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A REVIEW ON PHARMACOLOGICAL POTENTIAL OF MADHUNASHINI (*GYMNEMA SYLVESTRE*)

Biochemistry

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ABSTRACT

The naturopathic treatment for diseases has been explored extensively since ancient times and gaining momentum in the present scenario. *Gymnema sylvestre* is a plant included in Apocynaceae family and is located in many regions of Asia, Africa and Australia. This plant is widely used as a traditional therapy for different purposes. It is known to have blood glucose lowering potential, hence it is widely used in traditional and Ayurvedic systems of medicine. Although, *G. sylvestre* has been proven valuable through its numerous useful properties, not many studies especially clinical studies on this plant are available. Therefore, in this book chapter we narrated the clinical evidences on therapeutic potentials of *G. sylvestre* and future perspectives of *G. sylvestre* potentials as medicinal plant. Clinical studies reported in the literature evidenced that *G. sylvestre* constitutes mainly saponins, flavonol, glycosides, gymnemanol, gurmarin etc... and these phytochemicals are responsible for pharmacological activites such as anti-diabetic, anti-oxidative, anti-metastatic, anti-inflammatory, lipid-lowering and several other properties. The taste of *G. sylvestre* suppresses the ability to detect sweet tastes. It has an important place among such antidiabetic medicinal herbs. It has shown experimental or clinical anti-diabetic activity and it boosts human insulin level. Hence, it can be chosen as a source for the development of industrial products for treatment of diabetes mellitus. Future perspectives of *G. sylvestre* mainly includes: a modern effective and safe drug development could be recommended after extensive investigation of its pharmacodynamics, kinetics, proper standardization and clinical trials on this herb and its products including standardization of various parts and drug development program using *G. sylvestre* compounds for their better economic and therapeutic utilization and Information about genes which code for economically viable traits or pharmacologically important bioactive molecules holds great prospects in crop engineering and exploitable for medicinally important plant like *G. sylvestre* plant.

KEYWORDS

Gymnema Sylvestre, Madhunashini, Antidiabetic, Hypolipidaemic, Anti-inflammatory

INTRODUCTION:

The naturopathic treatment for diseases has been explored extensively since ancient times and gaining momentum in the present scenario. Indian flora accounts for about 45,000 plant species out of which several thousands have pharmacological significance[1]. Plants are a great concern for drug discovery exploration and a major source of our modern medicine. About 25% of modern medicines are derived from a plant source and merely 5-15% of plants have been investigated for their medicinal use[2]. Nowadays, natural plants, herbal medicines, phytomedicines and functional foods are extensively studied by scientists all over the world which resulted with the lucrative therapeutic potentials such as antidiabetic[3-6], anticancer[7,8], immunomodulating[9-13], antiobesity and lipid lowering[3,14], anti-inflammatory[15] and anti-bacterial activities[16].

Among the potential medicinal plants, *Gymnema sylvestre*, belongs to the family of Apocynaceae and is traditionally used for the treatment of various diseases. It is a wild herb found in India, Africa, Australia, and China. It is known as Meshashringi, Merasingi, Kavali, Kalikardori, Vakundi, Dhuleti, Mardashingi, Podapatri, Adigam, Cherukurinja, Sannagerasehambu, Chigengteng or Australian Cowplant, Waldschlinge in German, Periploca of the woods in English[17]. This plant is also recognized as 'Gurmur' due to having sugar lowering property[18]. *G. sylvestre* was considered as one of the major botanicals to treat diabetes in the Ayurvedic system of medicine and also is included in Indian Pharmacopoeia as an anti-diabetic plant[19]. As it is useful against major diseases such as cardiovascular diseases, asthma, cancer, diabetes and obesity, different formulation of this plant is found in a number of preparations such as tea bags, health tablets, and food supplements. In various studies, *G. sylvestre* is reported to be effective against arthritis, diuretic, anemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, constipation, microbial infections, indigestion, and as an antiinflammatory agent[18].

Though Madhunashini (*Gymnema sylvestre*) has been proven valuable through its numerous useful properties, not many studies especially clinical studies on this plant are available. Therefore, in this review article we aim to narrate the clinical evidences on therapeutic potentials of *G. sylvestre* and future perspectives of Gymnema *sylvestre* potential as medicinal plant.

TRADITIONAL PERSPECTIVES:

G. sylvestre is mentioned in Shushruta, an ancient book on medicine as a remedy for glycosuria and urinary disorder[20]. It is a therapeutic herb having multiple potentials as mentioned in folk medicine, Ayurveda, and Homeopathic systems of medicine[17]. Traditionally, it has been used to treat diabetes, malaria and snake bites as well as to treat diseases caused by phlegm and piles in the Ayurvedic system of medicine[19,21]. In Ayurveda, the plant is prescribed for the treatment of dyspepsia, constipation, jaundice, hemorrhoids, renal and vesicle calculi, cardiopathy, asthma, bronchitis, amenorrhea, and leucoderma[22-25], Furthermore, different parts of the plant such as the roots, stem, and leaves have been used as cardiotonic, digestive, diuretic, laxative, stimulant, stomachic and uterine tonic in traditional medicine systems[25]. Various parts of this plant are used by different tribes in India such as the Sahariya tribe of Madhya Pradesh, Junglee Irulas of Nilgiri hills, Kol tribe of Chhattisgarh and the Nayaks of Karnataka to treat mainly asthma, eye and gastric problems, parkinsonism, urinary problems and diabetes[24,26,27].

TAXONOMY:

G. sylvestre R. Br. is a perennial, woody climber belonging to family Asclepiadaceae or the "milk weed" family[28]. The genus is classified into 40 species, some of which like *G. sylvestre, G. montanum, G. yunnanense* and *G. inodorum* have medicinal properties (Table 1)[29-31]. The plant is found in tropical and subtropical regions, well distributed in parts of central and southern India and in the southern part of China, tropical Africa, Malaysia and Sri Lanka[19]. *G. sylvestre* is slow growing herb, found ideally in tropical and subtropical humid climate and common in hills of evergreen forests. It is a climber and generally requires support for growth. The seeds are sown in the months of November-December and harvested from September to February. The propagation through seed germination is difficult due to low viability

of the seeds; therefore, the alternative has been root cuttings which are generally planted in the months of June and July[32]. Terminal cuttings with three of four nodes have also been used as for vegetative propagation and usually planted in the month of February-March[33]. The leaves are opposite, usually elliptic or ovate (1.25–2.0 inch × 0.5–1.25 inch), inflorescence is lateral umbel in cymes; follicles are terete and lanceolate, up to 3 inches in height. Corolla is pale yellow in colour, valvate, campanulate with single corona with 5 fleshy scales. The calyx-lobes are long, ovate, obtuse and pubescent. Carpels-2, unilocular, ovules locules may be present, anther connective produced into a membranous tip (Figure 1)[27,34].

