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Review Article

Gymnema sylvestre – A Key for Diabetes Management – A Review

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Abstract

Traditional medicines derived from medicinal plants are used by about 60 per cent world population. Diabetes is an important human ailment officiating many from various walk of life in different countries including India. It providing to a major health problem, especially in the urban area: *Gymnema sylvestre* R.Br. (Asclepiadaceae) is a herb distributed throughout the world. The leaves of the plant are widely used for the treatment of diabetes and as diuretic in India proprietary medicine. *G. sylvestre*, an Ayurvedic herb, came to be known as "destroyer of sugar" because, in ancient times, Ayurvedia physicians observed that chewing a few leaves of *G. sylvestre* suppressed the taste of sugar. It is used totally all over India for controlling blood sugar. Several bio-active compounds have been isolated from the herb for diabetes care. It is believed to be used in dyspepsia, constipation, jaundice, haemorrhoids, cardiopathy, asthma, bronchitis and leucoderma. A scrutiny of literature revealed some notable pharmacological activities of the plant such as anti diabetic, antiobesity, hypolipidaemic, antimicrobial, free radical scavenging and anti-inflammatory. The present review is an attempton various ethanobotanical and traditional uses, phytochemical and pharmacological approaches of *G. sylvestre* .

Key words: *Gymnema sylvestre*, Ethanobotanical uses, phytochemistry, pharmacological activities.

1. Introduction

G. sylvestre is a woody, climbing plant belonging to the family Asclepiadaceae and widely distributed in India, Malaysia, Srilanka, Indonesia, Japan, Vietnam, tropical Africa and South Western region of the people's republic of China (WWF-India 2005). The pharmacological properties of *G. sylvestre* are attributed to a group of triterpene saponins, known as gymnemic acid S [I-XVIII and gymnemosaponins I-V]. Reports indicate that the oral administration of *G. sylvestre* to exert diverse range of effects targeting several of the etiologial factors connected to diabetes, including chronic inflammation [1], obesity [2 and 3] enzymatic defects and pancreatic β-cell function, increase in β-cell number and increase in Insulin release by increasing the cell permeability to insulin [4].

2. Taxonomy of *G. sylvestre* R.Br

Kingdom	:	Plantae
Subkingdom	:	Tracheobionta
Superdivision	:	Spermatophyta
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Subclass	:	Asteridae
Order	:	Gentianales
Family	:	Asclepiadaceae
Genus	:	*Gymnema*
Species	:	*sylvestre*

Vernacular name

English: Periploca of the wood

Hindi: Gudmar

Kannada: Kadhasige

Malayalam: Cakkarakkolli, Madhunasini

Tamil: Sirukurunja/ Sakkaraikkolli

Sanskrit: Mesasrngi

Telugu: Podapatra

2.1. Plant description

G. sylvestre is a slow growing, perennial, woody climber, distributed throughout India, in dry forests up to 600 m heigh. It is mainly present in the tropical forest of the Central and Southern India. It is also found in Banda, Konkan, Western ghats, Deccan extending to the parts of Western and Northern India [5-7]. The plant is large more or less pubescent woody climber. The leaves are opposite, usually elliptic or ovate (1.25-2.0 inch × 0.51-1.25 inch). Flowers are inches in length. The calyx-lobes are long, ovate, obtuse and pubescent; corolla is pale Yellow Campanulate, Valvate, and Corona single, with 5 fleshy scales. Scales adnate to throat of corolla tube between lobes; anther connective produced into a membranous tip, pollinia 2, erect, carpels 2 unilocular; locules many ovuled [6, 8-10]

2.2. Geographical distribution

G. sylvestre , is native to the tropical forests of Central and Southern India, had wider distribution and it grows in the plains from the coast, in scrub jungles and in thickets at an attitude ranging from 300-700 m. The genus *Gymnema* comprises 40 species distributed from Western Africa to Australia. *G. acuminatum* (Roxb.) wall, *G. aurantiacum, G. balsamicum, G. elegans* W and A *G. lactiferum, G. latifolium, G. montanum* Hook. F., *G. sylvestre* R.Br. *G. tingens* W and A *G. indorum, G.yunnanse* and *G. spartum* are some of the important species of *Gymnema.* They are mainly distributed in the Deccan Peninsula parts of northern and western India, Tropical Africa, Australia, Vietnam, Malaysia and Srilanka. (Fig 1).

