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Review on *Gymnema Sylvestre* as an Major Antidiabetic Agent

Rohit Sanjay Buddhiwant [1] ***, Shubhangi Ravsaheb Mali*** [2]

[1]Department of Pharmacognocy, Pratibhatai Pawar collage of pharmacy, wadala mahadev, shrirampur -413709,Maharashtra, India
[2]Department of Quality Assurance technology, Pratibhatai pawar collage of pharmacy, wadala mahadev, shrirampur

Abstract:-

Diabetes Mellitus (Madhumeha) is one of the leading metabolic disorder prevalent in the developing countries which is characterized by high blood sugar level and as associated with macro vascular and microvascular complication. The Indian Ayurveda describes several herbs for the management and treatment of diabetes Mellitus among which Gymnema Sylvestre (Asclepiadaceae) is potential treatment which popularly known as ‘ Gurmar’ Or ‘Sugar Destroyer ‘is a woody. Climbing traditional medicinal herb which has many therapeutic applications in Ayurvedic system of medicine. It is used for lowering serum cholesterol, triglycerides and blood glucose level (hypoglycemic or antihyperglycemic), hypolipidaemic, weight loss, stomach ailments, constipation, water retention and liver diseases, either high or low blood pressure, tachycardia or arrhythmias, and used as a purgative, in eye troubles, anti-inflammatory, smooth muscle relaxant, prevention of dental caries, cataract and as anticancer-cytotoxic agent. Its flowers, leaves, and fruits contains alkaloids, flavones, saponins, sapogenins, anthraquinones, hentri-acontane, pentatriacontane, α and β-chlorophylls, phytin, resins, d-quercitol, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides and stigmasterol having main principle bioactive compunds viz. gymnemic acids, gymnemasides, gymnemagenin, gurmarin, gymnemosides, gymnemanol, gymnemasins, gypenoside, and conduritol which act as therapeutic agent and play vital role in many therapeutic applications. It is a wild plant that grows in the open forest in India, China, Indonesia, Japan, Malaysia, Sri Lanka, Vietnam, South Africa and Australia that has beenbeen proven as antidiabetic drug. The herbal extract is used in dietary supplements since it reduces body weight, blood cholesterol, and triglyceride levels and holds great prospects in dietary as well as pharmacological applications. A number of gymnema products such as gymnema capsules, gymnema tea, bioshape®, and diaxinol® have been developed and using for the treatment of different diseases. The focus of the present review is to achieve the potential of therapeutic value of this herb and mechanism and action of their secondary metabolites. This review pretends to contribute to the knowledge of the pharmacology, phytochemistry and pharmacognostical aspects of the plant.

Keywords :-Diabetes Mellitus, Gymnemic acids, Gymnema sylvestre, phytochemistry, Pharmacology, Review.

[a] *For Correspondence Email: rohitbuddhiwant@gmail.com*

1.0 Introduction :-

Diabetes mellitus is a group of different metabolic diseases that are characterized by hyperglycemia due to defects in insulin action or abnormal insulin secretion. The chronic form of this condition associated with long-terms damage, failure and abnormal function of different organs such as the heart, kidneys, eyes, nerves and blood vessels. The pathogenesis of this disease is due to the autoimmune destruction of pancreatic β-cells leading to insulin deficiency and insulin resistance**(1)**. Insulin resistance is an etiopathology for type 2 diabetes which is the most common accounting for approximately 90% of all the diabetes cases (World Health Organization, 2015). As a result, there is deficient in insulin action thereby affecting the metabolism of the proteins, fats, and carbohydrates. Some of the symptoms of the condition include marked hyperglycemia, polyuria, weight loss and blurred vision. The symptoms may include life-threatening consequences such as nonketotic hyperosmolar syndrome and ketoacidosis. The condition may also have long term conditions such as retinopathy, amputations, abnormalities in lipid metabolism, nephropathy and cardiovascular conditions such as hypertension**(2)**. Medicinal plants have significant therapeutic values and are currently being used for the treatment of different diseases . A composition of phytochemicals such as pyrrolizidine alkaloids, phenols, flavonoids, naphthoquinones, and terpenoids have been reported to show significant biological and therapeutic activity such as antidiabetic, antioxidant and antilipidemic activity . The bioactive constituents found in many plant species are isolated for direct use as drugs, lead compounds, or pharmacological agents. These traditional approaches might offer a natural key to unlock diabetic complications. Various antidiabetic plant extracts like aloe (Aloe vera L), bitter Melon (Momordica charantia), fenugreek (Trigonella foenum-graecum), Asian ginseng (Panax ginseng C.A. Meyer) and American ginseng (Panax quinquefolius L), gymnema (Gymnema sylvestre), milk thistle (Silybum marianum), nopal (Opuntia streptacantha), salacia (Salacia oblonga; Salacia reticulata), and formulations like those of chromium have been used and clinically tested for their activity as well as potential side effect **(3)** .