Table 1: Taxonomy of Gymnema sylvestre

Kingdom Plantae
Sub kingdom Tracheobionta
Super division Spermatophyta
Division Magnoliophyta
Class Magnoliopsida
Subclass Rosidae
Order Gentianales
Family Apocynaceae Subfamily Asclepiadaceae
Genus *Gymnema*
Species *Gymnema sylvestre (Retz.)* R.Br. ex Sm[1]

Figure 1: *Gymnema sylvestre* plant

PHARMACOLOGICAL POTENTIALS:

G. sylvestre is one of the indispensable medicinal plants used in Ayurvedic system of medicine for the treatment of diverse diseases (Figure 2) and are well known for their sweet taste suppressing activity and are used for the treatment of diabetes mellitus. It is used in food additives against obesity. Authors group previously described some medicinal plants and biological entities (macrofungus) as golden gift for human kind[35-37]. In continuation, *G. sylvestre* has been the subject of extensive phytochemical and bioactive investigations due to its importance in traditional folk and Ayurvedic system of medicine.

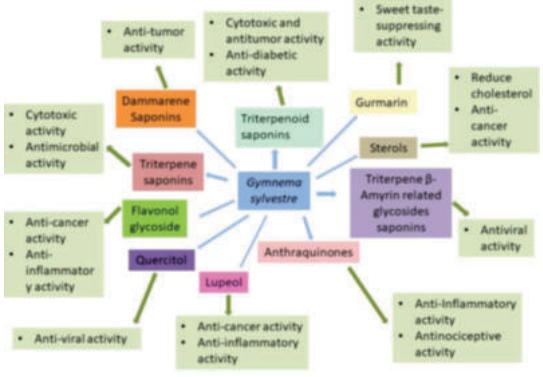

Figure 2: Pharmacological activities of *Gymnema sylvestre* Adapter from Khan et al 2019

Antidiabetic Activity:

The most widely known effect of *G. sylvestre* is antidiabetic activity. Ethanol extract of this plant is reported to reduce glucose level by 46% where the water extract reduced glucose level by 26% and methanol extract by 12%[38-42]. In dexamethasone-induced insulin resistance rats, aqueous extract of this plant was found to be improving the altered glucose, insulin and lipid profile[43]. Administration of this plant in a diabetic animal model resulted in reductions in the blood levels of insulin, protein, triglycerides, cholesterol and glucose, as well as a reduction in body weight and was found to improve liver histopathology[44]. In another study where alloxan-induced diabetic rats were used, this plant extract significantly ($p < 0.05$) reduced fasting blood glucose level, total cholesterol, serum triglycerides and increase HDL-cholesterol level and is also described to significantly alter ($p<0.05$) the elevated level of urea, uric acid and creatinine levels in diabetic rats to nearly normal levels[45,46].

Gymnema sylvestre reduced the level of blood glucose levels after both acute and chronic administration of methanolic extract of this plant on Wister rats[47]. In the case of Streptozotocin-induced diabetic rats, it has been shown that treatment using this plant significantly ($p<0.05$) decreased the elevated blood glucose, ALT, AST, triglycerides, total cholesterol, LDL-cholesterol and malondialdehyde and significantly ($p < 0.05$) increased insulin, HDL-cholesterol and erythrocyte superoxide dismutase levels in diabetic rats and also is capable of regenerating insulin producing β-cells[48-51]. Gymnemic acids (a type of triterpene saponins compounds) are the class of active constituents isolated form *Gymnema sylvestre*. It was found that gymnemic acid IV given at a dose of 3.4/13.4 mg/kg administered for 6 hours decreased blood glucose levels by 14.0–60.0% as compared to glibenclamide. Also, gymnemic acid IV increased plasma insulin levels in STZ diabetic mice when administered at a concentration of 13.4 mg/kg[52]. In a study, oral administration of small concentrations (0.2 g/kg) of this plant produced a reduction in the elevated levels of blood sugar induced by sucrose[53]. However, Galletto et al. (2004) also informed an absence of anti-diabetic activity of *G. sylvestre* in an alloxan treated animal model[54].

Shanmugasundaram et al investigated that patients received 200 mg Gymnema powder twice daily in addition to their usual doses of insulin, mean glycosylated hemoglobin (HbA 1c) decreased significantly from baseline (12.8 to 9.5%) at 6 months in a controlled trial of patients with type 1 diabetes[55]. Mozersky reported that 22 patients were given G. sylvestre extract along with their oral hypoglycemic drugs. All patients demonstrated improved blood sugar control. Twenty-one out of the twenty-two were able to reduce their oral hypoglycemic drug dosage considerably and five patients were able to discontinue their oral medication and maintain blood sugar control with the extract alone[56].

Mechanism of Action:

Several possible mechanisms have been proposed to explain the antidiabetic activity of *G. sylvestre* (Figure 3). Gymnemic acids can prevent absorption of sugar molecules by the intestine, which leads to a reduction in blood sugar levels[18]. One of the constituents of *G. sylvestre* is gymnemic acid which is a mixture of saponins[57]. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules and it blocks the receptor site for sugar in the intestines, preventing the absorption of sugar which reduces blood sugar level[58]. Rapid screening by Affinity Ultrafiltration-HPLC-MS shows that it contains α-glucosidase inhibitors[59].

It is reported to increase the activity of enzymes which are insulin dependent including hexokinase, glycogen synthetase, glyceraldehydes 3-phosphate dehydrogenase, and glucose 6-phosphate dehydrogenase and to decrease the activity of insulin-independent enzymes such as glycogen phosphorylase, gluconeogenic enzymes, glucose 6-phosphatase, fructose 1,6- diphosphatase and sorbitol dehydrogenase, which also increases phosphorylase activity. *G. sylvestre* was also found to increase the secretion of insulin and the possible role in regenerating insulin as well as β-cell was suggested[48,55,60]. In a study, methanol extract of this plant showed increased effect on β-cell regeneration and was extrapolated that this plant might be able to completely recover pancreatic-cells function and thus treating type I diabetes[61].

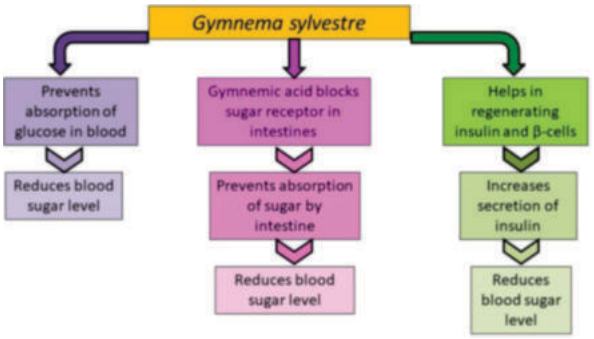

Figure 3: Possible mechanism of action of antidiabetic activity of *Gymnema sylvestre*
Adapter from Khan et al 2019

Anticancer and Cytotoxic Activity:
Many plant-derived saponins, namely, ginsenosides, soyasaponins, and saikosaponins have been found to exhibit significant anticancer activity. Anticancer potential of gymnemagenol on HeLa cancer cell lines in *in-vitro* conditions, was determined[62]. The cytotoxic activity of the saponins was tested by MTT cell proliferation assay. Different concentrations of gymnemagenol (5, 15, 25, and 50 µg/mL) were taken and plates were incubated for 48 hours. The IC_{50} value was found to be 37 µg/mL for gymnemagenol and after 96 hours, the extract at a concentration of 50 µg/mL showed good cytotoxic activity on 73 % on HeLa cells. The isolated bioactive constituent, gymnemagenol was found to show a high degree of inhibition to the proliferation of HeLa cancer cell line. Further, these saponins were not toxic to the growth of normal cells under *in-vitro* conditions[63]. With the rising percentage of cancer in people, the herbal formulation is a prospective medication in cancer therapy.