3. Phytochemistry

The leaves of *G. sylvestre* contain triterpene saponins belonging to oleanane and dammarene classes. Oleanane saponins are gymnemic acids and gymnema saponins, while dammarene saponins are gymnemsides, [11,12]. The leaves also contain resins, albumin, chlorophyll, carbohydrates, tartaric acid,

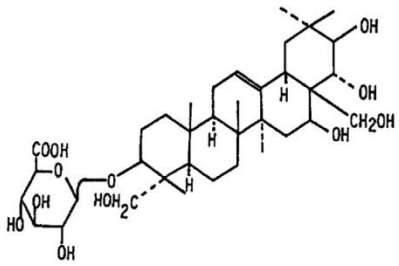
formic acid, butyric acid, anthraquinone derivatives, inositole alkaloids, organic acid (5.5%), parabin, calcium oxalate (7.3%) lignin (4.8%), and cellulose (22%) [13].

The gymnemic acid contain several acylated (tiglolyl, Methylbutyryol etc.) derivatives of deacylgymnemic acid (DAGA) which is a 3-0-β-glucuronide of gymnemagenin (3β, 16β, 21β, 22 α, 23, 28-hexahydroxy-olean-12-ene). The individual gymnemic acids (saponins) include gymnemic acids 1-VII, gymnemosides A-F, gymnemasaponins. The presence of gymnemic acids (+) quercitol, lupeol, (-) amyrin, stigma sterol etc. have been reported from *g. sylvestre*. A new flavonol glycoside namely kaempferol 3-0-beta-D-glucopyranosyl-(1-->4)-alpha-l-rhamnopyranosyl-(1-->6)-beta-D-glucuronopyranoside has also been found in aerial parts of *G. sylverste* [14, 15 16 and 17]. Three new oleanane type triterpene glucosdes i.e. beta-0-benzoyl sitakisogenin 3-0-beta-D-glucopyranosyl (1-->3)-beta-D-glucopyranoside and the potassium salt of 29-hydroxylongispinogenin 3-0-beta-D-glucopyranosyl (1-->3)-beta-D-glucopyranoside along with sodium salt of alternoside II were isolated from an ethanol extract of the leaves of *G. sylverstre* [7]. Four new triterpenoid saponins, gymnemasins A, B, C and D isolated from the leaves of *G. sylvestre* were identifies as 3-0-[beta-D-glucopyranosyl (1-->3)-beta-D-glucuronopyranosyl] -22-0 tiglyol gymnemanol, 3-0-[beta-D-glucopyranosyl-22-0-tiglolyl-gymnemanol and 3-0-beta-D-glucopyranosyl-gymnemanol respectively. The glycone, gymnemanol, which is a new compound, was characterized as 3 beta-22-alpha-23-2-8-pentahydroxyolean-12-ene. Gymnestrogenin, a new pentahydroxytriterpene from the leaves of *G. sylverstre* has been reported [18]. (Fig 2)

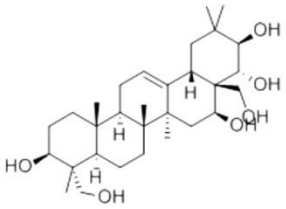
4. Ethanobotanical uses

There are over four hundred different tribal and other ethnic groups in India. Each tribal group is having their own traditional folk language, beliefs and knowledge about the use of natural resources as medicines. The plant is reported to be useful in ethanobotanical surveys conducted by ethnobotanists. It has been documented that the Jungle Irulas, inhabitants of Nagari hills of the Chittoor District, Bombay and Gujarat from India have the habit of chewing a few green leaves of *G. sylvestre* in the morning in order to keep the urine clear and to reduce glycosuria. Bourgeosis classes of Bombay and Gujarat also chew fresh leaves for the same effect. In Bombay and Madras, 'Vaids' are known to recommend the leaves in the treatment of furunculosis and Madhumeha. The Juice obtained from root is used to treat vomiting and in dysentery and the plant paste is applied with milk to treat mouth ulcer [6, 19,20].

