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Review

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, Srilanka, Australia, Indonesia, Japan, Vietnam, Tropical Africa and the South western region of the people's of republic of China (Bone, 2002; Saneja *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 Pundarikakshudu, 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 Avadhoot, 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 *Gymmema sylvestre* R.Br.
Source: Herbal garden of Jamia Hamdard University

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In India, it is known as Periploca of the woods (English); Gurmar (Hindi); Gurmar booti (Urdu); Meshashringi, Madhunashini (Sanskrit); Kavali, Kalikardori (Marathi); Dhueti, Mardashingi (Gujrathi); Adigam, Cherukurinja (Tamil); Podapatri (Telgu); and Sannagrasehambu (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).

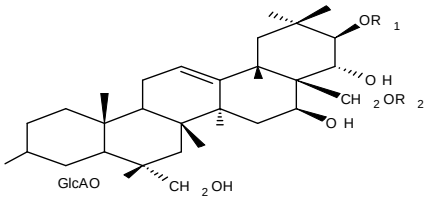
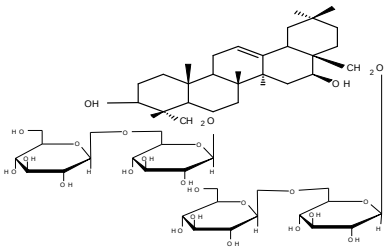
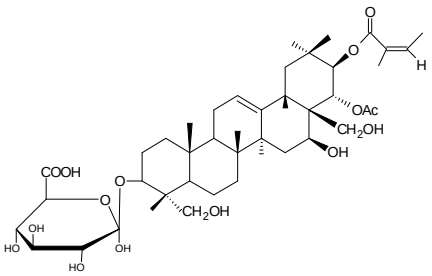
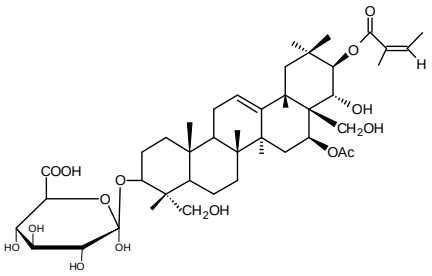
Gymnema has a long history of use in India's Ayurvedic and Homeopathic systems of medicine. Indians first used gymnema to treat diabetes almost 2,000 years ago (Nadkarni, 1992; Vandana *et al.*, 2013). The word *Gymnema* is probably derived from the Greek words "gymnos" means "naked" and "nema" means "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 Reitchenberg-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 geminate* 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.

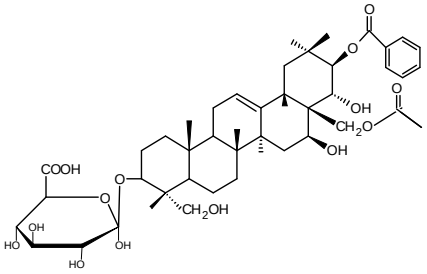
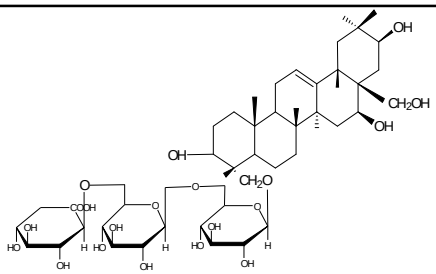
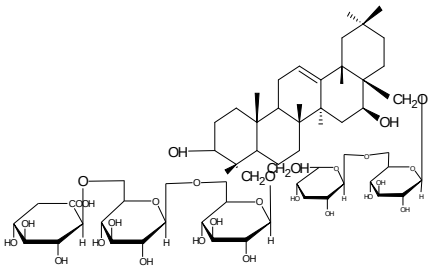
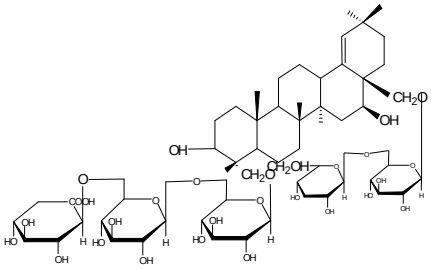
Figure 2: Geographical representationof *Gymnema sylvestre* R.Br., distribution through out world

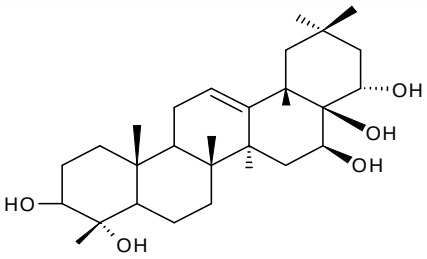
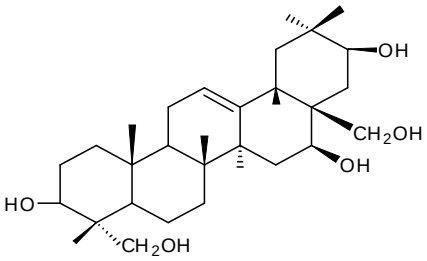
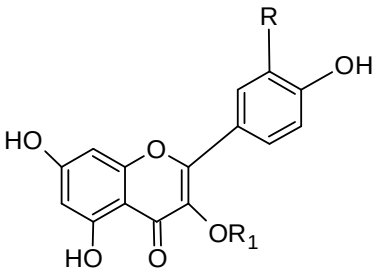
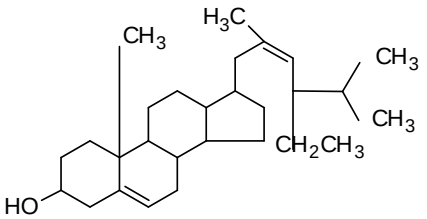
2. Phytochemistry of *G. sylvestre*

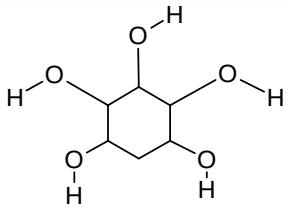
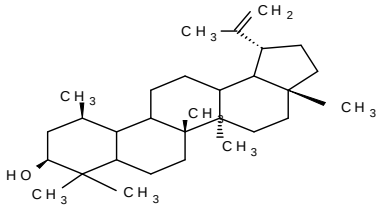
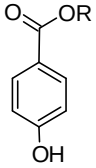
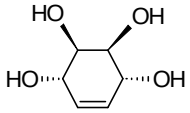
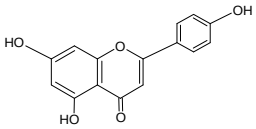
The leaves of *G. sylvestre* contain triterpenoidal saponins belonging to oleanane and dammarene classes. Oleanane saponins are gymnemic acids and gymnemasaponins, while dammarene saponins are gymnemasides (Khramov *et al.*, 2008; Yoshikawa *et al.*, 1992). Twenty different saponins and glycosides have been reported in *G. sylvestre* (Trivedi and Pundarikakshudu, 2008). Some important saponins are gymnemic acid, deacyl gymnemic acid, gymnemagenin and gymnestogenin (Manohar *et al.*, 2009). The gymnemic acids contain several acylated (tiglolyl, methylbutyroyl, *etc*.) derivatives of deacylgymnemic acid (DAGA), which is a 3-O-β-glucouronide of gymnemagenin (3β, 16β, 21β, 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, gymnemosides A-F, and gymnema saponins. The presence of gymnemic acids, (+) quercitol, 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; Qiu *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.

Phytoconstituents	Classification	Moleculer structure (References)	Pharmacological activity (References)
Triterpene Saponins	Gymnemic acids-acylated (tigloyl, methylbutyroyl) deacylgymnemic acid (DAGA) which is a 3-0-b-glucouronida of gymnemagenin (3b, 16b, 21b, 22a, 23, 28-Hexahydroxyolean -12-ene)	 Gymnemic acid types R_1 R_2 Gymnemic acid I Tigloyl Ac Gymnemic acid II 2-methylbutyroyl Ac Gymnemic acid III 2-methylbutyroyl H Gymnemic acid IV Tigloyl H (Liu *et al*., 1992)	Antidiabetic, Antiobesity, Hypolipidemic, Antiviral, (Saneja *et al*., 2010; Sinsheimer and Subbarao 1971; Sinsheimer and Manni, 1965; Maeda *et al*., 1989; Preuss *et al*., 2004; Sinsheimer *et al*., 1968;
Oleanane Saponins	Gymnemic acid and gymnemasaponins	 Gymnemasaponins V (Masayuki *et al*., 1997)	Antihyperglycemic Leishmanicidal-activity (Tiwari *et al*., 2014; Srikanth *et al*., 2010
	Gymnemosides A	 Gymnemoside A (Masayuki *et al*., 1997)	
Dammarene Saponins	Gymnemosides B	 Gymnemoside B (Masayuki *et al*., 1997)	Antidiabeitc (Vaidya, 2011)

