices [29]. *G. sylvestre* have numerous pharmacological activities reported by several authors and many experiments were carried out on *G. sylvestre* (Figure 6).

Antidiabetic activity: *G. sylvestre* can be useful in certain cases of non-insulin dependent diabetes as it reduces serum glucose concentration and improves glucose tolerance [30]. Administration of leaf extract of *G. sylvestre* (120 mg/kg/ day *p.o.*) for 7 days in STZ induced rats reduced amylase activity in serum, increased β-cell function, regenerated β-cells in pancreatic islets and showed higher levels of serum C-peptide [31]. The beneficial effect was observed in oral treatment to cure Non-Insulin Dependent Diabetes Mellitus (NIDDM) to use the 400 mg/kg of leaf extract, where there is a significant reduction of blood glucose, glycosylated hemoglobin and plasma protein and increase in serum insulin levels Shanmugasundaram et al. [31]. In another study on patients with type 2 diabetes, *G. sylvestre* leaf extract at a dose of 400 mg/day was administered for 18-20 months as a supplement to the conventional oral drugs, regenerated β-cells and raised insulin level in serum of the patients [31]. Chattopadhyay [32] explained that the possible mechanism behind the antihyperglycemic effect of *G. sylvestre* leaf extract is its potential to enhance insulin secretion. The *G. sylvestre* alcoholic extract also stimulates insulin secretion from rat islets of Langerhans and several pancreatic β-cells lines [33].

Sugihara et al. [34] investigated Gymnemic acid IV and observed that it increased plasma insulin levels which contributed to the antihyperglycemic effect by the leaves of *G. sylvestre*. Om Santal Adivasi (OSA*), a high molecular weight fraction isolated from *G. sylvestre* leaf extract, reversibly stimulates insulin secretion from isolated human islets and its insulin secretagogue effects in MIN6 cells and human islets were partially dependent on the presence of extracellular Ca^{2+}. These data indicate that low concentrations of the *G. sylvestre* isolate OSA stimulate insulin secretion *in vitro*, at least in part as a consequence



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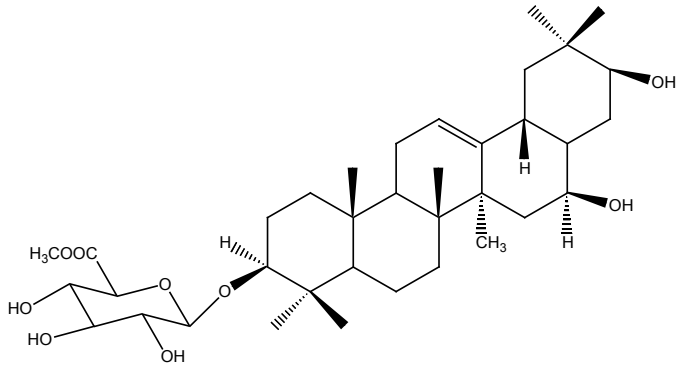

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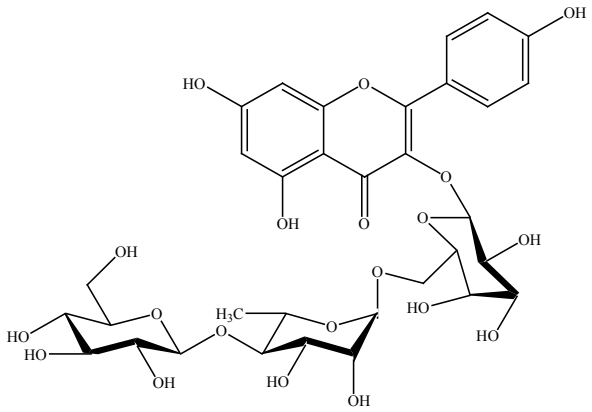
Figure 4: Structure of Oleanane type triterpenoid saponins 28 and 29.