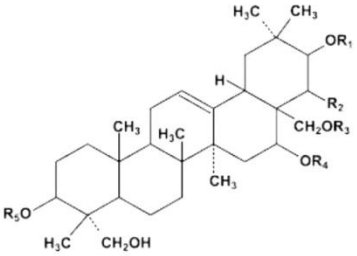
Fig.1. *Gymnema sylvestre* Habitat



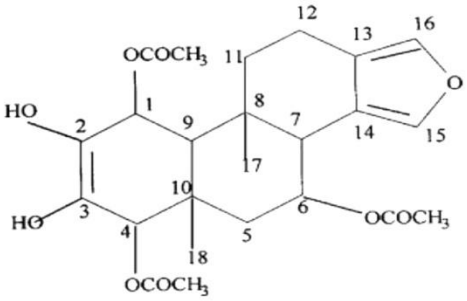
Deacyl Gymnemic acid



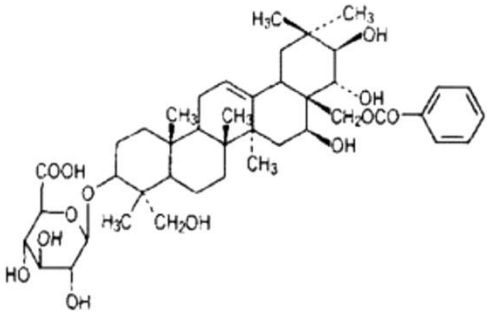
Gymnemagenin



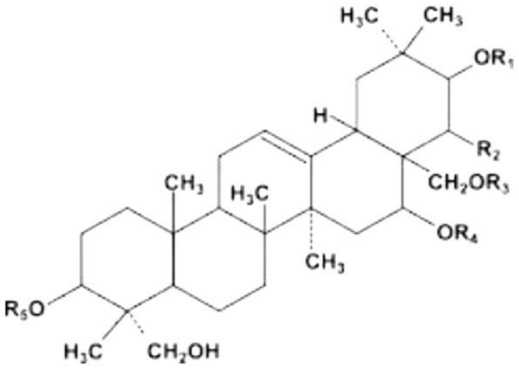
Gymnemic acid



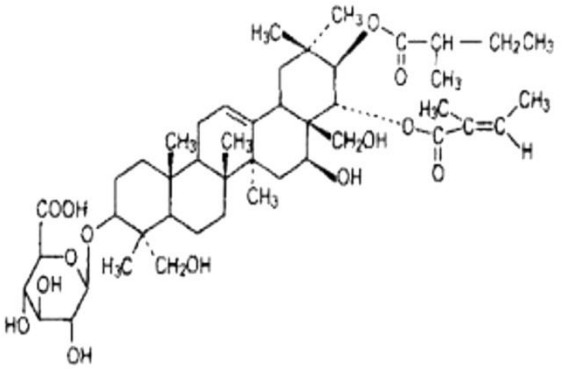
Dihydroxyl Gymnemic triacetate



Gymnemic X VIII acid



Triterpene



Gymnemic X V acid

Fig.2. Structure of some phytochemical isolated from *Gymnema sylvestre*

Table.1. Phytochemicals found in *G. sylvestre* are and their pharmacological actions