	Gymnemosides C	 Gymnemoside C (Masayuki *et al*., 1997)	
	Gymnemosides D	 Gymnemoside D (Masayuki *et al*., 1997)	
Dammarene Saponins	Gymnemosides E	 Gymnemoside E (Masayuki *et al*., 1997)	Antidiabeitc (Vaidya, 2011)
Gurmarin	Gymnemosides F A novel 35-amino acid peptide With a 4209 molecular weight	 Gymnemoside F <^{1}Glu-Gln-Cys-Val-^{5}Lys-Asp-Glu-Leu-^{10}Cys-Ile-Pro-Tyr-Tyr-^{15}Leu-Asp-Cys-Cys-Glu-^{20}Pro-Leu-Glu-Cys-Lys-^{25}Lys-Val-Asn-Trp-Trp-^{30}Asp-His-Lys-Cys-Ile-^{35}Gly> (Glu=pyroglutamic acid residue) (Imoto *et al*., 1991)	Antidiabetic, Inhibition of palatal taste response (Murata *et al*., 2003; Harada and Kasahara, 2000; Miyasaka and Imoto, 1995)
Triterpenoid Saponins Gymnemasins A Gymnemasins B Gymnemasins C Gymnemasins D	3-O[β-D-glucopyranosyl (1-3)-β-D-glucopyranosyl]-22-O-tigloyl gymnemanol 3-O[β-D-glucopyranosyl (1-3)-β-D-glucuronopyranosyl]-gymnemanol 3-O- β-D-glucuronopyranosyl-22-0-tigloyl gymnemanol 3-O-β-D-glucopyranosyl -gymnemanol	(Sahu *et al*., 1996)	Antidiabetic (Liu *et al*., 1992; Yew *et al*., 2001; Guclustundag and Mazza, 2007)

Gymnemanol (aglycone)	3, β-16, b-22, α-23-28-pentahydroxyolean-12-ene	 (Sahu *et al*., 1996)	Anticancer, Antilarvicidal, Antiviral, Antiparasitic (Khanna and Kannabiran, 2009; Khanna *et al*., 2011a; Srividya *et al*., 2010).
Gymmestrogenin	Pentahydroxytriterpene	 (Masayuki *et al*., 1997)	Antidiabetic (Saneja *et al*., 2010; Rao and Sinsheimer, 1971)
Flavonol glycoside	Kaempferol 3-O-β-D-glucopyranosy1-(1-4)-α-L-rhamnopyranosyl-(1-6)-β-D-galactopyranoside	 (Aleisa *et al*., 2014)	–
Sterols	–	 (Imoto *et al*., 1991; Preuss *et al*., 2004; Potawale *et al*., 2008)	–

d-Quercitol	–	 (Potawale *et al*., 2008)	–
Lupeol	–	 (Sinsheimer *et al*., 1970; Liu *et al*., 2014)	–
Paraben	–	 (Sinsheimer *et al*., 1970)	–
–	Conduritol A	 (Zhen *et al*., 2008; Liu *et al*., 2014)	–
–	Quercitol	 (Zhen *et al*., 2008)	–
β-Amyrin related glycosides	–	(Khramov *et al*., 2008)	–
Anthraquinones	–	(Khramov *et al*., 2008)	–

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.

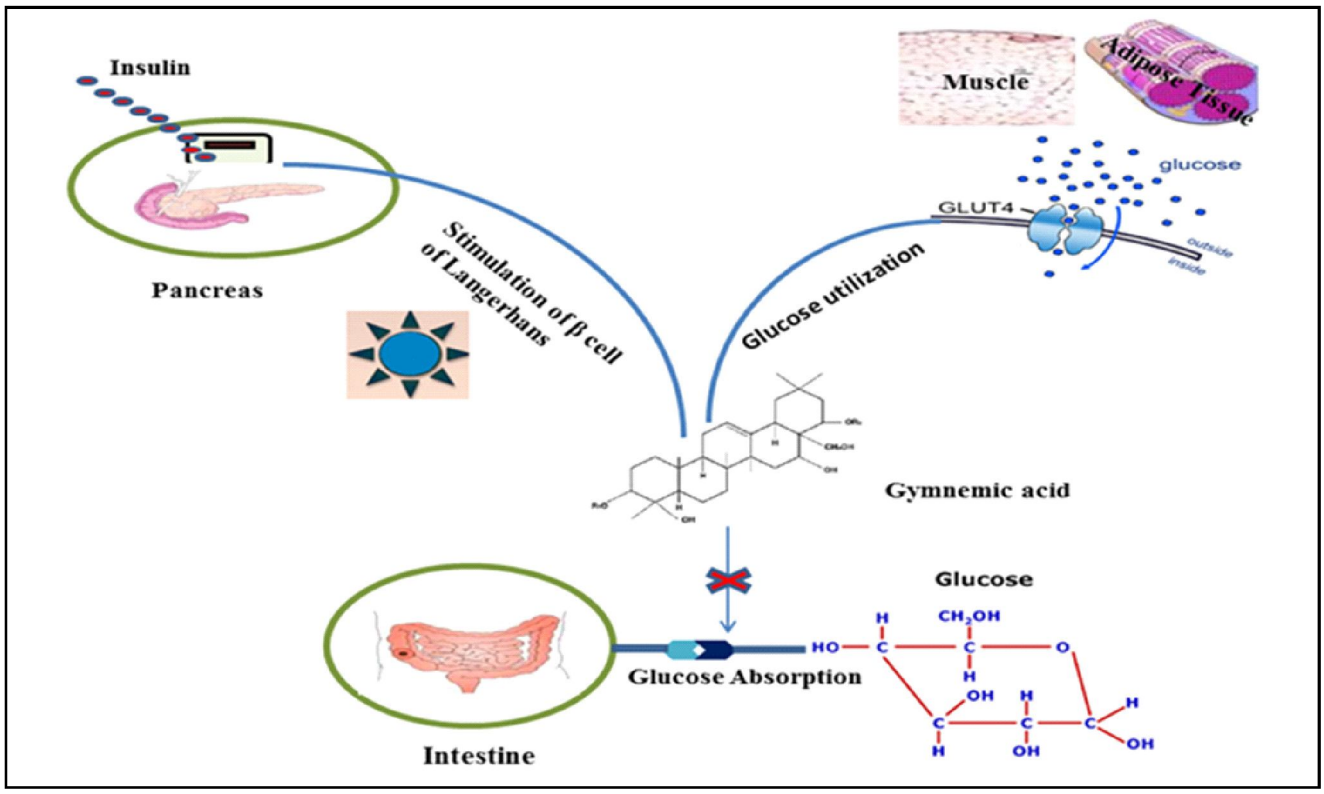


Figure 3: Possible mechanism of G. sylvestre in diabetes mellitus

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

***G. sylvestre* exracts**	**Chemical compounds References**	**Model used**	**Effect**	**Reference**
Aqueous	Alkaloids, anthraquinones, flavonoids, glycosides, phenols, phytosterols, proteins, resins, saponins tannins, triterpenoid (Selvi *et al*., 2007; Yadav *et al*., 2010; Patil *et al*., 2012; Thangavelu *et al*., 2012; Sudhanshu *et al*., 2012; Murugan *et al*., 2012; Ghana Sangeetha and Jegadeesen, 2012; Gopinath *et al*., 2012; Najafi and Deokule, 2011)	OLETF and LETO rats	↓Body weight ↓Serum TC,TG	Luo *et al*., 2007
		Wistar rats	↓Body weight, organ weight ↓Plasma TC, TG, VLDL, LDL-C	Reddy *et al*., 2011
		Mouse MIN 6 β-cells and Human Islets	↑ Insulin release	Liu *et al*., 2009
Ethanol	Alkaloids, flavonoids, glycosides, phenols, phytosterols, proteins, quinines, resins, saponins, tannins, (Selvi *et al*., 2007; Yadav *et al*., 2010; Patil *et al*., 2012; Thangavelu *et al*., 2012; Gopinath *et al*., 2012; Najafi and Deokule, 2011; Kiranmai *et al*., 2011).	Sprague-Dawley rats	↓Blood glucose ↓Serum TG, LDL, TC ↑ Serum insulin ↓Malonaldehyde in serum, liver and kidney ↑ Glutathione content ↑ GSH-Px, GST, catalase ↓SGOP, SGPT	Kang *et al*., 2012

		Wistar rats	↓ Body mass index ↓ Serum TC, TG, LDL, VLDL cholesterol ↓ Serum leptin, insulin, glucose, LDH, apo-B ↑ Gpx, GR, GST, SOD, catalase ↓ Perirenal, mesenteric and epididymalfat mass	Kumar *et al*., 2012
		Swiss albino mice	↑ SOD, CAT, GSH, LPO ↓ Blood glucose ↓ Serum parameters	Sharma and Kar, 2014
Methanol	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)	Wistar rats and ddY mice	↓ Blood glucose levels ↑ Plasma insulin ↓ Glucose uptake	Sugihara *et al*., 2000
		Wistar rats	↓ Plasma glucose ↓ Serum TC, VLDL, LDL ↓ Serum HDL	Ahmad *et al*., 2008
			↓ Blood glucose levels ↓ Blood glucose levels ↑ Serum insulin ↓ Total lipid levels	Yogalakshami *et al*., 2014 Prabhu and Vijayakumar, 2014
		Wistar rats	↑ Body liver and pancreas weights ↓ Plasma glucose ↓ Serum TC, VLDL, LDL ↑ Pancreatic granules of β-cells	Ahmad *et al*., 2010
Chloro-form	Alkaloids, flavonoids phenols, saponin, steroids, tannins, terpenoides, triterpenes, (Yadav *et al*., 2010; Sudhanshu *et al*., 2012; Devi and Ramasubramaniaraja, 2010; Sukesh *et al*., 2011)	–––	–––	–––
Petroleum ether	Flavonoides, phenols, saponins, steroids, tannins, terpenoides, triterpenes, (Yadav *et al*., 2010; Sudhanshu *et al*., 2012; Murugan *et al*., 2012)	–––	–––	–––
GYM 250 extract	___	Humans	↓ Body weight, BMI ↓ Serum leptin levels ↓ Serum TG, VLDL, LDL ↑ Urinary MDA, ACT, FA, ACON	Preuss *et al*., 2004
OSA capsule	___	Humans and pancreatic islets	↓ Fasting blood glucose ↓ Postprandial blood glucose ↑ Serum insulin, C-peptide	Al-Romanian *et al*., 2010
		Ob/ob mice and ICR mice	↓ Blood glucose ↑ Preproinsulin expression and insulin secretion	Al-Romanian *et al*., 2013
		Mouse and human islets	↑ Insulin secretion ↑ Protein kinase activity ↓ cAMP levels	Al-Romanian *et al*., 2012

