Bioactive principles of *Gymnema sylvestre* R.Br. From yesterday’s tradition to tomorrow’s drug

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**Abstract**

Periploca of woods (*Gymnema sylvestre* R. Br.) of the family Asclepiadaceae commonly known as “Miracle-fruit” is one of the most important medicinal plants of the central ecoregion. It is popularly known as Gurmar, which means “sugar killer” or “destroyer of sugar”. It grows in the tropical forests of India and has been used for more than 2,000 years in traditional systems of medicine to treat madhumeha or “honey urine.” Ethanolic extract of leaves is reported to have tannins, gum, flavonoids, proteins, saponins and also a minute amount of fixed oil. The principal constituent, gymnemic acid, is found in the gymnema saponins from aqueous leaf extract. Various parts of the plant are used in the treatment of skin problems, bronchitis, fungal infections, eye-disease, cancer, diabetes and urinogenital infection. The plant also has digestive, diuretic, emetic, expectorant, laxative, stimulant and stomachic properties. The presence of large number of triterpenoidal saponins, flavonoids, staroids and phenolic compounds are responsible for variety of activity of gymnema. This review is an attempt to highlight its various ethnobotanical and traditional uses with mechanistic approach of pharmacological reports in relation to phytochemistry.

**Key words:** *Gymnema sylvestre* R.Br., phytochemicals, pharmacological uses, medicinal plant, ethnomedicine

1. Introduction

Medicinal plants are the backbone of traditional medicine. An estimate of WHO demonstrates that about 80% of the population in developing countries relies on traditional medicine for primary healthcare because of its minimal side effects and the high cost of modern medicine (Sharma et al., 2008). There is, therefore, a need to screen medicinal plants for bioactive compounds as a basis for further pharmacological studies. *G. sylvestre* is widely distributed in India, Malaysia, Sri Lanka, Australia, Indonesia, Japan, Vietnam, Tropical Africa and the South western region of the people’s of republic of China (Bone, 2002; Sanjelyn et al., 2010; Stocklin, 1969; Shah, 2010). It is a woody vine like climbing plant that grows in the tropical forest of central and southern India. It came to be known as "destroyer of sugar" because in ancient times, Ayurvedic physicians observed that chewing its few leaves would suppress the taste of sugar (Shah, 2010; Yeh et al., 2003). In Hindi, the word “Gurmar” indicates that it might neutralize the excess of sugar in the body (Keshwamurthy and Yoganarasimhan, 1992). Leaves of *G. sylvestre* are commonly used in indigenous systems of medicine to control diabetes mellitus (Gymnema, 2000; Manohar et al., 2009; Trivedi and Pandarikakshdu, 2008). Using the *G. sylvestre* leaves for preparing tea can impair one’s ability to taste sugar by blocking sweet receptors on the tongue (Schroeder and Schroeder, 2005). In addition, it possesses antimicrobial, antihypercholesterolemic (Bishayee and Chatterjee, 1994), sweet suppressing (Kurihara, 1992) and hepatoprotective (Rana and A vadhoot, 1992) activities. It also acts as a feeding deterrent to caterpillar, Prodenia eridania (Granich et al., 1974), prevents dental caries caused by Streptococcus mutans (Hiji, 1990) and is used in skin cosmetics (Komalvalli and Rao, 2000). It is also used in the treatment of asthma, eye complaints, inflammations and snake bite (Kini and Gowda, 1982; Kini and Gowda, 1982), and also for treating dysentery in the north coastal areas of Andhra Pradesh, India (Pragada et al., 2012).

**Figure 1:** Herb of *Gymnema sylvestre* R.Br.

**Source:** Herbal garden of Jamia Hamdard University
In India, it is known as Periploca of the woods (English); Gurmar (Hindi); Gurmar booti (Urdu); Meshashringi, Madhumashini (Sanskrit); Kavali, Kalikardori (Marathi); Dhueti, Mardashingi (Gujarathi); Adigam, Cherukurinja (Tamil); Podapatri (Telgu); and Sannagracehambu (Kannada) (Saneja et al., 2010; Kanetkar et al., 2006; Paliwal et al., 2009; Rachh et al., 2010; Potawale et al., 2008; Arunakumara et al., 2005; Sastri, 1956).