The underlying goal of all diabetes treatment and management is to maintain an adequate blood glucose concentration. The treatment of DM is based on oral hypoglycemic agents and insulin.Four major classes of oral hypoglycemic agents have been used extensively viz. insulin secretagogues, biguanides, thiazolidinediones and alpha-glycosidase inhibitors. Each class of

drugs works on different mechanism of actions including stimulation of insulin secretion, reduction of hepatic gluconeogenesis, increase in insulin receptor sensitivity and delay of digestion and absorption of carbohydrate, respectively. The use of orally administered drug is limited by the adverse side effects including hematological, cutaneous and gastrointestinal reactions, Phytochemically the plant has been reported to contain gymnemagenin- the sapogenin. Gymnemic acid .-III, -IV, -V, -VIII, and -IX, were isolated in pure states from the hot water extract of leaves of G. sylvestre . The present study was aimed at assessing the regenerating ability of the extract of Gymnema sylvestre R.Br. leaves**(4)**. Also there is increasing evidence that many current drug therapies simply suppress symptoms and ignore the underlying disease process. In contrast, many natural products appear to address the cause of many diseases and yield superior clinical results. Unfortunately, most physicians and patients are not aware that these natural alternatives exist. But research in this field is a never ending process. Diabetes has almost become an epidemic in today's world. Thus, control of this disease has now attained utmost attention. And if such a disease has an herbal solution, then it is surely a boon to mankind. Gymnema sylvestre, commonly known as "Gurmar" in Hindi, has been reported in the ancient Aurvedic texts as an herbal solution for diabetes**(5)** .

Gymnema sylvestre is a plant used in India and parts of Asia as a natural treatment for Diabetes or "sweet urine." The hypoglycemic action of Gymnema leaves was first documented in The late 1920s. Gymnema is reported to increase glucose uptake and utilization. It also improve . The function of pancreatic β-cells and may also decrease glucose absorption in the gastrointestinal Trac**(6)** .

2.0 Vernacular Synonyms (The Wealth Of India, 1956) :-

It is known as "periploca of the woods" in English. The other synonyms of Gymnema sylvestre are; Sanskrit: Meshashringi (meaning "ram's horn"), madhunashini, Hindi: Gur-mar (The name"Gurmar" has Been derived from the two hindi words "Gur" means sugar, "mar" means to kill, thus Gurmaar means "The Sugar killer"), merasingi, Marathi: Kavali, kalikardori, vakundi, Gujrathi: Dhuleti, mardashingi, Telugu: Podapatri, Tamil: Adigam, cherukurinja, Kannada: Sannagerasehambu**(12)** .

2.1 Taxonomy :-

The plant Gymnema sylvestre belongs to the

Kingdom: Plantae

Subkingdom: Tracheobionta

Super division: Spermatophyta

Division: Magnoliophyta

Class: Magnoliopsida

Subclass: Asteridae

Order: Gentianales

Family: Asclepiadaceae

Genus: Gymnema**(8)**

2.2 Botanical Synonyms :-

Asclepias geminata Roxb.