Hypolipidaemic Activity:
G. sylvestre leaf extract was observed to possess very potent hypolipidaemic activity. In a study, G. sylvestre leaf extract was administered to Wister female rats. These rats were introduced to hyperlipidemia by high-fat diet. It was detected that this extract significantly lowered the level of cholesterol ($p<0.01$), low-density lipoprotein (LDL) ($p<0.01$) and triglyceride ($p<0.01$) as well as increased the level of high density lipoprotein (HDL) ($p<0.001$) effectively[64]. Furthermore, hydro-alcoholic leaf extract of G. sylvestre was also observed to have lipid-lowering potential. In this study, rats were given high cholesterol for seven days and a higher level of cholesterol, triglyceride, LDL and a lower level of HDL was observed. After seven days, these rats were treated with G. sylvestre extract and it was reported to lower the elevated cholesterol, triglyceride, LDL level and increase the HDL level. It was suggested that this plant renders lipid lowering potential due to the presence of acidic constituents such as flavonoids, saponins, tannins etc…[47,65] Similarly, in several other studies, it was reported to reduce triglyceride, cholesterol, very low density lipoprotein (VLDL) and low□density lipoprotein (LDL) in diabetic rats[66,67].

Antimicrobial Activity:
The antibiotic and antimicrobial activity of different extracts of *G. sylvestre* was determined against a number of pathogens, namely, *S. aureus, E. coli*, and *B. subtilis* while no activity was observed against gram-negative bacteria. *G. sylvestre* leaf extracts showed good prospects as an antibiotic herbal remedy was effective as herbal formulation for the treatment of microbe's related infections[68]. Bhuvaneswari et al demonstrated that the methanolic extracts of *G. sylvestre* were assessed for antimicrobial activity of aerial and root parts separately. The result exhibited that the methanol extracts in acidic range have good activity towards all the pathogens showing its broad spectrum nature[69]. In another study reported by Satdive et al the antimicrobial effect of ethanolic extract of *G. sylvestre* against *B. pumilus, B. subtilis, P. aeruginosa* and *S. aureus* showed promising antimicrobial effect[70]. It can be inferred from the studies that the methanolic and ethanolic leaf extract of *G. sylvestre* possesses considerable antibiotic and antimicrobial activity.

Antioxidant Activity:
Ethanol extract of this plant revealed significant ($p<0.05$) 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity and showed better antioxidant potential than A. bilimbi and *C. frutescent*[71]. Anti-oxidant activity of *G. sylvestre* against DPPH was also observed in an investigation by Rupanar et al[72]. This plant was found to have better DPPH radical scavenging than butylated hydroxyl toluene (BHT) and in another study it was also found to reduce LDL oxidation[72,73]. Recently, in another study, hydroxyl free radical scavenging activity and significant antioxidative potential of this plant against DPPH was reported where DPPH inhibition was at the level of 87.3% and hydroxyl free radical inhibition was 59.8%[74]. It was also found to have significant radical scavenging activity against ferric ($p<0.05$), super oxide ($p<0.05$) and also against hydrogen peroxide ($p < 0.05$)[75]. *G. sylvestre* showed antioxidant activity in several conditions such as against high fat diets, hydrogen peroxide, nitric oxide and superoxide radically induced oxidative stress in rats[76-79].

Anti-inflammatory Activity:
In the Ayurvedic system of medicine, the leaf of *G. sylvestre* has been widely used and is considered as bitter, acrid, thermogenic, digestive, liver tonic, anodyne and anti-inflammatory[79]. The bioactive constituents in *G. sylvestre* known as tannins and saponins are responsible for the anti-inflammatory activity of the plant[80]. In the study, carrageenin induced paw oedema and cotton pellet induced granuloma rats were taken and the aqueous extract of G. sylvestre leaf was investigated for its anti-inflammatory activity at the doses of 200, 300, and 500mg/kg with drug, phenyl butazone as standard. It was found that the Gymnema aqueous extract at a concentration of 300mg/kg significantly decreased the paw oedema volume by 48.5% within 4 hours of administration while the drug phenyl butazone decreased the paw oedema volume by 57.6%. Also, the aqueous extract at a concentration of 200 and 300 mg/kg exhibited reduction in granuloma when compared with the control group[81].

Immunomodulatory Activity:
Immunomodulation is referred to as the regulation or control of the immunity which involves the enhancement or reduction in the immune responses. The body response to a particular condition might be regulated by agent that enhances or suppresses its action[82]. *G. sylvestre* is reported to be an immunostimulatory plant and the leaves possess immunostimulatory effect[83]. The aqueous leaf extract was tested for immunostimulatory activities by detecting the movement of neutrophils, chemotaxis tests, phagocytosis of killed *C. albicans* and nitro blue tetrazolium assays. Aqueous leaf extract of *G. sylvestre* showed remarkable immunostimulatory activity at 10, 25, 50, 100, and 1000 µg/mL on human neutrophils under in vitro conditions[84].

Methanolic leaf extract of *G. sylvestre* (MLEGS) showed immunosuppressive activity in Swiss Albino mice when it was tested by performing hemagglutination antibody (HA) titer, delayed-type hypersensitivity (DTH) tests and flow cytometric techniques for the estimation of B lymphocytes (CD3 and CD19) and Th2 cytokines (IL-2, IFN-γ and IL-4). This plant significantly reduced primary and secondary antibody response and DTH response in a dose-related manner. At 200 mg/kg body weight, the maximal reductions occurred in the production of CD3, CD19, IL-2, IFN-γ and IL-4 at the level of 31.59, 32.12, 29.51, 32.45 and 33.53%, respectively[85]. However, it was also perceived that *G. sylvestre* enhances the level of myeloid and lymphoid components of the immune system. Methanolic extract of this plant significantly increased ($p<0.05$) the stimulation of Nitric oxide (NO) and Reactive Oxygen Species (ROS) by stimulation of macrophage activity and also significantly ($p<0.05$) reduced nitro blue tetrazolium[86]. Aqueous extract of *G. sylvestre* also stimulated the phagocytic function of human neutrophils suggesting an immunostimulatory activity[87]. Ethanol extract of this plant was observed to improve immunosuppressed condition induced by cyclophosphamide in Albino Rats. In this study, the plant extract significantly improved haemagglutination titer, phagocytic activity and decreased paw edema ($p<0.01$, $p<0.05$ and $p<0.05$ respectively), when compared with cyclophosphamide treated control[88]. In another study, potent immunostimulatory potential of the aqueous extract of this plant was observed[89].