Gymnema has a long history of use in India’s Ayurvedic and Homeopathic systems of medicine. Indians first used gymnema to treat diabetes almost 2,000 years ago (Nadkarni, 1992; Vandana et al., 2013). The word Gymnema is probably derived from the Greek words “gymnos” means “naked” and “nema” means “thread” and the word sylvestre means “of the forest” in Latin (Gymnema, 2011). This plant was first noticed by Edgeworth (1847) and the property of its leaves with reference to sweetness of sugar was tested carefully by Hooper in 1887. Excellent botanical description is available in Kirtikar and Basu (1998), Duke et al. (1997) and Reichenberg-Ullman (1996). There are 348 genera with about 2,900 species in the family Asclepiadaceae. Gymnema includes about 119 species, about 25 of them from tropical or subtropical Asia, South Africa, and Oceania. The botanical synonyms of G. sylvestre are Asclepias geminata Roxb., Periploca sylvestris Retz. (1781), Marsdenia sylvestris Retz., Gymnema affine Decaisne, Gymnema formosana Warburg, and Gymnema alternifolium (Lour) Merr (Pullaiah, 2006). Distributional range is given in Figure 2.

Figure 2: Geographical representation of Gymnema sylvestre R.Br., distribution through out world

2. Phytochemistry of G. sylvestre

The leaves of G. sylvestre contain triterpenoidal saponins belonging to oleanane and dammarene classes. Oleanane saponins are gymnemic acids and gymnemasaponins, while dammarene saponins are gymmemasides (Khramov et al., 2008; Yoshikawa et al., 1992). Twenty different saponins and glycosides have been reported in G. sylvestre (Trivedi and Pundarikakshudu, 2008). Some important saponins are gymnemic acid, deacyl gymnemic acid, gymmemagenin and gymmestogenin (Manohar et al., 2009). The gymnemic acids contain several acylated (tiglyl, methylbutyroyl, etc.) derivatives of deacylgymnemic acid (DAGA), which is a 3-O-ß-glucouronide of gymmemagenin (3ß, 16ß, 21ß, 22α, 23, 28-hexahydroxy-olean-12-ene) (Zarrelli et al., 2013a; Zarrelli et al., 2013b). The individual gymnemic acids (saponins) include gymnemic acids I-VII, gymmemosides A-F, and gymema saponins. The presence of gymnemic acids, (+) querctitol, lupeol, (-) amyrin, stigma sterol, etc. and some flavonol glycoside, namely; kaempferol 3-O-beta-D-glucopyranosyl-(1-4) - alpha- L-rhamnopyranosyl-(1-6)-beta-D-galactopyranoside, has also been reported in aerial parts of G. sylvestre (Hong et al., 1992; Sugihara et al., 2000). Several phytoconstituents have been isolated, and their chemistry and structures studied and elucidated (Sinsheimer et al., 1970; Qu et al., 2013; Sinsheimer and Subbarao, 1971; Liu et al., 2004). Table 1 presents their list along with their molecular structures and biological activities.
Table 1: Phytoconstituents and phytochemical structures with their pharmacological actions in *G. sylvestre* R.Br.