Phytochemical	**Pharmacological activity**
Ascorbic-acid	Acidulant, Aldose-Reductase – Inhibitor, Angiotensin – Receptor – Blocker, Anti AGE, Antimcrohn's, Antiaging, Antiatherosclerotic, Antidecubitic, Antidepressant, Antidote (Alumium), Antidote (Paraquate), Antiedemic Antiginvitic, Antihepatotoxic, Antihistaminic, Antiobesity, Antioxhitic, Antioxidant, Antihypertensive, Antiinflammatory, Antimeasles, Antimigrain, Antimutagenic, Antiseptic Apototic, Beta – Adrenergic Receptor Blocker, Beta – Glucuronidase-inhibitor, Colagenic, Fistula – Preventive, Hypotensive, Immunostimulant, Mucolytic, Urinary –Acidulant, Vulnerary.
Beta Carotene	Anti PMS, Antiacne, Antiaging, Antihyperteratotic, Antilupus, Antimastitic, Antimutagenic, Antioxidant, Antiphotophobic, Antiphorphyric, Antiproliferant, Antistress, Antitumor, Antixerophthalmic, Cox-1-inhibitor, colorant, Immunostimulant, Interferon – Synergist, Phagocytotic, Prooxidant, Thymoprotective.
Betaine	Antigastritic, Antihomocystinuric, Ethanolytic, Hepatoprotective.
Choline	Antialzheimeran, Antichoreic, Anticystinnuric, Antidementia, Antidyskinetic, Antimanic, Cardiodepressent, Cerebrotonic, Hepatoprotective, Hypotensive, Memoorgenic.
Conduritol – A	Aldose – Reductase – inhibitor, Antidiabetic, Antihistanimic Antiinflammatory, Antipyretic, Antiseptic, Antitesticular, Cyclooxygenase – Inhibitor, Fungicide, Gastrostimulant, Hypoglycemic, Hypotensive, Hypotehrmic, immunostimulant, Molluscidie, Mutagenic, Nematicide, Progesteronigenic, Ribosome – inactivator, sedative, serotoinnergic, Thyrotropic.
Gymnemic – acid	Antiflu, Antihistaminic, Antiinflammatory, Antiobesity, Antipyretic, Antiseptic, Antiviral, Cyclooxygenase – inhibitor, Fungicide, Gastrostimulant, Hypotensive, Hypothermic, Immunostimulant, Molluscicide, Mutagenic, Nematicide, Progresteronigenic, sedative, serotoninergic, Thyrotropic.
Gymnemic – acid - B	Antiflu, Antihistaminic, Antiinflammatory, Antiobesity, Antipyretic, Antiseptic, Antiviral, Cyclooxygenase – inhibitor, Fungicide, Gastrostimulant, Hypotensive, Hypothermic, Immunostimulant, Molluscicide, Mutagenic, Nematicide, Progresteronigenic, sedative, serotoninergic, Thyrotropic.
Niacin	Antimenierei's, Antiacrodynic, Antiallergic, Antiamblyopic, Antianginal, Antichilblain, Anticonvulsant, Antihistaminic, Antiinsomnic, Antineuralgic, Antiparkinsonian, Antiscotomic, Antipellagric, Antiscotomic, Hepatoprotective, Sedative, Serotoninergic.

5. Traditional uses

G. sylvestre is a potent antidiabetic plant, used in folk, ayurvedic and homeopathic systems of medicine. It is also used in the treatment of asthma, eye complaints, family planning, snake bite, urinary complaints, stomach problems, piles, chronic cough, breathing troubles, colic pain, cardiopathy, constipation, dyspepsia hemorrhoids, and hepatosplenomegally. In addition, it also possesses antimicrobial, antihypercholesterotemic, anti-inflammatory and sweet suppressing activities and it is also acts as feeding deterrents to caterpillar [6,10]. Susruta describes *G. sylvestre* as a destroyer of Madhumeha [glycosuria and other urinary disorder]. It is also reported to be bitter, astringent, acrid, thermogenic, anodyne, digestive, liver tonic emetic, diuretic, stomachic, stimulant, antihelmenthics, laxative, expectorant, antipyretic and uterine tonic. It is useful in constipation and Jaundice, renal and vesicle calculi, bronchitis, amenorrhoea, conjuctivitis and leucoderma [21-23]. The drug is also used in the composition of ayurvedic preparations like Ayaskri, Varunadi Kasaya, Varunadighrtam, Mahakalyanakaghrtam [24].

6. Pharmacological uses

Following the folk and traditional use of the plant, it has been investigated scientifically to validate the potential of plant in curing a variety of ailments.

7. General pharmacological activities

The LD_{50} of ethanol and water extract of *G. sylvestre* , administered intraperitoneally in mice, was found to be 375 mg/kg [25]. In an acute toxicity study in mice, no gross behavioral, neurologic, or autonomic effects were observed. The safety ratio (LD_{50}/ED_{50}) was 11 and 16 in normal and diabetic rates respectively [26]. The pharmacological activities of this plant are given below.

7.1. Antiobesity study

G. sylvestre helps to promote weight loss possibly through its ability to reduce cravings for sweets and control blood sugar level. It has been reported that the gurmar in peptide, block the ability to tasked sweet or bitter flavors and thus reduces sweet cravings [27, 28]. A standardized *G. sylvestre* extract in combination with niacin-bound chromium and hydroxycitric has been evaluated for antiobesity activity by monitoring changes in body weight, body mass index (BMI), appetite, lipid profiles, serum leptin and excretion of urinary fat metabolites. This study showed that the combination of *G. sylvestre* extract and hydroxycitric acid, niacin bound chromium can serve as an effective and safe weight loss formula that facilitate a reduction in excess body weight and BMI while promoting healthy blood lipid level [28].