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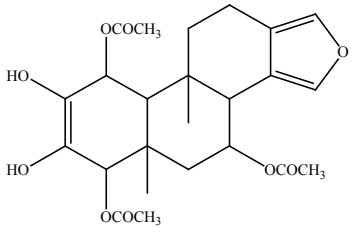

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Figure 5: Structure of compound 30 and 31.

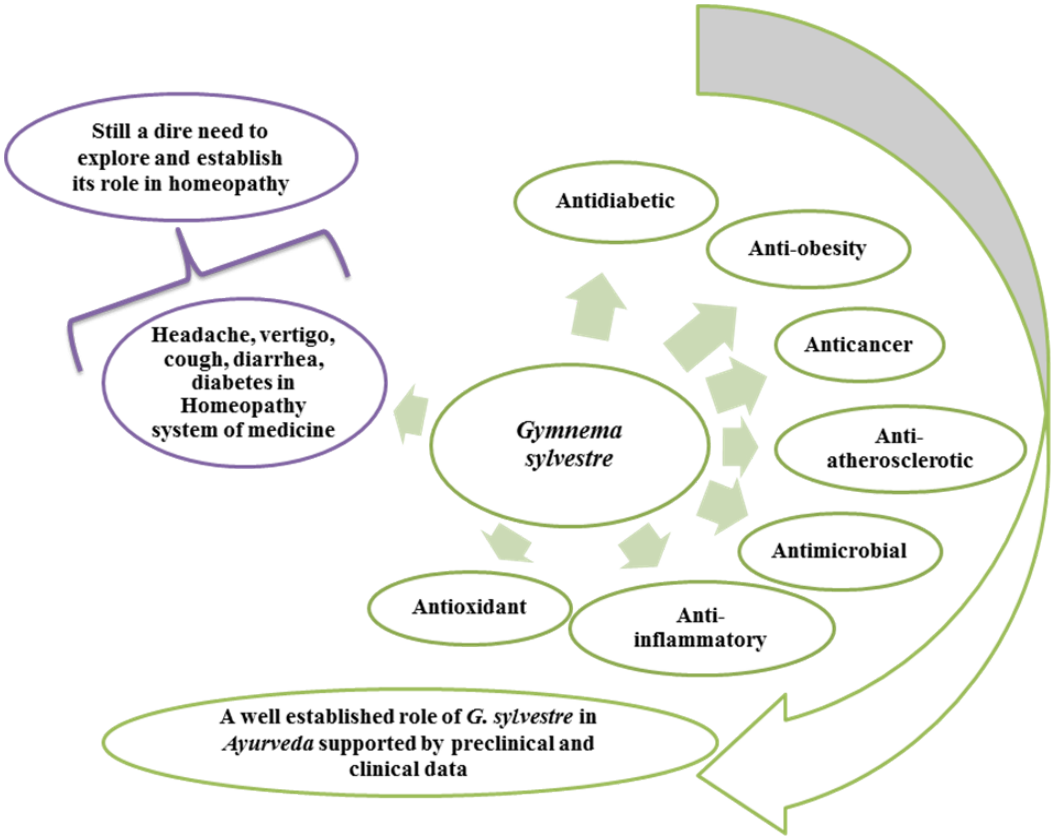

Figure 6: Role of *Gymnema sylvestre* in alternative medicine.

of Ca^{2+} influx, without compromising β-cell viability [35,36]. OSA® is effective in reducing blood glucose and increasing plasma insulin and C-peptide levels in humans. *In vitro* studies suggest that at least some of these effects of OSA® can be attributed to a direct stimulatory effect on insulin secretion from β-cells in the islets of Langerhans [37,38].