<table>
<thead>
<tr>
<th>Phytoconstituents</th>
<th>Classification</th>
<th>Molecular structure (References)</th>
<th>Pharmacological activity (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triterpene Saponins</td>
<td>Gymnemic acids-acylated (tigloyl, methylbutyroyl) deacylgynmmenic acid (DAGA) which is a 3-0-b-glucouronida of gymnemagenin (3b, 16b, 21b, 22a, 23, 28-Hexahydroxyolean-12-ene)</td>
<td><img src="image1" alt="Molecular structure" /></td>
<td>Antidiabetic, Antiobesity, Hypolipidemic, Antiviral, Leishmanicidal-activity (Tiwari et al., 2014; Srikanth et al., 2010; Sinsheimer and Manni, 1965; Maeda et al., 1989; Preuss et al., 2004; Sinsheimer et al., 1968; Sinsheimer et al., 1971)</td>
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<td>Oleanane Saponins</td>
<td>Gymnemic acid and gymnemasaponins</td>
<td><img src="image2" alt="Molecular structure" /></td>
<td>Antihyperglycemic (Masayuki et al., 1997)</td>
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<td><img src="image3" alt="Molecular structure" /></td>
<td>Leishmanicidal-activity (Tiwari et al., 2014; Srikanth et al., 2010)</td>
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<td><img src="image4" alt="Molecular structure" /></td>
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<td><img src="image6" alt="Molecular structure" /></td>
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<tr>
<td>Dammarene Saponins</td>
<td>Gymnemosides B</td>
<td><img src="image7" alt="Molecular structure" /></td>
<td>Antidiabetic (Vaidya, 2011)</td>
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<td>Dammarane</td>
<td>Saponins</td>
<td>Gymnemosides C</td>
<td>Gymnemoside C (Masayuki et al., 1997)</td>
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<td>Gymnemosides D</td>
<td>Gymnemoside D (Masayuki et al., 1997)</td>
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<tr>
<th>Gymnemosides E</th>
<th>Gymnemoside E (Masayuki et al., 1997)</th>
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<td>Antidiabetic (Vaidya, 2011)</td>
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<tr>
<th>Gurmarin</th>
<th>Gymnemosides F</th>
<th>Gymnemoside F</th>
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<tbody>
<tr>
<td>A novel 35-amino acid peptide With a 4209 molecular weight</td>
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<tr>
<td>Antidiabetic, Inhibition of palatal taste response (Murata et al., 2003; Harada and Kasahara, 2000; Miyasaka and Imoto, 1995)</td>
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<tr>
<th>Triterpenoid Saponins Gymnemasins A</th>
<th>Gymnemasins B</th>
<th>Gymnemasins C</th>
<th>Gymnemasins D</th>
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<tbody>
<tr>
<td>3-O-[β-D-glucopyranosyl (1-3)-β-D-glucopyranosyl]-22-O-tigloyl gymnemanol</td>
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<tr>
<td>3-O-[β-D-glucopyranosyl (1-3)-β-D-glucuronopyranosyl]-gymnemanol</td>
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<tr>
<td>3-O-β-D-glucuronopyranosyl-22-O-tigloyl gymnemanol</td>
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<td>3-O-β-D-glucopyranosyl-gymnemanol</td>
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<td>Antidiabetic (Liu et al., 1992; Yew et al., 2001; Guclustundag and Mazza, 2007)</td>
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<td>(Sahu et al., 1996)</td>
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<tr>
<td>Compound</td>
<td>Structure</td>
<td>Function/Compliance</td>
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<tr>
<td>Gymnemanol (aglycone)</td>
<td><img src="image" alt="Gymnemanol" /></td>
<td>Anticancer, Antifilaricidal, Antiviral, Antiparasitic (Khanna and Kannabiran, 2009; Khanna et al., 2011a; Srividya et al., 2010).</td>
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<tr>
<td>Gymmestrogenin</td>
<td><img src="image" alt="Gymmestrogenin" /></td>
<td>Antidiabetic (Saneja et al., 2010; Rao and Sinsheimer, 1971)</td>
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<tr>
<td>Flavonol glycoside</td>
<td><img src="image" alt="Flavonol glycoside" /></td>
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<tr>
<td>Sterols</td>
<td><img src="image" alt="Sterols" /></td>
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### 3. Mechanism of action of gymnemic acid and terpenoids

Gymnemic acid, major active constituent (Krishna, 2012) believed to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. These molecules fill the receptor locations on the taste buds, thereby preventing their activation by sugar molecules present in the food. Similarly, gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine, thereby preventing the sugar molecules absorption by the intestine, which results in low blood-sugar level (Sahu et al., 1996). Several studies suggest that gymnemic acids act as antidiabetic, and exhibit pharmacological actions; they promote regeneration of islet cells, increase insulin secretion (Kanetkar et al., 2004), inhibit glucose absorption, increase utilization of glucose by increasing the activities of enzymes in insulin-dependent pathways, increase phosphorylase activity and decrease the activity of gluconeogenic enzymes and sorbitol dehydrogenase (Saneja et al., 2010; Kanetkar et al., 2007; Shanmugasundaram et al., 1990; Baskaran et al., 1990). Gymnemic acids also inhibit sodium-dependent glucose transporter (Wang et al., 2014).

The gymnemic acid components are believed to block the absorption of glucose in the small intestine, the exact action being unknown. It could involve one or more mechanisms (Nakamura et al., 1999). A possible mechanism is depicted in Figure 3.
Figure 3: Possible mechanism of *G. sylvestre* in diabetes mellitus

Other pharmacological activities of *G. sylvestre* include increase in fecal excretion of cholesterol (Persaud *et al*., 1999). It overcomes diabetes mellitus (Agarwal *et al*., 2000) and is useful against obesity (Yoshikawa *et al*., 1993).

The water-soluble acidic fraction of leaves has been noted for lowering serum cholesterol and triglycerides. The primary chemical constituents include gymnemic acid, tartaric acid, gurmarin, calcium oxalate, glucose, stigmasterol, betaine, and choline. Some researchers have suggested gymnemic acid as one possible candidate, for lowering serum cholesterol, although further research is needed (Khare *et al*., 1983). The major constituent of the plant gymnemic acid is a complex mixture of at least nine closely related acidic glucosides (Sinsheimer and Subbarao, 1971; Iwashita and Kurihara, 1989; Manni and Sinsheimer, 1965). The basic function of the acid is to bind to the receptor on the intestine, and stop the glucose molecule from binding to the receptor. Thus, gymnemic acids prevent the absorption of excess glucose. Various extracts of *G. sylvestre* have been reported for hypoglycemic effect, which are listed in Table 2.