4. Pharmacological activities

G. sylvestre is listed in the Indian Pharmaceutical Codex and is popular in Indian systems of traditional medicine, such as Sidha, 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*., 2012; 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 antilithiatic 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 (Shanmugasundaram *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) (Giard *et al.,* 1972), and MCF7 (Human breast carcinoma) cell lines (Soule *et al.,* 1973). The alcoholic gymnemagenin and deacyl gymnemic acid have shown significant and good cytotoxic activity, compared to standard drug etoposide, and its cytotoxic activity is proportional to the dosage (Srikanth *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 be 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. aeroginosa, 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* (Satdive *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, *G. sylvestre* leaves, neem leaves (*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, acrid, thermogenic, anti-inflammatory, anodyne, digestive, liver tonic, emetic, diuretic, stomachic, stimulant, anthelmenthic, laxative, cardiotonic, 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 (Porchezhian 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 glycosuria. In eastern Africa, pounded leaves are rubbed onto scarifications 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 antidiabetic 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 hypercholestrolaemia, *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). A polyherbal formula, Diakyur, 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 foenumgraecum, Plumbago zeylanica, Syzygium cumini, Aegle marmelos, Terminalia chebula, Terminelia balerica, Emblica officinalis, Curcuma longa, Pterocarpus marsupium, Berberis aristata, Cytrullus culocynthis, Cyperus rotondus, 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, glucomannan, 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 lose 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 *Harpagophytum* (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 nondiabetic patients (Khare, 1983; Nicolaou *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; Praveen *et 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 (Chodisetti *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 gymnemagenin 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 (Devi and Srinivasan, 2011; Chodisetti *et al*., 2012; Chodisetti *et al*., 2013; Veerashree *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 and to protect it from being extinct.

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Conflict of interest

We declare that we have no conflict of interest.

References

Agarwal, S.K.; Singh, S.S.; Verma, S.; Lakshmi, V. and Sharma, A. (2000). Chemistry and medicinal uses of *Gymnema sylvestre* (*gur-mar*) Leaves: A Review. Indian. Drug., **37**:354-60.

Ahmed, A.B.A.; Rao, A.S. and Rao, M.V. (2008). Role of *in vivo* leaf and *in vitro* callus of *Gymnema sylvestre* in maintaining normal levels of blood glucose and lipid profile in diabetic Wistar rats. Biomedicine., **2**:134-38.

Ahmed, A.B.A.; Rao, A.S. and Rao, M.V. (2010). *In vitro* callus and *in vivo* leaf extract of *Gymnema sylvestre* stimulate cells regeneration and anti-diabetic activity in Wistar rats. Phytomedicine., **17**:1033-39.

Alam, G.; Singh, M.P. and Singh, A. (2011). Wound healing potential of some medicinal plants. Int. J. Pharmaceut. Sci. Rev. Res., **9**:136-45.

Aleisa, A.M.; Al-Rejaie, S.S.; Abuohashish, H.M.; Ola, M.S.; Parmar, M.Y. and Ahmed, M.M. (2014). Pretreatment of *Gymnema sylvestre* revealed the protection against acetic acid-induced ulcerative colitis in rats. *BMC Complement. Altern. Med*., **14**:49.

Al-Romaiyan, A.; King, A.J.; Persaud, S.J. and Jones, P. (2013). A novel extract of *Gymnema sylvestre* improves glucose tolerance *in vivo* and stimulates insulin secretion and synthesis *in vitro*. Phytother. Res., **27**:1006-11.

Al-Romaiyan, A.; Liu, B.; Asare-Anane, H.; Maity, C.R.; Chatterjee, S.K.; Koley, N.; Biswas, T.; Chatterji, A.K.; Huang, G.C.; Amiel, S.A.; Persaud, S.J. and Jones, P.M. (2010). A novel *Gymnema sylvestre* extract stimulates insulin secretion from human islets *in vivo* and *in vitro*. Phytother. Res., **24**:1370-76.

Al-Romaiyan, A.; Liu, B.; Docherty, R.; Huang, G.C.; Amiel, S.; Persaud, S.J. and Jones, P. (2012). Investigation of intracellular signalling cascades mediating stimulatory effect of a *Gymnema sylvestre* extract on insulin secretion from isolated mouse and human islets of Langerhans. Diabetes. Obes. Metab., **14**:1104-13.

Anonymous. (1996). Pharmacopoeia of India. Govt. of India, Ministry of Health, Controller of publication, New Delhi.

Anonymous. (1997). Gurmar buti: Standardization of single drugs of Unani Medicine: Part III. Council for Research in Unani Medicine, Ministry of Health and Family Welfare, Govt. of india, New Delhi, pp:115-123.

Anonymous. (2001). American Herbal Products Association. Use of Marker compounds in manufacturing and labeling botanically derived dietary supplements, Silver Spring, MD, American Herbal Products Association.

Arun, L.B.; Arunachalam, A.M.; Arunachalam, K.D.; Annamalai, S.K. and Kumar, K.A. (2014). *In vivo* anti-ulcer, anti-stress, anti-allergic, and functional properties of gymnemic acid isolated from *Gymnema sylvestre* R Br. *BMC Complement. Altern. Med.*, **14:**70.

Arunachalam, K.D.; Arun, L.B.; Annamalai, S.K. and Arunachalam, A.M. (2014). Potential anticancer properties of bioactive compounds of *Gymnema sylvestre* and its biofunctionalized silver nanoparticles. Int. J. Nanomed., **10**:31-41.

Arunakumara, K.K.I.U.; Wickramasinghe, U.; Walpola, B.C. and Subasinghe, S. (2005). An Assessment on natural regeneration of *Gymnema sylvestre*, A rare medicinal plant. Proceedings of the tenth Forestry and Environmental Symposium, Sri Jayawar-denepura University 2005.

Ashokkumar, H.G.; Murthy, H.N. and Paek, K.Y. (2002). Somatic embryogenesis and plant regeneration in *Gymnema sylvestre*. Plant Cell, Tissue and Organ Culture., **71**:85-88.

Baskaran, K.; KizarAhamath, B.; RadhaShanmugasundaram, K. and Shanmugasundaram, E.R. (1990). Antidiabetic effect of a leaf extracts from *Gymnema sylvestre* in non-insulin-dependent diabetes mellitus patients. J. Ethnopharmacol., **30**(3):295-300.

Baskaran, M.; Rathinavel, S.; Sellathurai, T.; Prema, S. and Natarajan, K.K. (2007). *In vitro* propagation and conservation of *Gymnema sylvestre* (Retz) R. Br. Plant. Archives., **7**:283-86.

Bhansali, S.; Shafiq, N.; Pandhi, P.; Singh, A.P.; Singh, I.; Singh, P.K.; Sharma, S. and Malhotra S. (2013). Effect of a deacyl gymnemic acid on glucose homeostasis & metabolic parameters in a rat model of metabolic syndrome. Indian. J. Med. Res., **137**(6):1174-1179.

Bhatt, H.V.; Mohan Rao, N. and Panchal, G.M. (2001). Differential diagnosis of byssinosis by blood histamine and pulmonary function test: A review and an appraisal. Int. J. Toxicol., **20**(5):321-327.

Bishayee, A. and Chatterjee, M. (1994). Hypolipidaemic and antiatherosclerotic effects of oral *Gymnema sylvestre* R. Br. Leaf extract in albino rats fed on a high fat diet. Phytother. Res., **8**(2): 118-20.

Bone, K. (2002). Phytotherapy review & commentary. Gymnema: A key herb in the management of diabetes. Townsend Letter for Doctors and patient., 94.

Bone, K. (2007). Gymnema: a key herb in the management of diabetes. (Phytotherapy Review & Commentary). National Institute of Herbalists Association of Australia. Available at: www.mediherb.com.au; Accessed-May 18, 2007.

Brala, P. and Hagen, R. (1983). Effects of sweetness perception and caloric value of a preload on short term intake. Physiol. Behav., **30**:1-9.

Brekhman, II. and Dardymov, IV. (1969). New substances of plant origin which, increase nonspecific resistance. Annu. Rev. Pharmacol., **14**:419-30.

Cane, D.E. (1990). Enzymatic formation of gymnemins. Chem. Rev., **90**:1089-1103.

Chakraborty, D.; Ghosh, S.; Bishayee, K.; Sikdar, S. and Khuda-Bukhsh, A.R.(2013). Antihyperglycemic drug *Gymnema sylvestre* also shows anticancer potentials in human melanoma A375 cells via reactive oxygen species generation and mitochondria-dependent caspase pathway. Integrative Cancer Therapies **12**: 433-441.

Chand, P.; Shaik, S.; Sadath, A. and Ziaullah, K. (2008). Anti-salmonella activity of selected medicinal plants. Turk. J. Biol., **33**: 59-64.

Chandraker, S.K. (2014). A miraculous endangered medicinal plant of Chhattisgarh- *Gymnema sylvestre*. Int. J. Pharm. Bio. Sci.,

Chen, B.H.; Hung, M.H.; Chen, J.Y.F.; Chang, H.W.; Yu, M.L. and Wan, L. (2012). Antiallergic activity of grapeseed extract (GSE) on RBL-2H3 mast cells. Food. Chem., **132**(2): 968-74.