7.2. Antidiabetic activity

The first scientific conformation of *G. sylvestre* use in human diabetics came almost a century back when it was demonstrated that the leaves of *G. sylvestre* reduce urine glucose in diabetics [29]. In an animal study, [30] investigated the sakkarakkolli leaf power had positive and encouraging effects over blood glucose levels. No adverse effect was observed on the health status of subjects and thus, it can thus be concluded that the sakkarakkolli powder is effective in lowering the fasting as well as post prandial blood glucose levels. Moreover, antihyperglycemic action of a crude saponin fraction and five triterpene glycosides derived from methanol extracts of *G. sylvestre* has also been investigated [31].

7.3. Antimicrobial activity

The ethanolic extract of *G. sylvestre* leaves showed good antimicrobial activity against *Bacillus pumilis, B. subtilis, Pseudomonas aeruginosa* and *Staphylococcus aureus* and no activity were found against *Proteus vulgaris* and *Escherichia coli* [18]. The aqueous and methanolic extracts of *G. sylverstre* leaves also showed moderate activity against the three pathogenic *Salmonella species* (*S. typhi, S. typhimurium* and *S. paratyphi*). Out of the two extracts used, aqueous extract showed higher activity against the *Salmonella species* [32]. Ethanolic, chloroform and ethyl acetate extracts of the aerial parts of *G. sylvestre* also reported to have antibacterial effects against *P. vulgaris, E. coli, P. aeruginosa*, *Klebsiella pneumoniae* and *S. aureus* [33].

7.4. Anti-inflammatory activity

The aqueous extract of *G. sylvestre* leaves was investigated for evaluation of anti-inflammatory

activity in rats at a dose 200, 300 and 500 mg/kg in carrageen induced paw edema and Cotton Pellet method. The aqueous extract at 300 mg/kg decreased the paw edema volume by 48.5 per cent with in 4 h after administration, while standard phenylbutazone decreased the paw edema volume by 57.6 per cent when compared with paw edema volume of control. The aqueous extract at dose of 200 mg/kg and 300 mg/kg produced significant reduction in granuloma weight, when compared to control group [16].

8. Dosage forms

In market, *G. sylvestre* is available in the form of crude powder, paste and solid in standardized form. The plant material is also available in the form of capsule or tablets in combination with other herbal products [34].

8.1. Adult dose: In liquid form (extract), 25 to 75 ml per week recommended best result of this medicine will come after 6 to 12 months of continuous use. It is also prescribed in tablet form; in this case 8 to 12 g per day of leaf equivalent is recommended.

8.2. Pediatric dose: In this case, there is insufficient evidence about its uses for pediatric population, so it cannot be recommended for them [34].

9. Diabetes mellitus

Diabetes mellitus is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormal high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the beta cells of the pancreas. Diabetes mellitus refers to the group of disease that lead to high blood glucose levels due to defects in either insulin secretion or insulin action [35]. Diabetes develops due to a diminished production of insulin (in type 1) or resistance to its effects. Both lead to hyperglycemia, which largely causes the acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. Monogenic forms eg. MODY, constitute 1-5 per cent of all cases.

The term diabetes, without qualification, usually refers to diabetes mellitus, which is associated with excessive sweet urine (known as "glycosuria") but there are several rare conditions also named diabetes. The most common of these is diabetes insipidus in which the urine is not sweet [Insipidus means "without taste" in latins]; it can be caused by either kidney (Nephrogenic DI) or Pituitary gland (central DI) damage. Most cases of Diabetes mellitus fall into one of two broad categories. The term "type I diabetes" has universally replaced several former terms including childhood-onset diabetes, Juvenile diabetes, and insulin-dependent diabetes (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult onset diabetes, (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as, among others, gestational diabetes, Insulin-resistant type 1 diabetes (or double diabetes), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes 9 adults (or LADA or "type 1.5" diabetes). There is also maturity onset diabetes of the young (MODY) which is a group of several single gene (Monogenic) disorders with strong family histories that present as type 2 diabetes before 30 years of age [19].