Table 2: Chemical compounds present in different extracts of *Gymnema sylvestre* with animal and clinical studies

<table>
<thead>
<tr>
<th><em>G. sylvestre</em> extracts</th>
<th>Chemical compounds References</th>
<th>Model used</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous</td>
<td>Alkaloids, anthraquinones, flavonoids, glycosides, phenols, phytosterols, proteins, resins, saponins tannins, triterpenoid (Selvi <em>et al</em>., 2007; Yadav <em>et al</em>., 2010; Patil <em>et al</em>., 2012; Thangavelu <em>et al</em>., 2012; Sudhanshu <em>et al</em>., 2012; Murugan <em>et al</em>., 2012; Ghana Sangeetha and Jegadeesan, 2012; Gopinath <em>et al</em>., 2012; Najafi and Deokule, 2011)</td>
<td>OLETF and LETO rats</td>
<td>↓ Body weight ↓ Serum TC,TG</td>
<td>Luo <em>et al</em>., 2007</td>
</tr>
<tr>
<td></td>
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<td>Wistar rats</td>
<td>↓ Body weight, organ weight ↓ Plasma TC, TG, VLDL, LDL-C</td>
<td>Reddy <em>et al</em>., 2011</td>
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<td></td>
<td></td>
<td>Mouse MIN 6 β-cells and Human Islets</td>
<td>↑ Insulin release</td>
<td>Liu <em>et al</em>., 2009</td>
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<tr>
<td>Treatment</td>
<td>Animals/Species</td>
<td>Changes</td>
<td>Reference</td>
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<tr>
<td>Methanol</td>
<td>Alkaloids, Anthraquinones, flavonoids, phenols, saponin, steroids, tannins, triterpenes, terpenoides, (Yadav et al., 2010; Sudhanshu et al., 2012; Murugan et al., 2012; Devi and Ramasubramaniaraja, 2010)</td>
<td>▼ Body mass index, ▼ Serum TC, TG, LDL, VLDL cholesterol, ▼ Serum leptin, insulin, glucose, LDH, apo-B, ▼ Gpx, GR, GST, SOD, catalase, ▼ Perirenal, mesenteric and epididymal fat mass</td>
<td>Kumar et al., 2012</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swiss albino mice</td>
<td>▼ SOD, CAT, GSH, LPO, ▼ Blood glucose, ▼ Serum parameters</td>
<td>Sharma and Kar, 2014</td>
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<tr>
<td></td>
<td>Wistar rats and ddY mice</td>
<td>▼ Blood glucose levels, ▼ Plasma insulin, ▼ Glucose uptake</td>
<td>Sugihara et al., 2000</td>
<td></td>
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<tr>
<td></td>
<td>Wistar rats</td>
<td>▼ Plasma glucose, ▼ Serum TC, VLDL, LDL, ▼ Serum HDL</td>
<td>Ahmad et al., 2008</td>
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<tr>
<td></td>
<td></td>
<td>▼ Blood glucose levels, ▼ Blood glucose levels, ▼ Serum insulin, ▼ Total lipid levels</td>
<td>Yogalakshami et al., 2014</td>
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<tr>
<td></td>
<td></td>
<td>▼ Body liver and pancreas weights, ▼ Plasma glucose, ▼ Serum TC, VLDL, LDL, ▼ Pancreatic granules of β-cells</td>
<td>Ahmad et al., 2010</td>
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<tr>
<td>Chloroform</td>
<td>Alkaloids, flavonoids phenols, saponin, steroids, tannins, terpenoides, triterpenes, (Yadav et al., 2010; Sudhanshu et al., 2012; Devi and Ramasubramaniaraja, 2010; Sukesh et al., 2011)</td>
<td>▼ ▼ ▼</td>
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<tr>
<td>Petroleum ether</td>
<td>Flavonoides, phenols, saponins, steroids, tannins, terpenoides, triterpenes, (Yadav et al., 2010; Sudhanshu et al., 2012; Murugan et al., 2012)</td>
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<tr>
<td>GYM 250 extract</td>
<td>Humans</td>
<td>▼ Body weight, BMI, ▼ Serum leptin levels, ▼ Serum TG, VLDL, LDL, ▼ Urinary MDA, ACT, FA, ACON</td>
<td>Preuss et al., 2004</td>
<td></td>
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<tr>
<td>OSA capsule</td>
<td>Humans and pancreatic islets</td>
<td>▼ Fasting blood glucose, ▼ Postprandial blood glucose, ▼ Serum insulin, C-peptide</td>
<td>Al-Romanian et al., 2010</td>
<td></td>
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<tr>
<td></td>
<td>Ob/ob mice and ICR mice</td>
<td>▼ Blood glucose, ▼ Preproinsulin expression and insulin secretion</td>
<td>Al-Romanian et al., 2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mouse and human islets</td>
<td>▼ Insulin secretion, ▼ Protein kinase activity, ▼ cAMP levels</td>
<td>Al-Romanian et al., 2012</td>
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</table>
4. Pharmacological activities