Antiarthritic Activity:
Aqueous and petroleum extract of *G. sylvestre* revealed significant ($p<0.01$) antiarthritic activity[90]. It was suggested that *G. sylvestre* may have reduced the release of inflammatory mediators which is necessary to reduce bone destruction in anti-arthritic condition[90]. In another study, ethanolic extract of the root of *G. sylvestre* reduced carrageenan rat paw oedema significantly ($p<0.01$) and inhibited 39-75% of histamine induced rat paw oedema[91].

Hepatoprotective Activity:
In an in-vitro investigation, hydro-alcoholic extract of *G. sylvestre* was observed to render anti-hepatotoxic function in a dose-dependent manner in isolated rat hepatocytes where hepatotoxicity was induced using D-galactosamine. A significant increase in the level of ASAT, ALAT, ALP, total bilirubin and direct bilirubin ($p< 0.001$) was observed[92]. It was reported to lower urea and creatinine levels after acute and chronic administration of methanolic extract of this plant in Wister rats[47]. In a study where methanolic poly herbal preparation containing this plant was used, it was observed that the preparation can reverse hepatotoxicity in Albino rats induced by paraffin and carbon tetrachloride[93].

CLINICAL STUDY EVIDENCES:
Apart from various investigations on animal models, different extracts of this plant were tested on humans to inspect its therapeutic potential on the human body. Clinical investigations on *G. sylvestre* revealed its potential to reduce body weight and glucose levels, triglyceride, LDL-c, total cholesterol and elevate the amount of insulin and C-peptide available in blood. A study conducted on 58 patients with type 2 diabetes mellitus for 90 days resulted in the reduction of fasting ($p<0.005$) and post prandial blood glucose levels ($p<0.001$) along with a reduction of triglyceride ($p< 0.05$)[94]. In another study, where 64 individuals with type 1 diabetes were treated with Gymnema leaf extract for 6 to 30 months resulted with the reduction of plasma glucose level, reduced external insulin dose and significant reduction in HbA1c ($p<0.001$)[94]. Significant ($p<0.05$) reduction in blood glucose level was observed in another study where 32 human subjects with type-2 diabetes were administered with *G. sylvestre* leaf powder in hard gelatin capsule for 30 days. Reduction in triglyceride, cholesterol and LDL level was also observed in this study[95]. The therapeutic potential of *G. sylvestre* (GS) observed from clinical studies so far conducted has been summarized in Table 1.

Table 1: List of outcomes of clinical studies on *Gymnema sylvestre*

Preparation of plant given	No. of Subjects	Duration	Therapeutic potential	Reference
OSA (Novel high molecular weight GS preparation)	11	60 days	• Significant reduction in fasting and postprandial blood glucose level ($p<0.005$ and $p<0.02$ respectively) • Significantly increased level of insulin and C-peptide in blood ($p<0.05$ and $p<0.001$, respectively)	Al-Romaiyan et al 2010[96]
Extract of leaves in capsule form	58 human subjects with type-2 diabetes	90 days	• Reduction in hyperglycemia and hypertriglyceridemia ($p < 0.05$) • Reduced fasting and post-prandial blood glucose levels significantly ($p<0.005$ and $p<0.001$, respectively) • Significantly increased HbA1c level ($p<0.001$) • Significantly reduced insulin resistance ($p<0.05$)	Kumar et al 2010[94]
GS leaf powder in hard gelatin capsule	32 human subjects with type-2 diabetes	30 days	• Significantly reduced glucose level ($p<0.05$) • Reduced triglyceride, cholesterol and LDL level	Li et al., 2015[95]
Aqueous GS leaf extract	8 healthy participants	90 min	• Reduced oral sweet taste sensation significantly ($p<0.05$) • Reduced blood glucose level	Kashima et al 2017[97]
Ethanol extract of GS leaves	22 type 2 diabetic patient	18-20 months	• Reduced glucose level significantly ($p<0.001$) • Elevated serum insulin in both the fasting and post-prandial state	Baskaran et al 1990[98]
Leaf extract of GS	64 individuals with type 1 diabetes	6 to 30 months	• HbA1c level was reduced significantly ($p<0.001$) • Reduced glucose level • Reduced requirement of Insulin	Shanmugasundaram et al 1990b[98]
G. sylvestre (Swanson Premium G. sylvestre leaf; Swanson Health Products, Fargo, ND, USA)	24 diabetic patients	12 weeks	• Reduction in body weight, body mass index (BMI) significantly ($p<0.05$ and $p<0.05$, respectively) • Decreased level of very low-density lipoprotein (VLDL) significantly ($p < 0.05$)	Zuniga et al., 2017[99]
Calcium-potassium salt of (-)-hydroxycitric acid, niacin-bound chromium and GS	90 obese subjects	8 weeks	• Reduced weight	Preuss et al., 2005[100]
Drops of GS "Q" with 1/4 cup of water	21 people type 2 diabetes	6 months	• Controlled blood glucose level	Kothe and Uppal, 1997[101]
Aqueous decoction of shade-dried powdered leaves of GS	10 healthy and 6 diabetic adults	10 days	• Reduced blood glucose level	Khare et al., 1983[102]

CONCLUSIONS:
Medicinal plants served as a platform for ancient Ayurvedic system of medicine. In the present scenario, herbal therapeutics are gaining momentum in pharmacological applications and as molecular targets in the drug development. The emerging trend in rising incidence of diseases and associated complications with commercial medications poses a serious threat to mankind. Naturopathic treatments offer respite from the high cost of expensive drugs as well as in being comparatively safe with less side effects. It is estimated that nearly 80% of population depends on the natural remedies for health care. Plants are a valuable source of a number of bioactive compounds like alkaloids, quinine, paclitaxel, opium alkaloids, quinine, atropine and cardiac glycosides (digitalis, ouabain) to name a few. The first antidiabetic drug, metformin, isolated from Galega officinalis, was a herbal formulation. Thus, it becomes very important to screen plants with pharmacological significance as a basis for the development of newer and more effective therapeutics.