An active compound dihydroxy gymnemic triacetate has been isolated from *G. sylvestre* acetone extract. Dihydroxy gymnemic triacetate (20 mg/kg body weight) was orally administered for 45 days to streptozotocin diabetic rats for the assessment of plasma glucose, insulin, glycated hemoglobin (HbA1c), and tissue glycogen and lipid parameters. It produced significant effects on all biochemical parameters studied, indicating that dihydroxy gymnemic triacetate possessed hypoglycemic and hypolipidemic activity in long-term treatment and hence it could be used as a drug for treating diabetes [26]. An open label study was conducted on the supplementation of *G. sylvestre* in type 2 diabetic patients for a period of 3 months. Supplementation of the diet with *G. sylvestre* reduced polyphagia, fatigue, blood glucose (fasting and post-prandial), and glycated hemoglobin and there was a favorable shift in lipid profiles and in other clinico-biochemical tests suggesting a beneficial effect of *G. sylvestre* in the management of diabetes mellitus [39]. The gymnemic acid of leaf and callus extracts significantly increases the regeneration of β-cells in treated rats, when compared with the standard diabetic rats. It could have potential as a pharmaceutical drug for insulin-dependent diabetes mellitus (IDDM). Feeding *G. sylvestre* leaf extract to the diabetic rats decreased the activity of glutathione peroxidase in cytosolic liver and glutamate pyruvate transaminase in serum to normal levels, reducing oxidative stress in diabetic rats [40]. Deacyl gymnemic acid isolated from *G. sylvestre* produces a significant decrease in insulin resistance accompanied with a decrease in systolic blood pressure and improves glucose and lipid profile without decreasing body weight in a rat model of metabolic syndrome [41]. *G. sylvestre* significantly increase plasma active GLP-1 levels, thus producing hypoglycemic effect *via* DPP-IV inhibition [42]. Saponins, 3-*O*-β-D-glucuronopyranosyl-21-*O*-2-tigloyl-22-*O*-2-tigloyl Gymnemagenin and 3-*O*-β-D-glucuronopyranosyl-21-*O*-2-methylbutyryl-22-*O*-2-tigloyl Gymnemagenin, isolated from *G. sylvestre* inhibited sodium-dependent glucose transporter 1 (SGLT1) thereby acting as potential antidiabetic agents by inhibiting glucose uptake from gastrointestinal tract [43].

Hypolipidemic and atherosclerotic activity

Obesity plays a central role in the insulin resistance syndrome, which is associated with hyperinsulinemia, hypertension, hyperlipidemia, type 2 diabetes mellitus, and an increased risk of atherosclerotic cardiovascular disease. Obesity is the main consequence from the accumulation of the carbohydrates and fats. A randomized, double-blind, placebo-controlled human study was conducted in Elluru, India for 8 weeks in 60 moderately obese subjects (ages 21-50, BMI >26 kg/m (2)). *G. sylvestre* extract along with (-)-hydroxycitric acid and niacin-bound chromium serve as an effective and safe weight-loss formula by facilitating reduction in excess body weight and body mass index [44]. Gymnemic acids curb the binding of carbohydrates to the receptors in the intestine and hence, the “empty calories” are taken care of so that the body does not go into obese stage. Gymnemic acids are also useful in curbing of diabetes by a similar mechanism [45]. Assessment of effect of *G. sylvestre* extract in the high fat diet-induced cellular obesity demonstrated that it causes significant reversal of increased body

mass index, organ weights and visceral fat pad weight. The possible mechanism for an anti-obesity effect of *G. sylvestre* extract may be via suppression of levels of leptin, insulin, dyslipidemia, apolipoproteins, lipids, visceral fat pad weights, and oxidative stress in obese rats fed with high fat diet [46]. Saponin-rich fraction of *G. sylvestre* aqueous leaf extract possess anti-obese action as it significantly decreases the body weight, food consumption, visceral organs weight, and the levels of triglycerides, total cholesterol, low-density lipoproteins, very low-density lipoproteins, atherogenic index, glucose, and increases the levels of high-density lipoproteins [47]. The anti-obesity effect of water soluble fraction of *G. sylvestre* extract (120 mg/kg, p.o. for 21 days) in high fat diet fed rats. It reduces body weight gain, food intake, serum lipids, leptin, insulin, glucose, apolipoproteins A_1 and B, lactate dehydrogenase levels and increases HDL and antioxidant enzymes level. Study concluded that *G. sylvestre* extract possess anti-obesity effect [48]. Bishayee and Chatterjee studied hypolipidemic and atherosclerotic effects of *G. sylvestre* leaf extract and observed that at a dose of 25-100 mg/kg *G. sylvestre* leaf extract reduced lipid level and increased serum HDL and antiatherogenic index [49].