10. Rasayana Therapy in Diabetes Mellitus

Rasayana is an important branch of Ayurveda. The main goal of Rasayana Therapy is better quality of life with increased lifespan. Rasayana includes drug formulation, dietary regimen and code of conduct. Many of the drugs used in Rasayana therapy in diabetes mellitus have excellent antioxidant properties, like *Phyllanthus emblica*, *Azadirachta indica*, *Ocimum sanctum*, G. *sylvestre* and *Tinospora cordifolia* [35].

The Rasayana approach to treat diabetes consist Aeara Rasayana (antistress), Ajasrika Rasayan (dietary control), Osad Rasayana (preventive), Naimittika Rasayana (hypoglycemic).

11. Mechanism of action of *G. sylvestre* (Gymnemic Acid)

G. sylvestre leaves have been found to cause hypoglycemia in laboratory animals and shown a use in herbal medicine to treat diabetes mellitus in adults.

When leaf extract of plant, administered to a diabetic patient, there is stimulation of pancreas by virtue of which there is an increase in insulin release. These compounds have also been found to increase fecal excretion of cholesterol [36,37]. There are some possible mechanisms by which the leaves extract of *G. sylvestre* or (Gymnemic acid) possess its hypoglycemic acid effects are:

i. It promotes regeneration of islet cells
ii. It increase secretion of insulin
iii. It causes inhibition of glucose absorption from intestine.
iv. It increases utilization of glucose as it increases the activities of enzymes responsible for utilization of glucose by insulin dependent pathways. An increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase [36]

12. Clinical indications

The primary clinical application for this botanical is as an antidiabetic agent, Gymnema has been the object of considerable research since the 1930's with promising results for both type 1 and type 2 diabetes. Numerous animal studies have confirmed the hypolglycemic effect of *Gymnema sylvestre* [38-40].

12.1. Type 1 diabetes

In a controlled study, a standardized extract of the plant was given to 27 type 1 diabetics at a dose of 400 mg daily for 6-30 months. Thirty-seven other diabetics continued on insulin therapy alone and were tracked for 10-12 months. In *Gymnema* group, insulin requirements were decreased by one half and the average blood glucose decreased from 232 to 152 mg/dL. The control group showed no significant decreases in blood sugar or insulin requirement. In addition, there was a statistically significant decrease in glycosylated hemoglobin (AbAIC) after 6-8 months of *Gymnema sylvestre* when compared to pretreatment levels or the control group [41].

12.2. Type 2 diabetes

Twenty-two type 2 diabetics were administered 400 mg *Gymnema* extract daily for 18-20 for months along with their oral hypoglycemic medications. This group experienced significant decreases in average blood sugar and HbAIC, and an increase in pancreatic release of insulin. Medication dosages were decreased and five participants were able to discontinue their medication entirely.

13. Lipid-lowering

Preliminary animal studies indicate Gymnema may be beneficial for lowering blood lipids. When fed to rats on either high-or-normal-fat diet for 10 weeks, *Gymnema sylvestre* suppressed body weight gain and liver lipid accumulation to the same extent as chitosan in those on a high-fat diet. In a three week study in rats, Gymnema feeding decreased total cholesterol and triglycerides and increased fecal fat elimination [42]. Further research is warranted to determine whether Gymnema has this same lipid – lowering effect in clinical practice.

14. Conclusion

Now-a-days traditional and ethno botanical uses of natural compounds, especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. They obviously deserve scrutiny on modern scientific lines such as physiochemical characterization, biological evaluation, toxicity studies, Investigation of molecular mechanism of action(s) of isolated phytoprinciple and their clinical trials. Diabetes is now becoming a common disease through the world and a lot of new drugs are being synthesized for the same. Many Indian herbs are being used in traditional practices to cure diabetes, *G. sylvestre*, has an important place among such antidiabetic medicinal plants. It possess hypoglycemic and hypolipidemic activity in long term treatment and is also capable of regenerating β-cells and hence it could be used as a drug for treating diabetes mellitus. Because it has regenerating ability of β-cells, at least the people in the earliest stages of the disease could be treated to delay or prevent full-blow clinical diabetes.

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