One of these therapeutically important plants that contain significant biologically important phytochemicals is *G. sylvestre*. *G. sylvestre* contain significant biologically important phytochemicals. It constitutes saponins, flavonol, glycosides, gymnemanol, gurmarin etc... These phytochemicals isolated from *G. sylvestre* can provide pharmacological activities such as anti-diabetic, anti-oxidative, anti-metastatic, anti-inflammatory, lipid-lowering and several other properties. The taste of Gymnema suppresses the ability to detect sweet tastes. It has an important place among such antidiabetic medicinal herbs. It has shown experimental or clinical anti-diabetic activity and it boosts our insulin level. Since each part of *G. sylvestre* has some medicinal property, it is very much commercially exploitable. During the last few decades' considerable progress has been achieved regarding its biological activity and medicinal

applications. Hence, it can be chosen as a source for the development of industrial products for treatment of diabetes mellitus. Medicinal value of this herb has become a matter of great significance particularly its antidiabetic action which is reported by several researchers with possible mechanism of action.

IMPENDING PERCEPTIONS:

In spite of the good prospects of herbal medicines, *G. sylvestre* gained little importance due to absence of scientific validation. The lack of availability of standards for herbal formulations is a major limitation. Although, a vast repertoire of plant resources is available but very few have experimentally validated and scientifically approved as medications for the treatment of diseases. Furthermore, many unauthorized preparations of this plant are found in the local market. People are using this plant as a cheap substitution for their anti-diabetic medicine without any knowledge of what part of the plant to be used which results in unnecessary destruction the whole plant. Thus, this plant is being wasted without being used up to their maximum potential. In order to prevent the waste of this plant, legal production of medicinal preparation from the plant should be ensured and sustainable use of this plant should be closely monitored. In addition to these, people should be also made aware of the proper use of the plant so that they can get maximum benefit from this plant.

A modern effective and safe drug can be developed after extensive investigation of its pharmacodynamics, kinetics, proper standardization and clinical trials. An extensive research should be undertaken on this herb and its products including standardization of various parts and subparts and drug development program using *G. sylvestre* compounds for their better economic and therapeutic utilization. Further research is needed to establish content and bioactivity of the many compounds present, their mode of actions and the effect of preparation and consumption differences on their medicinal activity.

One major factor that comes into play is that many medicinal plants of commercial importance face threat of extinction due to increase in demand and destruction of their habitats due to urbanization and industrialization. The prime initiative should focus on the cultivation and conservation of medicinal plants with pharmacological importance. Although, the herb has immense prospects in drug development, but it faces threat of extinction due to continuous deforestation and absence of established lines or varieties. The *in-vitro* propagation of plants, in plant tissue culture offers a promising alternative for the production of valuable secondary metabolite. *G. sylvestre*, being a valuable medicinal plant and source of bioactive substances, needs to be propagated and conserved. *In-vitro* propagation of plants with high bioactive content and cell culture technologies for large-scale production of such secondary metabolites with medicinal significance will be highly prospective and will provide new dimensions to this area of research.

The whole genome sequencing projects and functional elucidation of pathway genes have made significant contributions in deciphering the biological role and properties of biomolecules. With the functional characterization of genes, their relevance in the plant and functional role in the bioactivity of phytomolecules are being established. Information about such genes which code for economically viable traits or pharmacologically important bioactive molecules holds great prospects in crop engineering. The development of genetic transformation systems will provide an edge in the propagation and maintenance of such pharmacologically important plant having applications in drug discovery and development.