*G. sylvestre* is listed in the Indian Pharmaceutical Codex and is popular in Indian systems of traditional medicine, such as Siddha, Unani and Ayurveda. Various triterpenoids from *G. sylvestre*, with their different pharmacological actions, makes it a wonderful drug of choice for ensuring a healthy life (Triveni et al., 2013; DiFabio et al., 2013; DiFabio et al., 2014; DiFabio et al., 2015). *G. sylvestre*, a rich source with gymnemic acid, is an important antidiabetic medicinal plant (Sabitha Rani et al., 2012; Thakur et al., 2012; Singh et al., 2008), also shows antithiogenic activity (Sree Lakshmi et al., 2014) and ameliorative effect (Kumar et al., 2013). Biological activities depend on extraction types of *G. sylvestre*. Depending upon the presence of phytoconstituent present in different types of extract, the therapeutic use of the drug changes accordingly. The complete pharmacological profile of the drug is described here with respect to type of extract.

4.1 Aqueous extract

Numerous in vivo studies have confirmed its hypoglycemic effect of the aqueous extract (Doli et al., 2013; Pandey and Vijayakumar, 2013; El-Shafey et al., 2013; Bhansali et al., 2013; Bhatt et al., 2001; Srivastava et al., 1985). It has shown a drastic reversal of alloxan-induced toxicity in rats (Mall et al., 2009). GS3 and GS4 obtained from the aqueous extract have doubled the number of islet and beta cells in STZ treated rats. These compounds tend to attain blood glucose homeostasis by increasing serum-insulin levels through repair/ regeneration of the endocrine pancreas (Shamugasundaram et al., 1990). GS4 has shown significant results in patients with Type 2 diabetics. The raised insulin levels in the serum of the patients indicate that beta cells may have regenerated/ repaired (Baskaran et al., 1990). The aqueous *G. sylvestre* extract could increase the survival time of diabetic rats. It has reduced hyperglycemia in moderately diabetic rats and the effect of the drug persisted for a more than two months period after its discontinuation (Luo et al., 2001). The saponins-rich aqueous extract has shown antiobesity and anticancer effect (Rama et al., 2011; Arunachalam et al., 2014) and also exhibited wound-healing properties (Omale James and Ajidahun Bidemi, 2014). The aqueous extract was investigated for anti-inflammatory activity in rats, using the carrageenan-induced paw oedema and the cotton pellet method (Malik et al., 2007; Tayler, 1993; Smolinski and Pestka, 2003). It was significantly effective in controlling *Culex* larvae (Tandon and Sirohi, 2010) and potential larvicidal activity against the larvae of *A. subpictus* and *C. quinquefasciatus* (Khanna et al., 2011b). It has shown a moderate activity against three pathogenic *Salmonella* species, viz., *S. typhi*, *S. typhimurium* and *S. paratyphi* (Chand et al., 2008). The aqueous extracts of leaves have demonstrated to possess antiallergic activity (Arun et al., 2014), and potential to stabilize mast cells by antagonizing the milk-induced eosinophilia (Chen et al., 2012). The muscle-relaxant activity of aqueous extract of *G. sylvestre* may due to action of nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) (Luo, 1999).

4.2 Alcoholic extract

The alcoholic *G. sylvestre* extract is a potent anticancer agent on A549 (Human lung adenocarcinoma epithelial cell line) (Giardi et al., 1972), and MCF7 (Human breast carcinoma) cell lines (Soule et al., 1973). The alcoholic gymnemagenin and deacetyl gymnemic acid have shown significant and good cytotoxic activity, compared to standard drug etoposide, and its cytotoxic activity is proportional to the dosage (Srikant et al., 2011). Additionally, the alcoholic extract inhibits intestinal breast cancer resistance protein (BCRP) (Tamaki et al., 2010). Its wound-healing and antioxidant activities have been observed in rats (Malik et al., 2009; Singh and Deo, 2014).

4.3 Hydroalcoholic extract

The hydroalcoholic extracts of *G. sylvestre* leaves exhibit significant wound healing activity in rats (Alam et al., 2011). The increased wound-healing activity may due to free-radical-scavenging action and the presence of flavonoids, as detected by TLC and phytochemical analysis (Bhatt, 2001). Anthelmintic activity (Srinath Reddy et al., 2013), and activity against gram positive bacteria, viz: *B. subtilis*, *S. aureus* are also on record (Saumendu et al., 2010). The hepatoprotective effect of hydroalcoholic extract has also been evaluated (Srividya et al., 2010).