Chodisetti, B.; Rao, K.; Gandi, S. and Giri, A. (2012). Abiotic elicitation of gymnemic acid in the suspension cultures of *Gymnema sylvestre*. World. J. Microbiol. Biotechnol., **28**: 741-47.

Chodisetti, B.; Rao, K.; Gandi, S. and Giri, A. (2013). Improved gymnemic acid production in the suspension cultures of *Gymnema sylvestre* through biotic elicitation. Plan. Biotechnol. Rep., **7**(4): 519-525.

Chodisetti, B.; Rao, K.; Gandi, S. and Giri, A. (2014). Gymnemic acid enhancement in the suspension cultures of *Gymnema sylvestre* by using the signaling molecules-methyl jasmonate and salicylic acid. *In Vitro* Cell. Dev. Biol. Plant., Article in press

Chopra, R.N.; Nayar, S.L. and Chopra, I.C. (1992). Glossary of indian medicinal plants. Council of Scientific and Industrial Research, New Delhi, p:319-22.

Devi, BP. and Ramasubramaniaraja, R. (2010). Pharmacognostical and antimicrobial screening of G*ymnema sylvestre* R.Br and evaluation of gurmar herbal tooth paste and powder, composed of G*ymnema sylvestre* R.Br, extracts in dental caries. Int. J. Pharma. Bio. Sci., **1**:1-16.

Devi, C.S. and Srinivasan, V.M. (2011). "*In- vitro* studies on stimulation of gymnemic acid production using fungal elicitor in suspension and bioreactor based cell cultures of *Gymnema sylvestre* R.Br." Recent Research in Science and Technology., **3**:101-04.

Devi, C.S.; Murugesh, S. and Srinivasan, V.M. (2006). Gymnemic acid production in suspension cell cultures of *Gymnema sylvestre*. J. App. Sci., **6**:2263-68.

DiFabio, G; Romanucci, V.; Zarrelli, M.; Giordano, M. and Zarrelli, A. (2013). C-4 gem-dimethylated oleanes of *Gymnema sylvestre* and their pharmacological activities. Molecules., **18**:14892-14919.

DiFabio, G.; Romanucci, V.; DeMarco, A. and Zarrelli, A. (2014). Triterpenoids from *Gymnema sylvestre* and their pharmacological activities. Molecules., **19**(8):10956-81.

DiFabio, G.; Romanucci, V.; DiMarino, C.; Pisanti, A. and Zarrelli, A. (2015). *Gymnema sylvestre* R.Br., an Indian medicinal herb: traditional uses, chemical composition and biological activity. Current Pharmaceutical Biotechnology., **16**:506-16.

Dodson, D.; Mitchell, D.R. and Dodson, D.C. (2001). The Diet Pill Guide: The Consumer's Book of Over-the-Counter and Prescription Weight-Loss Pills and Supplements. St. Martin's Press.

Doli, S.K.; Raparla, R. and Kannappan. (2013). *In vivo* antidiabetic evalution of *Gymnema sylvestre* extract in streptozotocin induced diabetic rats. Int. J. Pharmaceut. Sci. Rev. Res., **23**(2):142-146.

Duke, J.A.; Jones, P.M.; Danny, B.; Jony, D. and Bully, P. (1997). The Green Pharmacy. Emmaus, Pennsylvania: Rodale Press, Inc.

Edgeworth, P. (1847). *Gymnema sylvestre*. Pharm. J., **48**:351.

Ekka, N.R. and Dixit, V.K. (2007). Ethnopharmacognostical studies of medicinal plants of Jashpur district (Chhattisgarh). Int. J. Green. Pharmacy., **1**:1-4.

El-Shafey, A.A.M.; El-Ezabi, M.M.; Seliem, M.M.E.; Ouda, H.H.M. and Ibrahim, D.S. (2013). Effect of *Gymnema sylvestre* R.Br. leaves extract on certain physiological parameters of diabetic rats. J. King Saud University-Science **25**(2):135-141.

Gholap, S. and Kar, A. (2005). Gymnemic acids from *Gymnema sylvestre* potentially regulates dexamethasone-induced hyperglyce-mia in mice. Pharm. Biol., **43**:192-5.

Giard, D.J.; Aaronson, S.A.; Todaro, G.J.; Arnstein, P.; Keren, J.H.; Dosik, K. and Parks, W.P. (1972). *In vitro* cultivation of humen tumors: Establishment of cell lines derived from a series of solid tumors. J. Nat. Cancer. Inst., **51**: 1415.

Ghnana Sangeetha, D. and Jegadeesan, M. (2012). Phytochemical studies on selected medicinal plant *Gymnema sylvestre*. J. Res. Plant. Sci., **1**: 77-82.

Gopinath, S.M.; Rakesh, C.K.; Narasimha Murthy, T.P. and Dayananda, K.S. (2012). Preliminary phytochemical evaluation of leaf extracts of *Gymnema sylvestre*, *Phyllanthus amarus*, *Phyllanthus reticulatus* of Siddarabetta,Tumkur district, Karnataka. Int. J. Pharmacogn. Phytochem. Res., **4**: 109-111.

Granich, M.S.; Halpern, B.P. and Eisner, T. (1974). Gymnemic acids: Secondary plant substances of dual defensive action. J. Insect. Physiol., **20**(2): 435-39.

Guclustundag, O. and Mazza, G. (2007). Saponins: Properties, applications and processing. Crit. Rev. Food. Sci. Nutr., 47: 231-58.

Gueritte, F. (2001). General and recent aspects of the chemistry and structure-activity relationships of gymnemic acids. Curr. Pharm. Design., **7(13)**: 1229-1249.

Gupta, P.; Ganguly, S. and Singh, P. (2012). A miracle fruit plant- *Gymnema sylvestre* R. Br. (Retz). Pharmacie. Globale., **12**(1): 1-4.

Gymnema (2000). In: The Review of Natural Products, Facts and Comparisons. 54rd Ed. US 2000.

Gymnema (2011). The New International Encyclopaedia. Retrieved pp:5-8.

Harada, S. and Kasahara, Y. (2000). Inhibitory effect of gurmarin on palatal taste responses to amino acids in the rats. Am. J. Physiol. Reg. Integr. Comp. Physiol., **278**(6):1513-17.

Hichi, Y. (1988). Jpn. Kokai Tokkyo Koho 4 . Application: JP 87-31206 19870213

Hiji, Y. (1990). Cariostatic materials and foods, and method for preventing dental caries. United States Patent. Patent no. 4,912,089.

Hooper, D. (1887). An examination of the leaves of *Gymnema sylvestre*. J. Soc. Chem. Ind.,**6**:380.

Hong, I.M.; Fumiyuki K. and Yoshisuke, T. (1992). Isolation and structural elucidation of gymnemic acids, anti-sweet principles of *Gymnema sylvestre*. Chem. Pharm. Bull., **40**(6):1366-75.

Imoto, T.; Miyasaka, A.; Ishima, R. and Akasaka, K. (1991). A novel peptide isolated from the leaves of *Gymnema sylvestre*. Characterization and its suppressive effect on the neural responses tosweet taste stimuli in the rat. Comp. Biochem. Physiol. A Comp. Physiol., **100**(2):309-14.

Iwashita, T. and Kurihara, Y. (1989). Studies on taste modifiers II: Purification and structure determination of gymnemic acids, antisweet active principle from *Gymnema sylvestre* leaves. Tetr. Lett., **30**:1547-50.

Joffe, D.J. and Freed, S.H. (2001). Effect of extended release *Gymnema sylvestre* leaf extract (Beta Fast G-XR) alone or in combination with oral hypoglycemics or insulin regimens for type 1 and type 2 diabetes. Diabetes in Control Newsletter., **76(**1).

Joshi, C.; Priya, E.S. and Venkataraman, S. (2007). Hypoglycemic and anti-lipidperoxidative effects of a polyherbal formulation, Diakyur, in experimental animal models. J. Health. Sci., **53**(6): 734-9.

Joy, P.P. and Thomas, J. (1998). Medicinal plants. Aromatic and Medicinal Plants Research Station, Kerala Agriculture University, pp:16.

Kamaraj, C.; Kaushik, N.K.; Mohanakrishnan, D.; Elango, G.; Bagavan, A.; Zahir, A.A.; Rahuman, A.A. and Sahal, D. (2012). Antiplasmodial potential of medicinal plant extracts from Malaiyur and Jsvadhu hills of South India. Parasitol. Res., **111**(2): 703-15.

Kanetkar, P.V.; Laddha, K.S. and Kamat, M.Y. (2004). Gymnemic acids: A molecular perspective of its action on carbohydrate. Poster presented at *the 16th ICFOST meet organized by CFTRI and DFRL*. Mysore, India.

Kanetkar, P.; Singhal, R. and Kamat, M. (2007). *Gymnema sylvestre*: A Memoir. J. of Clinical. Biochem. Nutr., **41**(2):77-81.

Kanetkar, P.V.; Singhal, R.S.; Laddha, K.S. and Kamat, M.Y. (2006). Extraction and quantification of gymnemic acids through gymnemagenin from callus cultures of *Gymnema sylvestre*. Phytochem. Anal., **17**:409-13.

Kang, M.H.; Lee, M.S.; Choi, M.K.; Min, K.S. and Shibamoto, T. (2012). Hypoglycemic activity of *Gymnema sylvestre* extracts on oxidative stress and antioxidant status in diabetic rats. J. Agric. Food. Chem., **60**:2517-24.