REFERENCES

1. Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. Journal of ethnopharmacology. 2002;81(1):81-100.
2. Gurnani N, Mehta D, Gupta M, Mehta BK. Natural Products: source of potential drugs. Afr J Basic Appl Sci. 2014; 6:171-86.
3. Rahman Sarker M, Zihad MA, Islam M, Nahar M, Islam M, Imam H, Ghosh A, Mustapha MS, Ismail NE. Antihyperglycemic, insulin-sensitivity and antihyperlipidemic potential of *Ganoderma lucidum*, a dietary mushroom, on alloxan- and glucocorticoid-induced diabetic Long-Evans rats. Functional Foods in Health & Disease. 2015;5(12).
4. Shah MA, Sarker MM, Gousuddin M. Antidiabetic potential of *Brassica Oleracea* Var. Italica in type 2 diabetic sprague dawley (sd) rats. Int J Pharmacogn Phytochem Res. 2016;8(3):462-9.
5. Rouhi SZ, Sarker MM, Rahmat A, Alkahtani SA, Othman F. The effect of pomegranate fresh juice versus pomegranate seed powder on metabolic indices, lipid profile, inflammatory biomarkers, and the histopathology of pancreatic islets of Langerhans in streptozotocin-nicotinamide induced type 2 diabetic Sprague–Dawley rats. BMC complementary and alternative medicine. 2017;17(1):1-3.
6. Chen Y, Liu Y, Sarker MM, Yan X, Yang C, Zhao L, Lv X, Liu B, Zhao C. Structural characterization and antidiabetic potential of a novel heteropolysaccharide from *Grifola frondosa* via IRS1/PI3K-JNK signaling pathways. Carbohydrate polymers. 2018; 198:452-61.
7. Sheikh BY, Sarker MM, Kamarudin MN, Ismail A. Prophetic medicine as potential functional food elements in the intervention of cancer: A review. Biomedicine & Pharmacotherapy. 2017a; 95:614-48.
8. Sheikh BY, Sarker MM, Kamarudin MN, Mohan G. Antiproliferative and apoptosis inducing effects of citral via p53 and ROS-induced mitochondrial-mediated apoptosis in human colorectal HCT116 and HT29 cell lines. Biomedicine & Pharmacotherapy. 2017b; 96:834-46.
9. Goto T, Sarker MM, Zhong M, Tanaka S, Gohda E. Enhancement of immunoglobulin M production in B cells by the extract of red bell pepper. Journal of Health Science. 2010;56(3):304-9.
10. Sarker MM, Mazumder ME, Rashid MH. In vitro enhancement of polyclonal IgM production by ethanolic extract of *Nigella sativa* L. seeds in whole spleen cells of female BALB/c mice. Bangladesh Pharm J. 2011;14(1):73-7.
11. Sarker MM, Nahar S, Shahriar M, Seraj S, Choudhuri MS. Preliminary study of the immunostimulating activity of an ayurvedic preparation, Kanakasava, on the splenic cells of BALB/c mice in vitro. Pharmaceutical biology. 2012a;50(11):1467-72.
12. Sarker MM, Nimmi I, Kawsar MH. Preliminary screening of six popular fruits of Bangladesh for in vitro IgM production and proliferation of splenocytes. Bangladesh Pharm J. 2012b;15(1):31-7.
13. Sarker MM, Gohda E. Promotion of anti-keyhole limpet hemocyanin IgM and IgG antibody productions in vitro by red bell pepper extract. Journal of Functional Foods. 2013;5(4):1918-26.
14. Kazemipoor M, Cordell GA, Sarker MM, Radzi CW, Hajifaraji M, En Kiat P. Alternative treatments for weight loss: Safety/risks and effectiveness of anti-obesity medicinal plants. International journal of food properties. 2015;18(9):1942-63.
15. Imam H, Mahbub NU, Khan MF, Hana HK, Sarker MM. Alpha amylase enzyme inhibitory and anti-inflammatory effect of Lawsonia inermis. Pakistan journal of biological sciences: PJBS. 2013;16(23):1796-800.
16. Yasmin H, Kaiser MA, Sarker MM, Rahman MS, Rashid MA. Preliminary anti-bacterial activity of some indigenous plants of Bangladesh. Dhaka University Journal of Pharmaceutical Sciences. 2009;8(1):61-5.
17. Kanetkar P, Singhal R, Kamat M. *Gymnema sylvestre*: a memoir. Journal of clinical biochemistry and nutrition. 2007;41(2):77-81.
18. Tiwari P, Mishra BN, Sangwan NS. Phytochemical and pharmacological properties of *Gymnema sylvestre*: an important medicinal plant. BioMed Research International, 2014:1-18.
19. Singh VK, Umar S, Ansari SA, Iqbal M. *Gymnema sylvestre* for diabetics. Journal of herbs, spices & medicinal plants. 2008;14(1-2):88-106.
20. Nadkarni KM. "*Gymnema sylvestre*," in Indian Materia Medica with Ayurvedic Unani, vol. I (Bombay, India: Popular Prakashan). 1986:596–599.
21. Kirtikar KR, Basu BD. Indian medicinal Plants, periodical experts, Delhi. Vol III. 1975;215.
22. Sastry BS. *Gymnema sylvestre*. Bhav Prakash Nighantu, Chaukhambha, Varanasi, India. 1994.
23. Nadkarni KM. [Indian materia medica]; Dr. KM Nadkarni's Indian materia medica: with Ayurvedic, Unani-Tibbi, Siddha, allopathic, homeopathic, naturopathic & home remedies, appendices & indexes. 1. Popular Prakashan; 1996.
24. Anis M, Sharma MP, Iqbal M. Herbal ethnomedicine of the Gwalior forest division in Madhya Pradesh, India. Pharmaceutical Biology. 2000;38(4):241-53.
25. Mathew M. Aromatic and Medicinal Plants Research Station, Odakkali-A Centre for Promoting Medicinal and Aromatic Plants. Indian Coconut Journal Cochin. 2004;34(10):10-5.
26. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian medicinal plants. National Institute of Science Communication and Information Resources, New Delhi, India. 2002.
27. Potawale SE, Shinde VM, Harle UN, Borade SB, Libi A, Dhalawat HJ, Deshmukh RS. Bidens pilosa L.: a comprehensive review. Pharmacol. Online. 2008; 2:185-96.
28. Saneja A, Sharma C, Aneja KR, Pahwa R. *Gymnema sylvestre* (Gurmar): A review. Der Pharmacia Lettre. 2010;2(1):275-84.
29. Persaud SJ, Al-Majed H, Raman A, Jones PM. *Gymnema sylvestre* stimulates insulin release in vitro by increased membrane permeability. Journal of Endocrinology. 1999;163(2):207-12.
30. Shimizu K, Ozeki M, Iino A, Nakajyo S, Urakawa N, Atsuchi M. Structure-activity relationships of triterpenoid derivatives extracted from *Gymnema inodorum* leaves on glucose absorption. Japanese Journal of Pharmacology. 2001;86(2):223-9.
31. Xie JT, Wang A, Mehendale S, Wu J, Aung HH, Dey L, Qiu S, Yuan CS. Anti-diabetic effects of *Gymnema yunnanense* extract. Pharmacological research. 2003;47(4):323-9.
32. Reddy SP, Gopal RG, Sita LG. In vitro multiplication of *Gymnema sylvestre* R. Br.–An important medicinal plant. Current Science. 2004; 10:1-4
33. National Medicinal Plants Board, Department of Ayush, Ministry of Health and Family Welfare, Government of India, 2008.
34. Gurav S, Gulkari V, Duragkar N, Patil A. Systemic review: Pharmacognosy, phytochemistry, pharmacology and clinical applications of Gymnema sylvestre R Br. Pharmacognosy reviews. 2007;1(2):338-343.
35. Thakur GS, Bag M, Sanodiya BS et al. Chlorophytum borivilianum: A White Gold for Biopharmaceuticals and Neutraceuticals. Curr Pharm Biotechnol. 2009; 10: 650-666.
36. Thakur GS, Bag M, Sanodiya BS, et al. Momordica balsamina- A Medicinal and Neutraceutical Plant for Health Care Management. Curr Pharm Biotechnol. 2009; 10: 667-682.
37. Sanodiya BS, Thakur GS, Baghel RK, Prasad GB, Bisen PS. *Ganoderma lucidum*: a potent pharmacological macrofungus. Current pharmaceutical biotechnology. 2009;10(8):717-42.
38. McBurney DH, Gent JF. Taste of methyl-α-D-mannopyranoside: Effects of cross adaptation and *Gymnema sylvestre*. Chemical Senses. 1978;3(1):45-50.
39. Luo H, Kashiwagi A, Shibahara T, Yamada K. Decreased bodyweight without rebound and regulated lipoprotein metabolism by gymnemate in genetic multifactor syndrome animal. Molecular and cellular biochemistry. 2007;299(1):93-8.
40. Kosta S, Tiwari A. Screening and assessment of anti-diabetic and reactive oxygen scavenging (ros), effects of herbs in streptozotacin induced mice. Pharmacol. online. 2009; 3:695-704.
41. Shah KK, Shiradkar MR, Bindu VH. Transdermal delivery of aceclofenac: effect of *Gymnema sylvestre* and *Caralluma adscendens* with its mechanism of action. Res. J. Pharm. Biol. Chem. Sci. 2011;2(3):762-72.
42. Shah KK, Shiradkar MR, Bindu VH. In vitro permeation of aceclofenac through the shed skin of two different species. Der. Pharmacia Sinica. 2012;3(1):11-9.
43. Kumar VH, Nayak IM, Huilgol SV, Yendigeri SM, Narendar K. Antidiabetic and hypolipidemic activity of *Gymnema sylvestre* in dexamethasone induced insulin resistance in albino rats. International Journal of Medical Research & Health Sciences. 2015;4(3):639-45.
44. Sujin RM. Anti-diabetic effect of *Gymnema sylvestre* (asclepiadaceae) powder in the stomach of rats. Ethnobotanical leaflets. 2008;2008(1):1158-1167.
45. Sathya S, Kokilavani R, Gurusamy K. Hypoglycemic effect of *Gymnema sylvestre*