4.4 Methanolic extract

The methanolic extract of *G. sylvestre* has shown antiparasitic activity against the CQ-resistant INDO strain of *Plasmodium falciparum*. (Kamaraj et al., 2012). It has shown antimicrobial activity against *C. albicans*, *E. coli*, *P. aeruginosa*, *S. aureus* and *S. epidermis* (Kiran and Khatak, 2014), and leishmanicidal activity with an IC_{50} value, and reduced the parasitic population (Khanna et al., 2009).

4.5 Ethanolic extract

Ethanol extracts of gymnema leaves have exhibited antitumour activity in an *in vivo* two-stage carcinogenesis test in mice (Yasukawa et al., 2014). The extract showed a good antimicrobial activity against *B. pumilis*, *B. subtilis*, *P. aeruginosa* and *S. aureus* and no activity was found against *P. vulgaris* and *E. coli* (Sadive et al., 2003). Ethanolic extract is known for its antioxidant activities (Rahman et al., 2014) and significant anticancer effect on A375 cells (Chakraborty et al., 2013). It has provided protection against acetic acid-induced ulcerative colitis in rats (Aleisa et al., 2014).

5. Uses

5.1 Traditional uses

In Unani and Siddha systems of medicine, gymnema leaves are used as an ingredient of different antidiabetic formulations (Anonymous, 1997). It is a component of the Ayurvedic medicinal compound, “ Tribang shila,” a mixture of tin, lead, zinc, compound, “Tribang shila,” a mixture of tin, lead, zinc, and jambul seeds (Azadirachta indica A. Juss.), *Enicostemma littorale*, and jambul seeds (Syzygium cumini (L.) Skeels. Traditional healers observed that chewing the leaves of gymnema resulted in a reversible loss of sweet-taste perception. Susruta describes *G. sylvestre*, as a destroyer of madhumeha (glycosuria) and used it in several urinary disorders (Nadkarni, 1986). It is also reported to be used as a bitter, astringent, acid, thermogenic, anti-inflammatory, anodyne, digestive, liver tonic, emetic, diuretic, stomachic, stimulant, anthelmintic, laxative, cardiotoxic, expectorant, antipyretic and uterine tonic. It is useful in dyspepsia, dysentery, constipation and jaundice, haemorrhoids, renal and vesicle calculi, cardiopathy, asthma, bronchitis, amenorrhoea, conjunctivitis and leucoderma (Nadkarni, 1993; Vaidyaratnam, 1995; Chopra et al., 1992). The drug is also used in various ayurvedic preparations like Ayaskri, Varunadi kasaya, Varunadighrtam and Mahakalyanakaghrtam (Joy and Thomas, 1998).
5.2 Ethnobotanical and medicinal uses

There are over four hundred different tribal and other ethnic groups in India, each having its own tradition, folk language, beliefs and knowledge about the use of natural resources as medicines. In Sri Lanka, the plant is utilized to cure bone fractures and gastric ulcer (Arun et al., 2014). Paste of leaves is applied with mother milk to treat mouth ulcer. *G. sylvestre* preparations possess antiallergic activity (Porczezhian and Dobriyal, 2003; Wechsler, 2007; Brekhman and Dardymov, 1969). Snakebite is treated by dusting the wound with powdered root, or applying a paste of the root powder to the wound (Russell, 1980). The potassium salt of gymnemic acid, which is a triterpenoid glycoside isolated from *G. sylvestre*, inhibits ATPase in *Naja naja* venom and *Vipera russelli* venom (Kini and Gowda, 1982a; Kini and Gowda, 1982b; Brekhman and Dardymov, 1969; Hichi, 1988). The leaves are given in gastric troubles in Rajasthan. Traditional healers of Maharashtra prescribe the plant in urinary problems, whereas in Madhya Pradesh, it is used in stomachache. In Andhra Pradesh, it is used in glossocoria. In eastern Africa, pounded leaves are rubbed onto scarring in the side to treat stitch. In Tanzania, pounded cooked roots in food are taken to treat epilepsy. In Angola, leaf and stem preparations are taken to treat cancer. In Botswana, pounded cooked roots or root powder are applied externally to treat boils. In Madagascar, infusion of leafy twigs is taken to treat gonorrhea (Kritikar and Basu, 1998; Ekka and Dixit, 2007; Anonymous, 1996). The drug actually reduces cravings for sugar by blocking sugar receptors in the tongue; this effect lasts for about two hours (Lemon et al., 2003).