Keshwamurthy, K.R. and Yoganarasimhan. (1992). Flora of coorg-Karnataka. Vimsat Publishers, Banglore, India, pp:282.

Khanna, V.G. and Kannabiran, K. (2009). Anticancer-cytotoxic activity of saponins isolated from theleaves of *Gymnema sylvestre* and *Eclipta prostrata* on HeLa cells. Int. J. Green. Pharma., **3**(3): 227-29.

Khanna, V.G.; Kannabiran, K. and Getti, G. (2009). Leishmanicidal activity of saponins isolated from the leaves of *Eclipta prostrate* and *Gymnema sylvestre*. Indian. J. Pharmacol., **41**:32-35.

Khanna, V.G.; Kannabiran, K.; Babu, V.S. and Hameed, A.S.S. (2011a). Inhibition of fish nodavirus by gymnemagenol extracted from *Gymnema sylvestre*. J. Ocean. Univ. China. online published.

Khanna, V.G.; Kannabiran, K.; Rajakumar, G.; Rahuman, A.A. and Santhosh kumar, T. (2011b). Biolarvicidal compound gymnemagenol isolated from leaf extract of miracle fruit plant, *Gymnema sylvestre* (Retz) Schult against malaria and filariasis vectors. Parasitol. Res., **109**(5):1373-86.

Khare, A.K.; Tondon, R.N. and Tewari, J.P. (1983). Hypoglycemic activity of an indigenous drug *Gymnema sylvestre* in normal and diabetic persons. Ind. J. Physiol. Pharmacol., **27**: 257-61.

Khramov, V.A.; Spasov, A.A. and Samokhina, M.P. (2008). Chemical composition of dry extracts of *Gymnema sylvestre* leaves. Pharm. Chem. J., **42**(1):29-31.

Khramov, V.A.; Spasov, A.A. and Samokhina, M.P. (2008). Chemical composition of dry extracts of *Gymnema sylvestre* leaves. Pharm. Chem. J., **42**:29-31.

Kini, R.M. and Gowda, T.V. (1982a). Studies on snake venom enzymes: Part I purification of ATPase, a toxic component of, *naja naja* venom and its inhibition by potassium gymnemate. Indian. J. Biochem. Biophys., **22**(2):152-54.

Kini, R.M. and Gowda, T.V. (1982b). Studies on snake venom enzymes: Part II Partial characterization of ATPases from Russell's viper (Vipera russelli) venom & their interaction with potassium gymnemate. Indian. J. Biochem. Biophys., **19**(5):342-46.

Kiran, Malik, D.K. and Khatak, S. (2014). Comparative antimicrobial activity of leaves and callus of *Gymnema sylvestre* against pathogenic bacteria. J. Pure. Appl. Microbiol., **8**:3253-3261.

Kiranmai, M.; Kazim, S.M. and Ibrahim, M. (2011). Combined wound healing activity of G*ymnema sylvestere and Tagetes erecta* Linn. Int. J. Pharm. Appl., **2**:135-140.

Komalavalli, N. and Rao, M.V. (2000). *In vitro* micro-propagation of *Gymnema sylvestre*- A multipurpose medicinal plant. Plant. Cell. Tiss. Org., **61**:97-105.

Kosaraju, J.; Dubala, A.; Chinni, S.; SatishKumar, M.N. and Basavan, D. (2014). A molecular connection of *Pterocarpus marsupium, Eugenia jambolana* and *Gymnema sylvestre* with dipeptidyl peptidase-4 in the treatment of diabetes. Pharm. Biol., **52**(2):268-71.

Kirtikar, K.R. and Basu, B.D. (1998). Indian medicinal plants. International Book Distributors, Dehradun, India, pp:16-25.

Krishna, R.B.; Reddy, S.R.; Javangula, H.; Swapna, D. and Reddy, K.J. (2012). Isolation and characterization of gymnemic acid from *Gymnema sylvestre* R. Br. in control of diabetes. International Journal of Life Science and Pharmaceutical Research., **2(1)**:1-9.

Kumar, V.; Bhandari, U.; Tripathi, C.D. and Khanna, G. (2012). Evaluation of antiobesity and cardioprotective effect of *Gymnema sylvestre* extract in murine model. Indian. J. Pharmacol., **44**:607-13.

Kumar, V.; Bhandari, U.; Tripathi, C.D. and Khanna, G. (2013). Ameliorative effect of ethanolic *Gymnema sylvestre* extract on diabetic cardiomyopathy against streptozotocin-induced diabetes in wistar rats. Int. J. Green. Pharm., **7**:6-11.

Kurihara, Y. (1992). Characteristics of antisweet substances, sweet proteins, and sweetness inducing proteins. Crit. Rev. Food. Sci. Nutr., **32**(3): 231-52.

Lawless, H.T. (1979). Evidence for neural inhibition in bitter sweet taste mixtures. J. Comp. Physiol. Psychol., **93**(3):538-47.

Lemon, C.H.; Imoto, T. and Smith D.V. (2003). "Differential gurmarin suppression of sweet taste responses in rat solitary nucleus neurons". J. Neurophysiol., **90**(2):911-23.

Liu, B.; Anane, H.A.; Romaiyan, A.A.; Huang, G.; Amiel, S.A. and Jones, P.M. (2009). Characterisation of the insulinotropic activity of an aqueous extract of *Gymnema sylvestre* in mouse β-cells and human islets of Langerhans. Cell. Physiol. Biochem., **23**:125-32.

Liu, H.M.; Kiuchi, F. and Tsuda, Y. (1992). Isolation and structure elucidation of Gymnemic acids, antisweet principles of *Gymnema sylvestre*. Chem. Pharm. Bull., **40**:1366-75.

Liu, X.; Ye, W.; Yu, B.; Zhao, S.; Wu, H. and Che, C. (2004). Two new flavonol glycosides from *Gymnema sylvestre* and *Euphorbia ebracteolata*. Carb. Res., **339**(4):891-95.

Liu, Y.; Xu, T.H.; Zhang, M.Q.; Liu, T.H. and Xu, D.M. (2014). Chemical constituents from the stems of *Gymnema sylvestre*. Chinese journal of natural medicines **12**(4):300-304.

Luo, H. (1999). Possible participation of NO and EDHF in the relaxation of rat intestinal circular muscle induced by Gymnema water extracts containing gymnemic acids. J. Yonago. Med. Association **50**:22-31.

Luo, H.; Kashiwagi, A.; Shibahara, T. and Yamada, K. (2007). Decreased body weight without rebound and regulated lipoprotein metabolism by gymnemate in genetic multifactor syndrome animal. Mol. Cell. Biochem., **299**:93-98.

Luo, H.; Wang, L.F.; Imoto, T. and Hiji, Y. (2001)."Inhibitory effect and mechanism of acarbose combined with gymnemic acid on maltose absorption in rat intestine". World. J. Gastroenterol., **7**(1):9-15.

Luo, T.H.; Zhao, Y.; Li, G.; Yuan, W.T.; Zhao, J.J.; Chen, J.L.; Huang, W. and Luo, M. (2001). A genome- wide search for Type II diabetes susceptibility genes in Chinese Hans. Diabetologia., **44**(4):501-06.

Luo, X.D. and Shen, C.C. (1987). The chemistry, pharmacology, and clinical-applications of gymnemic acids and its derivatives. Med. Res. Rev., **7**(1):29-52.

Maeda, M.; Iwashita, T. and Kurihara, Y. (1989). Studies on taste modifiers II: Purification and structure determination of gymnemic acids, antisweet active principle from *Gymnema sylvestre* leaves. Tetr. Lett., **30**:1547-50.

Malik, J.K.; Manvi, F.V.; Alagawadi, K.R. and Noolvi, M. (2007). Evaluation of anti-inflammatory activity of *Gymnema sylvestre* leaves extract in rats. Int. J. Green. Pharm., **2**:114-15.

Malik, J.K.; Manvi, F.V.; Nanjware, B.R. and Singh, S. (2009). Wound healing properties of alcoholic extract of *Gymnema sylvestre* R.Br. leaves in rats. *J. Pharm. Res.* **2**:1029-30.

Mall, G.K.; Mishra, P.K. and Prakash, V. (2009). Antidiabetic and hypolipidemic activity of *Gymnema sylvestre* in alloxan induced diabetic rats. Global. J. Biotech. & Biochem., **4**(1):37-42.

Manni, P.E. and Sinsheimer, J.E. (1965). Constituents from *Gymnema sylvestre* leaves. J. Pharm. Sci., **54**:1541-44.

Manohar, S.H.; Naik, P.M.; Praveen, N. and Murthy, H.N. (2009). Distribution of gymnemic acid in various organs of *Gymnema sylvestre*. J. For. Res., **20(3)**:268-270.

Masayuki, Y.; Toshiyuki, M.; Masashi, K.; Yuhao, L.; Nubotoshi, M. and Johji, Y. (1997). Medicinal foodstuffs (IX1) the inhibitors of glucose absorption from the leaves of *Gymnema sylvestre* R.Br. (Asclepiadaceae) structures of gymneomosides A and B. Chem. Pharm. Bull., **45**(10):1671-76.

Meiselman, H.L. and Halpern, B.P. (1970a). Effects of *Gymnema sylvestre* on complex tastes elicited by amino acids and sucrose. Physiol. Behav., **5**:1379-84.

Meiselman, H.L. and Halpern, B.P. (1970b). Human judgments of *Gymnema sylvestre* and sucrose mixtures. Physiol. Behav., **5**:945-98.