(retz.,) R. Br leaf in normal and alloxan induced diabetic rats. Ancient science of life. 2008;28(2):12-14.
46. Mall GK, Mishra PK, Prakash V. Antidiabetic and hypolipidemic activity of *Gymnema sylvestre* in alloxan induced diabetic rats. Global Journal of biotechnology and biochemistry. 2009;4(1):37-42.
47. Dholi SK, Raparla R. In vivo anti diabetic evaluation of gymnemic acid in streptozotocin induced rats. The Pharma Innovation. 2014;3(7, Part B):82.
48. Aralelimath VR, Bhise SB. Anti-diabetic effects of *Gymnema sylvestre* extract on streptozotocin induced diabetic rats and possible b-cell protective and regenerative evaluations. Digest Journal of Nanomaterials & Biostructures. 2012;7(1):135-142.
49. El Shafey AA, El-Ezabi MM, Seliem MM, Ouda HH, Ibrahim DS. Effect of *Gymnema sylvestre* R. Br. leaves extract on certain physiological parameters of diabetic rats. Journal of King Saud University-Science. 2013;25(2):135-41.
50. Kumar P, Rani S, Arunjyothi B, Chakrapani P, Rojarani A. Evaluation of antidiabetic activity of *Gymnema sylvestre* and Andrographis paniculata in Streptozotocin induced diabetic rats. Int. J. Pharmacogn. Phytochem. Res. 2017; 9:22-5.
51. Ahmed SK, Cheekavolu C, Alasyam, N, Sunil M. Evaluation of hypoglycemic property of gurmar (*Gymnema sylvestre*) leaves methanolic extract (GSLME) in streptozocin (STZ) induced Diabetic Albino Rats. J. Med. Sci. Clin. Res. 2017; 5(12), 31753–31760.
52. Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I. Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice. Journal of Asian natural products research. 2000;2(4):321-7.
53. Kang JS, Koh HC, Suh TK. Effect of gymnemic acid on the elevation of blood glucose concentration induced with oral sucrose in streptozotocin-diabetic rats. Hanyang Uidae Haksulchi. 1990;10(1):587-601.
54. Galletto R, Siqueira VL, Ferreira EB, Oliveira AJ, Bazotte RB. Absence of antidiabetic and hypolipidemic effect of *Gymnema sylvestre* in non-diabetic and alloxan-diabetic rats. Brazilian Archives of Biology and Technology. 2004;47(4):545-51.
55. Shanmugasundaram ER, Gopinath KL, Shanmugasundaram KR, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. Journal of ethnopharmacology. 1990;30(3):265-79.
56. Mozersky RP. Herbal products and supplemental nutrients used in the management of diabetes. The Journal of the American Osteopathic Association. 1999;99(12 Suppl):S4-9.
57. Yoshikawa K, Kondo Y, Arihara S, MATSUURA K. Antisweet natural products. IX. Structures of gymnemic acids XV-XVIII from *Gymnema sylvestre* R. Br. V. Chemical and pharmaceutical bulletin. 1993;41(10):1730-2.
58. Sahu NP, Mahato SB, Sarkar SK, Poddar G. Triterpenoid saponins from *Gymnema sylvestre*. Phytochemistry. 1996;41(4):1181-5.
59. Chen G, Guo M. Rapid screening for α-glucosidase inhibitors from *Gymnema sylvestre* by affinity ultrafiltration–HPLC-MS. Frontiers in pharmacology. 2017; 8:228.
60. Nakamura Y, Tsumura Y, Tonogai Y, Shibata T. Fecal steroid excretion is increased in rats by oral administration of gymnemic acids contained in *Gymnema sylvestre* leaves. The Journal of nutrition. 1999;129(6):1214-22.
61. Ahmed AB, Rao AS, Rao MV. In vitro callus and in vivo leaf extract of *Gymnema sylvestre* stimulate β-cells regeneration and anti-diabetic activity in Wistar rats. Phytomedicine. 2010;17(13):1033-9.
62. Jain KS, Kathiravan MK, Somani RS, Shishoo CJ. The biology and chemistry of hyperlipidemia. Bioorganic & medicinal chemistry. 2007;15(14):4674-99.
63. Khanna VG, Kannabiran K. Anticancer-cytotoxic activity of saponins isolated from the leaves of *Gymnema sylvestre* and *Eclipta prostrata* on HeLa cells. International Journal of Green Pharmacy (IJGP). 2009;3(3):227-229.
64. Singh DK, Kumar N, Sachan A, Lakhani P, Tutu S, Nath R, Sachan AK, Dixit RK. Hypolipidaemic effects of *Gymnema sylvestre* on high fat diet induced dyslipidaemia in wistar rats. Journal of clinical and diagnostic research: JCDR. 2017;11(5):FF01.
65. Rachh PR, Rachh MR, Ghadiya NR, Modi DC, Modi KP, Patel NM, Rupareliya MT. Antihyperlipidemic activity of *Gymenma sylvestre* R. Br. leaf extract on rats fed with high cholesterol diet. IJP-International Journal of Pharmacology. 2010;6(2):138-41.
66. Bishayee A, Chatterjee M. Hypolipidaemic and antiatherosclerotic effects of oral *Gymnema sylvestre* R. Br. Leaf extract in albino rats fed on a high fat diet. Phytotherapy Research. 1994;8(2):118-20.
67. Kumar V, Bhandari U, Tripathi CD, Khanna G. Anti-obesity effect of *Gymnema sylvestre* extract on high fat diet-induced obesity in Wistar rats. Drug Res (Stuttg). 2013;63(12):625-32.
68. Saumendu DR. In vitro antibiotic activity of various extracts of *Gymnema sylvestre*. International Journal of Pharmaceutical Research and Development. 2010; 2:1–3.
69. Bhuvaneswari CH, Rao K, Giri A. Evaluation of *Gymnema sylvestre* antimicrobial activity in methanol. Recent Research in Science and Technology. 2011;3(8):73-75.
70. Satdive RK, Abhilash P, Fulzele DP. Antimicrobial activity of *Gymnema sylvestre* leaf extract. Fitoterapia (Milano). 2003;74(7-8):699-701.
71. Rahman MM, Habib MR, Hasan MA, Al Amin M, Saha A, Mannan A. Comparative assessment on in vitro antioxidant activities of ethanol extracts of Averrhoa bilimbi, *Gymnema sylvestre* and *Capsicum frutescens*. Pharmacognosy research. 2014;6(1):36.
72. Rupanar SV, Pingale SS, Dandge CN, Kshirsagar D. Phytochemical screening and In vitro evaluation of antioxidant antimicrobial activity of *Gymnema sylvestre*. Int. J. curr. Res. 2012;8 (12):43480–43486.
73. Ohmori R, Iwamoto T, Tago M, Takeo T, Unno T, Itakura H, Kondo K. Antioxidant activity of various teas against free radicals and LDL oxidation. Lipids. 2005;40(8):849-53.