6. Dosage and administration

The most common doses of *G. sylvestre* used for blood sugar control are 400 mg to 600 mg per day. Standardization of herbal products is not required by the U.S. Food and Drug Administration (FDA), so not every product may contain the same amounts of active ingredients. Typically, clinical studies investigating antidiabetic effects have used 200 or 400 mg of an extract standardized to contain 25% gymnemic acids, to administer twice daily (Rachh et al., 2009).

In liquid form (extract), 25 to 75 mL per week, and in tablet form; 8 to 12 g of leaf equivalent per day may be consumed. Information regarding safety and efficacy during pregnancy and lactation periods is lacking (Joffe and Freed, 2001).

7. Combination with other plant drugs

A combination of *G. sylvestre*, *P. marsupium* and *Syzygium cumini* with dipeptidyl peptidase-4 has been found to be useful in the treatment of diabetes (Kosaraju et al., 2014). Another combination of *G. sylvestre*, *N. sativa*, *S. cumini* and *A. paniculata* has shown anti-diabetic effect (Rastogi et al., 2014). *G. sylvestre* can be taken along with *Trigonella foenum-graecum* (fenugreek), *Galega officinalis* (goat’s rue) and the *Azadirachta indica* (neem) leaves for treatment of diabetes. In the case of hypercholesterolaemia, *G. sylvestre* is recommended with *Curcuma longa* (turmeric), *Silybum marianum*, *Cynara scolymus* (globe artichoke) and *Allium sativum* (garlic) (Bone, 2007). A combination of *G. sylvestre*, *Acacia catechu* and *Pterocarpus marsupium* significantly elevated serum insulin levels in an animal model (Wadood et al., 2007). An apolipid formula, Diakyr, containing *G. sylvestre*, *Cassia auriculata*, *Mucuna pruriens*, *Terminalia arjuna*, and crude powder of *Cassia javanica*, demonstrated significant hypoglycaemic activity and antilipidperoxidative effect (Joshi et al., 2007). Diabegon, another polyherbal formula containing 18 plant extracts, including *G. sylvestre*, *Momordica charantia*, *Swertia chirata*, *Trigonella foenum-graecum*, *Plumbago zeylanica*, *Syzygium cumini*, *Aegle marmelos*, *Terminalia chebula*, *Terminalia bellerica*, *Emblica officinalis*, *Curcuma longa*, *Pterocarpus marsupium*, *Berberis aristata*, *Cytisus calocynthis*, *Cyperus rotundus*, *Piper longum*, root of *Piper longum*, *Zingiber officinale*, and *Asphaltum punjabinum* improved insulin resistance and dyslipidaemia in rats (Yadav et al., 2007). Dianex, a polyherbal formulation consisting of the aqueous extracts of 8 drugs, including *G. sylvestre*, *Syzygium cumini*, *Momordica charantia*, *Azadirachta indica*, *Cassia auriculata*, *Aegle marmelos*, *Withania somnifera* and *Curcuma longa*, produced significant hypoglycemic activity in both normal and streptozotocin-induced diabetic mice (Mutalik et al., 2005).

8. Side effects and toxicity

Theoretically, gastric irritation can occur, because of the saponin content. There are two case reports of hepatotoxicity resulting from the consumption of a weight-loss formula containing gymnema and other herbs, including *Garcinia cambogia*, willow bark, glucocmannan, green tea and guarana (Stevens et al., 2005). In one study, gymnema showed a toxic effect in mice, producing increased lipid peroxidation at doses of 26.8 mg/kg, but was safe and antiperoxidative at doses of 13.4 mg/kg (Gholap and Kar, 2005). Another study concluded that there was no toxic effect in rats treated with gymnema at doses of more than 500 mg/kg for 52 weeks (Ogawa et al., 2004).

Short-term uses of low doses of *G. sylvestre* may have unnoticeable side effects (Dodson et al., 2001). Extremely high doses have the potential to induce hypoglycemia (abnormally low blood sugar levels), symptoms of weakness, confusion, fatigue, shakiness, excessive sweating and loss control of muscles may appear (Schmid and Hofheinz, 1983). *G. sylvestre*, when taken in empty stomach, may cause gastrointestinal distress including abdominal cramping, nausea and vomiting. Studies on spontaneously hypersensitive rats (SHR) consuming *G. sylvestre* has shown neither decrease nor increase in the systolic blood pressure (Khramov et al., 2008). One of the major side effects or actions of *G. sylvestre* is taste alteration (Brala and Hagen, 1983; Lawless, 1979; Meiselman and Halpern, 1970a; Meiselman and Halpern, 1970b; Min and Sakamoto, 1998; Warren et al., 1969). No toxicological reactions were reported in a long-term study of insulin-dependent diabetic patients. A 52-weeks study in wistar rats did not show any toxic effects as, none of the animals died during this period (Ogawa et al., 2004). *G. sylvestre* has been reported to cause toxic hepatitis or Drug-Induced Liver Injury (DILI) in patients treated with this drug for diabetes mellitus (Shiyovich et al., 2010). A study with D-400, having *G. sylvestre* as one of its major components, has shown no adverse effects on rats, which exhibits lack of teratogenicity of the extract (Muralidhar et al., 1993). It might show side effects if taken with herbs such as *Aloe vera* and *Harpagophyllum* (Devil’s Claw) (Luo and Shen, 1987). It is better for people taking prescribed drugs or being allergic to plants of the family Asclepiadaceae to avoid use of *G. sylvestre*. Or else, they should take accurate doses with proper medical supervision (Mukaiyama et al., 1999).
9. Contraindications and interactions