Antimicrobial activity

The ethanolic extract of *Gymnema sylvestre* leaves demonstrated antimicrobial activity against *Bacillus pumilis*, *B. subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and inactive against *Proteus vulgaris* and *Escherichia coli* providing justification for the use of the plant in folk medicine to treat various infection disorders [50]. *Candida albicans* is an opportunistic and polymorphic fungal pathogen that causes mucosal, disseminated and invasive infections in humans. The triterpenoid saponin family of gymnemic acids is inhibitor of *C. albicans* morphogenesis. Purified gymnemic acids had no effect on the growth and viability of *C. albicans* yeast cells but inhibited its yeast-to-hypha conversion under several hypha-inducing conditions, including the presence of serum [51]. *G. sylvestre* possess larvicidal activity against the Japanese Encephalitis vector, *Culex tritaeniorynchus* and thus can be used as an important component in the Vector control Programme [52].

Anticancer activity

Ethanolic extract of Gymnema sylvestre leaves have significant anticancer effect on A375 cells. It induces nuclear DNA fragmentation and shows an increase level of mRNA expression of apoptotic signal related genes cytochrome c, caspase 3, PARP, Bax, and reduces expression level of ICAD, EGFR, and the anti-apoptotic gene Bcl_2 indicating the possibility of its palliative use in cancer patients [53].

Anti-inflammatory activity

The aqueous extract of *G. sylvestre* leaves was investigated for evaluation of anti-inflammatory activity in rats at a dose 200, 300 and 500 mg/kg in carrageenan-induced paw oedema and cotton pellet method. The aqueous extract at the dose of 200 mg/kg and 300 mg/kg produced significant reduction in granuloma weight, when compared to control group.

Antioxidant activity

In vitro, the inhibitory effects of DPPH radicals and LDL oxidation were found with aqueous extract of *G. sylvestre*. *G. sylvestre* require 32.1 µl, for scavenging 50% of the DPPH radicals [54].

Role of *Gymnema sylvestre* in Homeopathy

In homoeopathy, a drug obtained from the leaves and roots of *G. sylvestre* is prescribed for both diabetes mellitus and insipid us. A multi-centric, double-blind, randomized homeopathic pathogenetic trial was conducted on *G. sylvestre*. The drug was proved in two potencies (6C and 30C) on 63 apparently healthy volunteers who were selected after conducting pre-trial medical examination by the medical specialists and routine laboratory investigations. In the first phase volunteers were given 56 doses (4 doses per day for 14 days) of placebo. In the next two phases 56 doses (4 doses per day for 14 days) of each potency or placebo were consumed. This drug seems to be useful in clinical conditions such as headache, vertigo, common cold, cough, diarrhea, etc. Further, work is necessary to find out the real value of the drug in diabetes (Figure 6) [55,56].

Conclusion

Ayurveda practice continues today to treat human diseases and provides positive health benefits to the people. Considering the widespread use and popularity of Ayurveda, proper standardization and validation method are being developed for promoting Ayurvedic drugs. *G. sylvestre* is a multipurpose potential medicinal plant having high market potential all over the world. In case of herbal medicinal plants, there is sufficient evidence of pharmacological and phytochemical studies to draw a definite conclusion about the efficacy of the *G. sylvestre* for the treatment of diabetes and obesity, though there is still inadequate literature related to other activities. But, the reported studies on the effect of *G. sylvestre* as homeopathic medicine are not sufficient. The use of *G. sylvestre* mentioned in homeopathic system of medicine should be explored in the form of preclinical and clinical data for various ailments, with the modern scientific approaches for better leads in the health care. Furthermore, in future study, the isolated principals from *G. sylvestre* needs to be evaluated in scientific manner using various innovative experimental models and clinical trials for better understanding of its mechanism of action, so that its therapeutic uses can be widely explored as alternative medicine.

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