74. Gunasekaran V, Srinivasan S, Rani SS. Potential antioxidant and antimicrobial activity of *Gymnema sylvestre* related to diabetes. Journal of Medicinal Plants. 2019;7(2):05-11.
75. Rachh PR, Patel SR, Hirpara HV, Rupareliya MT, Rachh MR, Bhargava AS, Patel NM, Modi DC. In vitro evaluation of antioxidant activity of *Gymnema sylvestre* r. br. leaf extract. Rom. J. Biol. Plant Biol. 2009;54(2):141-8.
76. Arun LB, Arunachalam AM, Arunachalam KD, Annamalai SK, Kumar KA. *In-vivo* anti-ulcer, anti-stress, anti-allergic and functional properties of Gymnemic Acid Isolated from *Gymnema sylvestre* R Br. BMC complementary and alternative medicine. 2014;14(1):1-1.
77. Kishore L, Singh R. Protective effect of *Gymnema sylvestre* L. against advanced glycation end-product, sorbitol accumulation and aldose reductase activity in Homoeopathic Formulation. Indian J. Res. Homoeopathy. 2015;9 (4):240–248.
78. Chakrapani LN, Periandavan K. Protective role of gymnemic acid in curbing high fat diet and high fructose induced pancreatic oxidative stress mediated type-2 diabetes in wistar rats. International Journal of Pharmaceutical Sciences and Research. 2018;9(5):2130-9.
79. Kokate CK, Purohit AP, Gokhale C. Pharmacognosy, vol. 12. Nirali Prakashan. 1999.
80. Diwan PV, Margaret I, Ramakrishna S. Influence of Gymnema sylvestre on inflammation. Inflammopharmacology. 1995;3(3):271-7.
81. Malik JK, Manvi FV, Alagawadi KR, Noolvi M. Evaluation of anti-inflammatory activity of *Gymnema sylvestre* leaves extract in rats. International Journal of Green Pharmacy (IJGP). 2008;2(2).
82. Trease GE, Evans WC. Pharmacognosy, vol. 12. Balliere Tindale, London, UK. 1983.
83. Gupta SN, Pramanik S, Tiwari OP, Thacker N, Pande M, Upmanyu N. "Immunomodulatory activity of *Gymnema sylvestre* leaves," Internet Journal of Pharmacology. 2010;8(2):1531–2976.
84. Malik JK, Manvi FV, Nanjware BR, Sanjiv S. Wound healing properties of alcoholic extract of *Gymnema sylvestre* R. Br. leaves in rats. Journal of Pharmacy Research. 2009;2(6):1029-30.
85. Ahirwal L, Singh S, Dubey MK, Bharti V, Mehta A, Shukla S. In vivo immunomodulatory effects of the methanolic leaf extract of *Gymnema sylvestre* in Swiss albino mice. Archives of Biological Sciences. 2015;67(2):561-70.
86. Singh VK, Dwivedi P, Chaudhary BR, Singh R. Immunomodulatory effect of *Gymnema sylvestre* ®. Br.) leaf extract: an in vitro study in Rat model. PloS one. 2015;10(10):e0139631.
87. Malik JK, Manvi FV, Nanjwade BK, Alagawadi KR, Sanjiv S. Immunomodulatory activity of *Gymnema sylvestre* R. Br. leaves on in-vitro human neutrophils. Journal of Pharmacy Research. 2009;2(8):1284-6.
88. Kar PP, Rath B, Ramani YR, Maharana CS. Amelioration of Cyclophosphamide induced immunosupression by the hydro-alcoholic extract of *Gymnema sylvestre* leaves in albino rats. Biomedical and Pharmacology Journal. 2019;12(1):251-8.
89. Gupta SP, Pramanik S, Tiwari O, Thacker N, Pande M, Upmanyu N. Immunomodulatory Activity of *Gymnema sylvestre* Leaves. Internet J. Pharmacol. 2009;8 (2).
90. Malik JK, Manvi FV, Nanjware BR, Dwivedi DK, Pankaj P, Sandeep C. Anti-arthritic activity of leaves of *Gymnema sylvestre* R. Br. leaves in rats. Der Pharmacia Lettre. 2010;2(1):336-41.
91. Shankar KR, Rao BG. Anti-arthritic activity of *Gymnema sylvestre* root extract. Biosci. Biotechnol. Res. Asia. 2008; 5(1):469–471.
92. Srividya AR, Varma S, Dhanapal SP, Vadivelan R, Vijayan P. In vitro and in vivo evaluation of hepatoprotective activity of *Gymnema sylvestre*. Int. J. Pharm. Sci. Nanotechnol. 2010; 2:768–773.
93. Yogi B, Mishra A. Hepatoprotective effects of polyherbal formulation against carbon tetrachloride-induced hepatic injury in albino rats: a toxicity screening approach. Asian J. Pharm. Clin. Res. 2016;10(1):192-8.
94. Kumar SN, Mani UV, Mani I. An open label study on the supplementation of *Gymnema sylvestre* in type 2 diabetics. Journal of dietary supplements. 2010;7(3):273-8.
95. Li Y, Zheng M, Zhai X, Huang Y, Khalid A, Malik A, Shah P, Karim S, Azhar S, Hou X. Effect of *Gymnema sylvestre, Citrullus colocynthis* and *Artemisia absinthium* on blood glucose and lipid profile in diabetic human. Acta Pol Pharm. 2015;72(5):981-5.
96. Al.Romaiyan A, Liu B, Asare.Anane H, Maity CR, Chatterjee SK, Koley N, Biswas T, Chatterji AK, Huang GC, Amiel SA, Persaud SJ. A novel *Gymnema sylvestre* extract stimulates insulin secretion from human islets in vivo and in vitro. Phytotherapy Research. 2010;24(9):1370-6.
97. Kashima H, Eguchi K, Miyamoto K, Fujimoto M, Endo MY, Aso-Someya N, Kobayashi T, Hayashi N, Fukuba Y. Suppression of oral sweet taste sensation with *Gymnema sylvestre* affects postprandial gastrointestinal blood flow and gastric emptying in humans. Chemical senses. 2017;42(4):295-302.
98. Shanmugasundaram ER, Rajeswari G, Baskaran K, Kumar BR, Shanmugasundaram KR, Ahmath BK. Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. Journal of ethnopharmacology. 1990b;30(3):281-94.
99. Zuniga LY, González-Ortiz M, Martinez-Abundis E. Effect of *Gymnema sylvestre* administration on metabolic syndrome, insulin sensitivity and insulin secretion. Journal of medicinal food. 2017;20(8):750-4.
100. Preuss HG, Garis RI, Bramble JD, Bagchi D, Bagchi M, Rao CV, Satyanarayana S. Efficacy of a novel calcium/potassium salt of (-)-hydroxycitric acid in weight control. International Journal of Clinical Pharmacology Research. 2005;25(3):133-44.
101. Kothe A, Uppal R. Antidiabetic effects of *Gymnema sylvestre* in NIDDM-a short study. Indian Journal of Homoeopathic Medicine. 1997; 32:61-2.
102. Khare AK, Tondon RN, Tewari JP. Hypoglycaemic activity of an indigenous drug (*Gymnema sylvestre*,'Gurmar') in normal and diabetic persons. Indian Journal of Physiology and Pharmacology. 1983;27(3):257-8.