Min, B.C. and Sakamoto, K. (1998). Influence of sweet suppressing agent on gustatory brain evoked potentials generated by taste stimuli. Appl. Human. Sci., **17**:9-17.

Miyasaka, A. and Imoto, T. (1995). Electrophysiological characteri-zation of the inhibitory effect of a novel peptide gurmarin on the sweet taste response in rats. Brain. Res., **676**(1):63-68.

Mukaiyama, T.; Shiina, I. and Iwadare, H. (1999). Asymmetric total synthesis of gymnemic acid. Chem. Euro. J., **5**(1):121-161.

Muralidhar, T.S.; Gopumadhavan, S.; Chauhan, B.L. and Kulkarni, R.D. (1993). Lack of teratogenicity after administration of D-400, an oral hypoglycemic ayurvedic formulation, during gestation and lactation. J. Biol. Chem. Res., **12**:151-56.

Murata, Y.; Nakashima, K.; Yamada, A.; Shigemura, N.; Sasamoto, K. and Ninomiya, Y. (2003). Gurmarin suppression of licking responses to sweetener-quinine mixtures in C57BL mice. Chem. Senses., **28**:237-43.

Murugan, M.; Mohan, V.R. and Thamodharan, V. (2012). Phytochemical screening and antibacterial activity of *Gymnema sylvestre* (Retz) R.Br ex. Schultes and *Morinda pubescens* J.E. Smith var. *pubescens*. J. Appl. Pharm. Sci. **2**:73-76.

Mutalik, S.; Chetana, M.; Sulochana, B.; UmaDevi, P. and Udupa, N. (2005). Effect of Dianex, an herbal formulation on experimentally induced diabetes mellitus. Phytother. Res., **19**(5):409-415.

Nadkarni, A.K. (1992)."Indian Materia Medica Vol I **In:** *Gymnema sylvestre*", Popular Prakashan, Bombay, India, pp:596-597.

Nadkarni, K.M. (1986). *Gymnema sylvestre*: Indian Materia Medica with Ayurvedic Unani, Popular prakashan, Bombay, pp:596-99.

Nadkarni, K.M. (1993). Indian Materia Medica. Popular prakashan, Bombay, pp:596-9.

Najafi, S. and Deokule, S.S. (2011). Studies on *Gymnema sylvestre*- a medicinally important plant of the family Asclepiadaceae. Trakia. J. Sci., **9**:26-32.

Nakamura, Y.; Tsumura, Y.; Tonogai, Y. and Shibata, T. (1999). Fecal steroid excretion is increased in rats by oral administration of gymnemic acids contained in *Gymnema sylvestre* leaves. J. Nutr., **129**:1214-22.

Nan, K. and Wtpsk, S. (2013). Callus induction and *in vitro* plantlet regeneration of *Gymnema sylvestre* R. Br. (Retz.) and the phyto-chemical screening of natural plants and callus cultures. Plant tissue Culture Biotechnol., **23**(2):201-210.

Nicolaou, K.C.; Ueno, H.; Liu, J.J.; Nantermet, P.G.; Yang, Z.; Renaud, J.; Paulvannan, K. and Chadha, R. (1995). Total synthesis of gymnemic acids. 4. The final stages and completion of the synthesis. J. Am. Chem. Soc., **117**(2):653-659.

Ninomiya, Y. and Imoto, T. (1995). Gurmarin inhibition of sweet taste responses in mice. Am. J. Physiol., **268**:1019-25.

Ogawa, Y.; Sekita, K.; Umemura, T.; Saito, M.; Ono, A.; Kawasaki, Y.; Uchida, O.; Matsushima, Y.; Inoue, T. and Kanno, J. (2004). *Gymnema sylvestre* Leaf Extract: A 52-Week Dietary Toxicity Study in Wistar Rats. Shokuhin. Eiseigaku. Zasshi., **45**(1):8-18.

Omale James. and Ajidahun Bidemi Sunday. (2014). Evaluation of acute dermal irritation and wound contraction by *Gymnema sylvestre* and *Datura metel* extracts in rats. A. J. B. L. S., **2**(4): 83-88.

Paliwal, R.; Kothari, S. and Upadhyay, B. (2009). Effect of gurmar (*Gymnema sylvestre)* powder intervention on the blood glucose levels among diabetics. Ethno-Med., **3**(2):133-35.

Pandey, A.K. (2012). Cultivation technique of an important medicinal plant *Gymnema sylvestre* R. Br. (Gudmar). Academic Journal of Plant Sciences., **5**(3):84-89.

Pandey, M. and Vijayakumar (2013). Pharmacological screening of some plant extract for hypoglycemic activity. J. Chem. Pharmaceut. Res., **5**:187-193.

Patil, P.M.; Chaudhari, P.D.; Duragkar, N.J. and Katolkar, P.P. (2012). Formulation of anti-diabetic liquid preparation of *Gymnema sylvestre* and qualitative estimated by TLC. Asian. J. Pharm. Clin. Res., **5**:16-19.

Persaud, S.J.; Al-Majed, H.; Raman, A. and Jones, P.M. (1999). *Gymnema sylvestre* stimulates insulin release *in vitro* by increased membrane permeability. J. Endocrinol., **163**: 207-12.

Porchezhian, E. and Dobriyal, R.M. (2003). An overview on the advances of *Gymnema sylvestre:* chemistry, pharmacology and patents. Pharmazie., **58**(1):5-12.

Potawale, S.E.; Shinde, V.M.; Anandi, L.; Borade, S.; Dhalawat, H. and Deshmukh, R.S. (2008). *Gymnema sylvestre*: a comprehensive review. J. Pharmacologyonline., **2**:144-57.

Prabhu, S. and Vijayakumar, S. (2014). Antidiabetic, hypolipidemic and histopathological analysis of *Gymnema sylvestre* (R. Br.) leaves extract on streptozotocin induced diabetic rats. Biomedicine and Preventive Nutrition **4**(3):425-430.

Pragada, P.M.; Rao, D.S. and Venkaiah, M. (2012). Study of some ethnomedicinal plants for treatment of dysentery of North Coastal Andhra Pradesh, India. Int. J. Biosci., **2**(1):18-24.

Praveen, N.; Murthy, H.N. and Chung, I.M. (2011). Improvement of growth and gymnemic acid production by altering the macro-elements concentration and nitrogen source supply in cell suspension cultures of *Gymnema sylvestre* R.Br. Industrial Crops and Products., **33**:282-86.

Praveen, N.; Thiruvengadam, M.; Jung, S.J.; Murthy, H.N. and Chung, I.M. (2013). Establishment of *Gymnema sylvestre* hairy root cultures for the production of gymnemic acid. Acta. Physiologiae. Plantarum., **35**:3067-3073.

Praveen, N.; Thiruvengadam, M.; Yang, Y.S.; Murthy, H.N. and Chung, I.M. (2014). Production of gymnemic acid from hairy root cultures of *Gymnema sylvestre* R. Br. as influenced by polyunsaturated fatty acids (PUFAs) and their antioxidant activity. Industrial Crops and Products **54**:54-61.

Preuss, H.G.; Bagchi, D.; Bagchi, M.; Rao, C.V.; Dey, D.K. and Satyanarayana, S. (2004). Effects of a natural extract of (-) hydroxycitric acid (HCA-SX) and a combination of HCA-SX plus niacin-bound chromium and *Gymnema sylvestre* extract on weight loss. Diabetes. Obes. Metab., **6**:171-80.

Preuss, H.G.; Garis, R.I.; Bramble, J.D.; Bagchi, D.; Bagchi, M.; Rao, C.V. and Satyanarayana, S. (2005). Efficacy of a novel calcium / potassium salt of (-)-hydroxycitric acid in weight control. Int. J. Clin. Pharmacol. Res., **25**(3):133-44.

Preuss, H.G.; Bagchi, D.; Bagchi, M.; Rao, C.V.; Satyanarayana, S. and Dey, D.K. (2004). Efficacy of a novel, natural extract of (–)-hydroxycitric acid (HCA-SX) and acombination of HCA-SX, niacin-bound chromium and *Gymnema sylvestre* extract in weight management in human volunteers: a pilot study. Nutr Res., **24**(1): 45-58.

Pullaiah, T. (2006). Encyclopedia of World Medicinal Plants. Regency Publications, New Delhi, 2nd volume.

Qiu, Q.; Zhen, H.S. and Huang, P.Q. (2013). Study on volatile components from flowers of *Gymnema sylvestre*. Journal Chinese medicinal materials **36**(4):575-577

Rachh, P.R.; Patel, S.R.; Hirpara, H.V.; Rupareliya, M.T.; Rachh, M.R. and Bhargava, A.S. (2009). *In vitro* evaluation of antioxidant activity of *Gymnema sylvestre* R. BR. Leaf extract. Rom. J. Biol. Plant. Biol., **54**:141-48.

Rachh, P.R.; Rachh, M.R.; Ghadiya, N.R.; Modi, D.C.; Modi, K.P.; Patel, N.M. and Rupareliya, M.T. (2010). Antihyperlipidemic activity of *Gymnema sylvestre* R.Br. leaf extract on rats fed with high cholesterol diet. Int. J. Pharmacol., 1-4.

Rahman, M.M.; Habib, M.R.; Hasan, M.A.; Saha, A. and Mannan, A. (2014). Comparative assessment on *in vitro* antioxidant activities of ethanol extracts of *Averrhoa bilimbi, Gymnema sylvestre* and *Capsicum frutescens*. Pharmacog. Res., **6**:36-41.

Rama, M.R.; Vijaya, T.; Pushpalatha, B. and Dattatreya, R.S. (2011). Saponins rich aqueous extract of *Gymnema sylvestre* R.Br. reduces high fat diet induced obesity in wistar rats. J. Pharmacy. Res., **4**:1237-9.