- One must be cautious about the use of *G. sylvestre* for diabetic patients using hypoglycemic medications, due to possible potentiation of effects. Serum glucose levels should be monitored, and doses of concomitant hypoglycemic drugs may require adjustment under the supervision of a healthcare professional. Hypoglycemia may also occur in non-diabetic patients (Khare, 1983; Nicolau et al., 1995).

- *G. sylvestre* extract has been used in combination with other weight-loss agents (acarbose, hydroxycitric acid and NBC), although the mechanism of action is unclear (Preuss et al., 2005; Luo et al., 2001).

- Reductions in levels of serum triglycerides, total cholesterol, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) have been observed in animals following administration of *G. sylvestre* (Terasawa et al., 1994).

- *G. sylvestre* may interact with the blood-sugar-control drugs such as glipizide, minodiab and glyburide (Cane, 1990).

- *G. sylvestre* may lower blood cholesterol levels (Shanmugasundaram et al., 1990).

- Absorption of oleic acid (a fatty acid) may be decreased by *G. sylvestre* (Wang et al., 1998).

- *G. sylvestre* may have additive effects with herbs and supplements that help with weight loss. It may interact with chromium, fat-soluble vitamins, and garcinia (Preuss et al., 2005).

10. In vitro cultivation of *G. sylvestre*

The plant cell and tissue culture has been successfully exploited for micropropagation of several important medicinal plants, including *G. sylvestre* (Pandey, 2012; Devi et al., 2006). Linolenic acid as an elicitor for gymnemic acid production in *G. sylvestre* and hairy root cultures has been reported (Praveen et al., 2014; Praveet al., 2013); much work has done on establishing the reliable protocols for plant regeneration and large-scale multiplication *in vitro* (Nan and Wtpsk, 2013). Cultured plant cells and tissues are widely recognized as promising alternatives for the production of valuable secondary metabolites (Sabir et al., 2011; Sabir et al., 2012; Rao and Ravishankar, 2002). Various techniques have been employed for shoot regeneration from mature nodal explants of *G. sylvestre* through *in vitro* multiplication (Reddy et al., 1998; Reddy et al., 2004) and for a large-scale production of gymnemic acids in plant cell suspension cultures (Chodissetti et al., 2014). Somatic embryogenesis was optimized and whole-plant regeneration achieved in callus cultures derived from hypocotyl, cotyledon, and leaf explants excised from seedlings of *G. sylvestre* (Ashokkumar et al., 2002). In another study, extraction, detection and quantification of gymnemic acid through gynemagenin from different callus cultures was reported (Kanetkar et al., 2006). The large-scale production of gymnemic acids under *in vitro* conditions, *via* mediation of fungal elicitors has been reported. The use of bioelicitors, such as *Aspergillus niger* cell extract significantly enhanced the production of secondary metabolite, namely; gymnemic acids from suspension culture. The technique is a potential means for establishment of large-scale production of gymnemic acids (Dev and Srinivasan, 2011; Chodissetti et al., 2012; Chodissetti et al., 2013; Veerashee et al., 2012).

11. Conclusion

Today, several herbal medicines are available in developing countries as an alternative therapeutics for treating various metabolic disorders. Among them, *G. sylvestre* has an important place with its diverse ethnobotanical, traditional uses and economic uses in different systems of medicine not in India but also throughout the world. It exhibits enormous hypoglycemic activity along with hypolipidemic and antioxidant property. The wide varieties of compounds isolated from this plant have extensive range of pharmacological activities, which need to be studied in depth to establish their therapeutic potential. It is bothersome that the plant is now rarely available and has been categorized as a rare plant. Unawareness about its uses in general public as well as its difficulty in natural reproduction may be the causes for its decline. So, different methods like tissue culture techniques should be applied for its proper conservation and propagation to protect it from being extinct.

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Conflict of interest

We declare that we have no conflict of interest.

References