Rana, A.C. and Avadhoot, Y. (1992). Experimental evaluation of hepatoprotective activity of *Gymnema sylvestre* and *Curcuma zedoaria*. Fitoterapia., **63**:60.

Rao, G.S. and Sinsheimer, J.E. (1971). Constituents from *Gymnema sylvestre* leaves VIII. Isolation, chemistry, and derivatives of gymnemagenin and gymnestrogenin. J. Pharm. Sci., **60**(2):190-3.

Rao, S.R. and Ravishankar, G.A. (2002). Plant cell cultures: chemical factories of secondary metabolites. Biotechnol. Adv., **20**:101-53.

Rapini, A.; Chase, M.W.; Goyder, D.J. and Griffiths, J. (2003). Asclepiadaceae classification evaluating the phylogenetic relationships of New World Asclepiadaceae (Apocynaceae). Taxon., **52**:33-50.

Rastogi, A.; Mythili, S. and Sathiavelu, A. (2014). *In vitro* anti-diabetic activity of aqueous extract of the medicinal plants *Nigella sativa, Eugenia jambolana, Andrographis paniculata* and *Gymnema sylvestre*. Res. J. Biotechnol., **9**(2):41-45.

Reddy, P.S.; Gopal, G.R. and Sita, G.L. (1998). *In vitro* multiplication of *Gymnema sylvestre* R.Br.- an important medicinal plant. Curr. Sci., **75**:843-45.

Reddy, P.S.; Gopal, G.R. and Sita, G.L. (2004). "*In vitro* multiplication of *Gymnema sylvestre* R.Br., an important medicinal plant." Curr. Sci., **10**:1-4.

Reddy, R.M.; Vijaya, T.; Latha, P.B. and Rao, D.S. (2011). Saponins rich aqueous extract of *Gymnema sylvestre* R.Br reduces high fat diet induced obesity in Wistar rats. J. Pharm. Res., **4**: 1237-39.

Reitchenberg -Ullman, Judith. (1996). ''Can you just say no sugar"? Health world online. http://www.healthworldonline.com (January 17, 2001).

Russell, F.E. (1980). Snake Venom Poisoning in the United States. Ann. Rev. Med., **31**:247-59.

Sabir, F.; Sangwan, R.S.; Singh, J.; Misra, L.N.; Pathak, N. and Sangwan, N.S. (2011). "Biotransformation of withanolides by cell suspension cultures of *Withania somnifera* (Dunal)." Plant. Biotechnol. Rep., **5**:127-34.

Sabir, F.; Sangwan, R.S.; Kumar, R. and Sangwan, N.S. (2012). Salt stress-induced responses in growth and metabolism in callus cultures and differentiating *in vitro* shoots of indian ginseng (*Withania somnifera* Dunal). Journal of Plant Growth Regulation., pp. 1-12.

Sabitha Rani, A.; Nagamani, V.; Patnaik, S. and Saidulu, B. (2012). *Gymnema sylvestre: an important antidiabetic plant of india. A review. Plant Sciences Feed, 2(12):174-79.*

Sahu, N.P.; Mahato, S.B.; Sarkar, S.K. and Poddar, G. (1996). Triterpenoid Saponins from *Gymnema sylvestre*. Phytochem., **41**: 1181-85.

Saneja, A.; Sharma, C.; Aneja, K.R. and Pahwa, R. (2010). *Gymnema sylvestre* (Gurmar): A Review. Der. Pharmacia. Lettre., **2**(1):275-84.

Saraswathy, S.; Manavalan, R.S.A.; Vadivel, E.; Chezhiyan, N. and Vijaykumar, M. (2002). *In vitro* propagation studies in gymnema (*Gymnema sylvestre* R.Br.). South Indian Horticulture **50**:664-66.

Sastri, B.N. (1956). The Wealth of India. Raw materials, vol. IV. Council of Scientific and Industrial Research. A Dictionary of Indian Raw materials and Industrial products. Council of Scientific and Industrial Research, New Delhi, pp: 276-77.

Satdive, R.K.; Abhilash, P. and Fulzele, D.P. (2003). Antimicrobial activity of *Gymnema sylvestre* leaf extract. Fitoterapia., **74**:699-701.

Saumendu, D.R.; Sarkar, K.; Dipankar, S.; Singh, T. and Prabha, B. (2010). *In-vitro* antibiotic activity of various extracts of *Gymnema sylvestre*. Int. J. Pharm. Res. Dev., **2**:1-3.

Schmid, G. and Hofheinz, W. (1983). Total synthesis of gymnemic acids. J. Am. Chem. Soc., **105**:624-625.

Schroeder, J.A. and Schroeder, E.F. (2005). Use of the herb *Gymnema sylvestre* to illustrate principles of gaustatory sensation: An undergraduate Neuroscience Laboratory excersise. J. Uundergrad. Neurosci. Educ., **3**(2):A59-A62.

Selvi, S.; Uma Devi, P.; Chinnaswamy, P.; Giji, T.M. and Sharmila, S.P. (2007). Antibacterial efficacy and phytochemical observation of some indian medicinal plants. Anc. Sci. Life., **26**:16-22.

Shah, M. (2010). A Review on *Gymnema sylvesre* R. Br. http: //www.doyou know .in / /Articles/ Pharmaceutical. views., 2334.

Shanmugasundaram, E.R.; Rajeswari, G.; Baskaran, K.; RajeshKumar, B.R.; RadhaShanmugasundaram, K. and KizarAhmath, B. (1990). Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J. Ethnopharmacol., **30**(3):281-94.

Sharma, A.; Shanker, C.; Tyagi L.K.; Singh, M. and Rao, C.V. (2008). Herbal medicine for market potential in India: An overview. Acad. J. Plant. Sci., **1**:26-36.

Sharma, N. and Kar, A. (2014). Combined effects of *Gymnema sylvestre* and glibenclamide on alloxan induced diabetic mice. Int. J. App. Pharm., **6**(2):11-14.

Shimizu, K.; Iino, A.; Nakajima, J.; Tanaka, K.; Nakajyo, S.; Urakawa, N.; Atsuchi, M. and Wada. (1997). Suppression of glucose absorption by some fractions extracted from *Gymnema sylvestre* leaves. J. Vet. Med. Sci., **59**(4):245-51.

Shiyovich, A.; Sztarkier, I. and Nesher, L. (2010). Toxic hepatitis induced by *Gymnema sylvestre*, a natural remedy for type 2 diabetes mellitus. Am. J. Med. Sci., **340**(6):514-17.

Singh, K. and Deo, B. (2014). Phytochemical evaluation and *in vitro* antioxidant activity of *Gymnema sylvestre* R.Br. J. M. P. S., **2**(4):19-23.

Singh, V.K.; Umar, S. and Iqbal, M. (2008). *Gymnema sylvestre* for diabetics. Journal of Herbs, Spices and Medicinal Plants., **14**:88-106.

Sinsheimer, J.E. and Manni, P.E. (1965). Constituents from *Gymnema sylvestre* leaves. J. Pharm. Sci., **54**:1541-44.

Sinsheimer, J.E.; Rao, G.S.; Mcllhenny, H.M.; Smith, R.V.; Maassab, H.F. and Cochran, K.W. (1968). Isolation and antiviral activity of the gymnemic acids. Experimentia., **24**(3):302-3.

Sinsheimer, J.E.; Rao, G.S. and McIlhenny, H.M. (1970). Constituents from *Gymnema sylvestre* Leaves V: Isolation and preliminary characterization of Gymnemic acids. J. Pharm. Sci., **59**:622-28.

Sinsheimer, J.E. and Subbarao, G. (1971). Constituents from *Gymnema sylvestre* VIII: Isolation, Chemistry and Derivatives of gymnemagenimn and gymnemastrogenin. J. Pharm. Sci., **60**:190-93.

Smolinski, A.T.; and Pestka, J.J. (2003). Modulation of lipopolysaccharide-induced proinflammatory cytokine production *in vitro* and *in vivo* by the herbal constituents apigenin (chamomile), ginsenoside Rb-1 (ginseng) and parthenolide (feverfew). Food. Chem. Toxicol., **41**(10): 1381-1390.

Soule, H.D.; Vasquenz, J.; Long, A.; Albert, S. and Bernann, M. (1973). A humen cell line from pleural effussion derived from breast carcinoma. J. Nat. Cancer. Inst., **51**: 1409-16.

Sree Lakshmi, K.; Prabhakaran, V.; Mallikarjuna, G. and Gowthami, A. (2014). Antilithiatic activity of *Trianthema portulacastrum* I. and *Gymnema sylvestre* R. Br. against ethylene glycol induced urolithiasis. Int. J. Pharmaceut. Sci. Rev. Res., **25**:16-22.

Srikanth, A.V.; Ravikiran, A.; Ravi, K.P.; Lakshmi, N.M. and Madhava, R.B. (2011). Cytotoxic activity of *Gymnema sylvestre*. Int. J. Pharma. Sci. Nanotech., published online.

Srikanth, A.V.; Sayeeda, M.; Lakshmi, N.M.; Ravi, K.P. and Madhava, R.B. (2010). Anticancer activity of *Gymnema sylvestre* R.Br. Int. J. Pharma. Sci. Nanotech., **3**(1):897-99.

Srinath Reddy, T.; Arafath, S.; Shafeen, S.; Adithya, N. and Nagarjuna, S. (2013). *In vitro* evaluation of anthelmintic activity of *Gymnema sylvestre* leaves against *Pheretima posthuma*. Int. J. Drug. Dev. & Res., **5** (2):382-386.

Srivastava, Y.; Nigam, S.K.; Bhatt, H.V.; Verma, Y. and Prem, A.S. (1985). Hypoglycemic and Lifeprolonging properties of *Gymnema sylvestre* leaf extract in diabetic rats. Isr. J. Med. Sci., **21**(6):540-42.

Srividya, A.R.; Varma, S.K.; Dhanapal, S.P.; Vadivelan, R. and Vijayan, P. (2010). *In vitro* and *in vivo* evaluation of hepatoprotective activity of *Gymnema sylvestre*. Int. J. Pharmaceut. Sci. Nanotech., **2**:768-73.

Stevens, T.; Qadri, A. and Zein, N.N. (2005). Two patients with acute liver injury associated with use of the herbal weight-loss supplement Hydroxycut. Ann. Intern. Med., **142**(6):477-8.

Stocklin, W. (1969). Chemistry and physiological properties of Gymnemic acid,the antisaccharine principle of the leaves of *Gymnema sylvestre*. J. Ethnopharmacol., **7**:205-34.

Sudhanshu.; Mittal, S.; Rao, N.; Soni, M. and Menghani, E. (2012). Phytochemical potentials of *Gymnema sylvestre*, *Adiantum lunulatum*, *Bryonia laciniosa*. Asian. J. Biochem. Pharm. Res., **3**(2):8-13.

Sugihara, Y.; Nojima, H.; Marsuda, H.; Murakami, T.; Yoshikawa, M. and Kimura, I. (2000). Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice. J. Asian. Nat. Prod. Res., **2**(4):321-27.

Sukesh, K.; Shafi Thompson, T. and Densingh, J. (2011). Phytochemical investigation and antibacterial activity of *Gymnema sylvestre* and *Andrographis paniculata* from western ghats. Int. J. Phytomed., **3**:254-60.

Tamaki, H.; Satoh, H.; Hori, S.; Ohtani, H. and Sawada, Y. (2010). Inhibitory effects of herbal extracts on breast cancer resistance protein (BCRP) and structure-inhibitory potency relationship of isoflavonoids. Drug. Metab. Pharmacokinet., **25**:170-79.

Tandon, P. and Sirohi, A. (2010). Assessment of larvicidal properties of aqueous extracts of four plants against *Culex quinquefasciatus* larvae. J. J. B. S., **3**(1):1-6.

Tayler, V.E. (1993). The honest herbal-a sensible guide to the use of herbs and related remedies, 3rd ed. The Haworth Press, New York, pp.218-26.

Terasawa, H.; Miyoshi, M. and Imoto, T. (1994). Effects of long-term administration of *Gymnema sylvestre* watery-extract on variations of body weight, plasma glucose, serum triglyceride, total cholesterol and insulin inWistar fatty rats. Yonago. Acta. Med., **37**:117-27.

Thakur, G.S.; Sharma, R.; Sanodiya, B.S.; Pandey, M.; Prasad, G.B.K.S. and Bisen, P.S. (2012). *Gymnema sylvestre:* an alternative therapeutic agent for management of diabetes. J. A. P. S., **2**(12):1-6.

Thangavelu, D.; Thangavelu, T.; Vembu, T.; Venkatachalam, K.; Selladurai, E. and Jegadeesan, M. (2012). Pharmacognostic and phytochemical studies on *Gymnema sylvestre* R. Br. hairy variant. Int. J. Pharm. Phytopharmacol. Res., **2**:143-47.

The Welth of India. (1956). Raw materials vol. IV. Council of Scientific and Industrial Research; New Delhi. A Dictionary of Indian Raw materials and industrial products. pp.276-77.

Tiwari, P.; Mishra, B.N. and Sangwan, N.S. (2014). Phytochemical and Pharmacological Properties of *Gymnema sylvestre*: An Important Medicinal Plant", Hindawi Publishing Corporation. Biomed. Res. Int., pp:1-18.

Trivedi, P.D. and Pundarikakshudu, K. (2008). A validated high performance thin-layer chromatographic method for the estimation of gymnemic acids through gymnemagenin in *Gymnema sylvestre*, materials, extracts and formulations. Int. J. Appl. Sci., **6**:1-19.

Triveni, K.B.; Lakshmi, V.K.; Shashidhara, S. and Anitha, S. (2012). *Gymnema sylvestre*: A Comprehensive Review. Pharma Science Monitor. An Int. J. Pharmaceut. Sci., **3**(4):2402-20.

Vaidya, S. (2011). Review on Gymnema: An herbal medicine for Diabetes Management. Pharmacia., **1**(2):37-42.

Vaidyaratnam, P. (1995). Indian medicinal plants. Orient Longman Publisher, Madras, pp:107-9.

Vandana, G.; Bipin, B.K.; Tiwari, S.K. and NarsimhaMurthy, K.H.H.V.S.S. (2013). A review on antidiabetic actions of Asandi Gana. Int. J. Res. Ayurveda. Pharm., **4**(5):638-46.

Vats, S. and Kamal, R. (2013). *In vivo* and *in vitro* evaluation of sterols from *Gymnema sylvestre* R. Br. Pakistan Journal of Biological Sciences **16**(23):1771-1775.

Veerashree, V.; Anuradha, C.M. and Kumar, V. (2012). Elicitor-enhanced production of gymnemic acid in cell suspension cultures of *Gymnema sylvestre* R.Br. Plant Cell, Tissue and Organ Culture **108**:27-35.

Wadood, N.; Nisar, M.; Rashid, A.; Wadood, A.; Gul-Nawab. and Khan, A. (2007). Effect of a compound recipe (medicinal plants) on serum insulin levels of alloxan induced diabetic rabbits. J. Ayub. Med. Coll. Abbottabad., **19**(1):32-8.

Wang, L.F.; Luo, H.; Miyoshi, M.; Imoto, T.; Hiji, Y. and Sasaki, T. (1998). Inhibitory effect of gymnemic acid on intestinal absorption of oleic-acid in rats. Can. J. Physiol. Pharmacol., **76**:1017-1023.

Wang, Y.; Dawid, C.; Kottra, G.; Daniel, H. and Hofmann, T. (2014). Gymnemic acids inhibit sodium-dependent glucose transporter. J. Agric. Food. Chem., **62**(25):5925-31.

Warren, R.P.; Warren, R.M. and Weninger, M.G. (1969). Inhibition of the sweet taste by *Gymnema sylvestre*. Nature., **223**:94-95.

Wechsler, M.E. (2007). Pulmonary eosinophilic syndromes. Immunol. Allergy. Clin. North. Am., **14**:477-92.

Yadav, H.; Jain, S.; Prasad, G.B.K.S. and Yadav, M. (2007). Preventive Effect of Diabegon, a polyherbal preparation, during progression of diabetes induced by high-fructose feeding in rats. J. Pharmacol. Sci., **105**:12-21.

Yadav, M.; Lavania, A.; Tomar, R.; Prasad, G.B.; Jain, S. and Yadav, H. (2010). Complementary and comparative study on hypoglycemic and antihyperglycemic activity of various extracts of *Eugenia jambolana* seed, *Momordica charantia* fruits, *Gymnema sylvestre*, and *Trigonella foenum graecum* seeds in rats. Appl. Biochem. Biotechnol., **160**:2388-2400.

Yasukawa, K.; Okuda, S. and Nobushi, Y. (2014). Inhibitory effects of gymnema (*Gymnema sylvestre*) leaves on tumour promotion in two-stage mouse skin carcinogenesis. Evidance based Complementary and Alternative Medicine 2014, Article ID 328684, 5 pages

Yeh, G.Y.; Eisenberg, D.M.; Kaptchuk, T.J. and Phillips, R.S. (2003). Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes. Care., **26**:1277-94.

Yew, W.; Liu, X.; Zhang, Q.; Che, C.T. and Zhao S. (2001). Antisweet saponins from *Gymnema sylvestre*. J. Nat. Prod., 64:232-35.

Yogalakshmi, K.; Vaidehi J. and Ramakotti, P. (2014). Hypoglycemic effect of *Gymnema sylvestre* leaf extract on normal and streptozotocin induced diabetic rats. Int. J. Chem. Tech. Res., **6**(12):5146-5150.

Yoshikawa, K.; Nakagawa, M.; Yamamoto, R.; Arihara, S. and Matsuura, K. (1992). Antisweet natural products. V. Structures of gymnemic acids VIII-XII from *Gymnema sylvestre* R.Br. Chem. Pharm. Bull., **40**:1779-82.

Yoshikawa, K.; Kondo, Y.; Arihara, S. and Matsuura, K. (1993). Antisweet natural products IX structures of gymnemic acids XV-XVIII from *Gymnema sylvestre* R. Br. Chem. Pharm. Bull., **41**: 1730-32.

Zarrelli, A.; DellaGreca, M.; Ladhari, A.; Haouala, R. and Previtera, L. (2013a). New Triterpenes from *Gymnema sylvestre*. Helv. Chim. Acta., **96**:1036-1045.

Zarrelli, A.; Ladhari, A.; Haouala, R.; Di Fabio, G; Previtera, L. and DellaGreca, M. (2013b). New acylated oleane and lupane triterpenes from *Gymnema sylvestre*. Helv. Chim. Acta., **96**:2200-2206.

Zhen, H.S.; Zhu, X.Y.; Lu, R.M.; Liang, J.; Qiu, Q. and Meng, Q.M. (2008). Research on chemical constituents from stem of *Gymnema sylvestre*. Journal of Chinese Medicinal Materials **31**:1154-56.