Periploca sylvestris Retz**(9).**

2.3 Geographical Distribution :-

It is distributed through out India, in a dry forest up to 600-meter height. It is found in Banda, Konkan, Western Ghats, and Deccan extending to the part of the northern and western India. It is distributed in Asia,Tropical Africa, Malaysia and Srilanka. It is occasionally cultivated as medicinal plants**(18)** .

2.4 Morphology :-

Gymnema sylvestre is a perennial, woody climbing plant that grows in the tropical forests of central and southern India.6,7 It is a large climber, rooting at nodes, leaves are elliptic, acuminate, the base is acute to acuminate, glabrous above sparsely or densely tomentose beneath; the flowers are small, in axillary and lateral umbel like cymes, pedicels are long; Calyx-lobes are long, ovate, obtuse, pubescent; Corolla is pale yellow campanulate, valvate, corona single, with 5 fleshy scales. Scales are adnate to throat of corolla tube between lobes; Anther is connective produced into a membranous tip, pollinia 2, erect, carpels 2, unilocular; locules many

ovuled; Follicle long, fusiform**(6)** .

Figure 1:- plant of *Gymnema sylvestre*

3.0 Phytochemistry :-

The leaves of G. sylvestre contain triterpene saponins belonging to oleanane and dammarane classes. The major constituents like gymnemic acids and gymnemasaponins are members of oleanane type of saponins while gymnemasides aredammarane saponins . Other phytoconstituents include anthraquinones, flavones, hentriacontane, pentatriacontane, phytin, resins, tartaric acid, formic acid, butyric acid,lupeol, β-amyrin related glycosides, stigmasterol, and calcium oxalate .The presence of alkaloids had been detectedin plant extracts. Leaves of G.

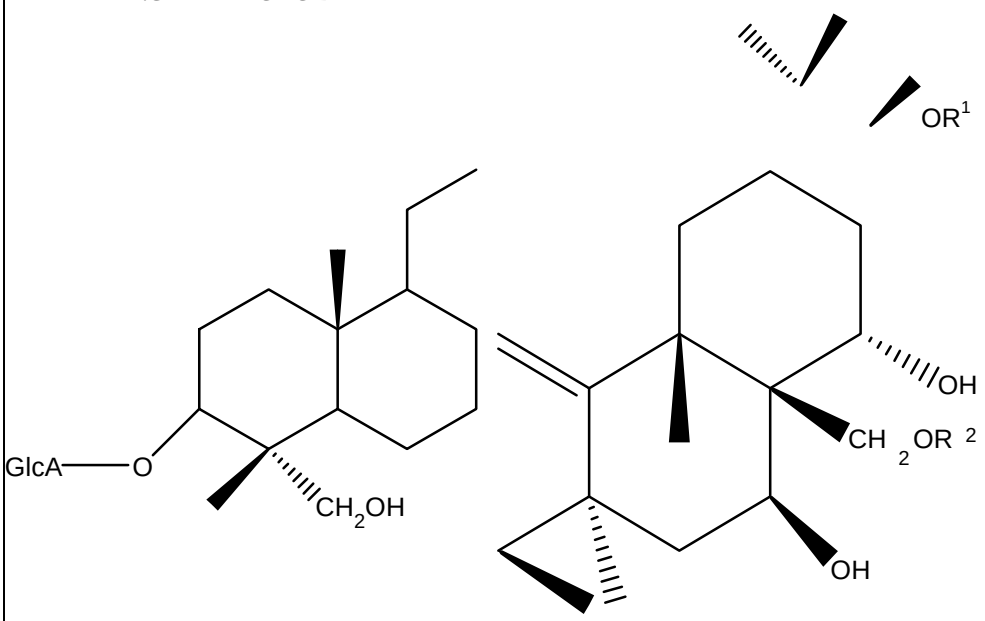
sylvestre have acidic glycosidesand anthraquinones and their derivatives .The major sec-secondary metabolites in Gymnema includes a group of nineclosely related acidic glycosides, the main are gymnemic acidA–D and found in all parts of the plant in the maximum content ofgymnemic acid is found in shoot tips (54.29 mg-g−1 DW) andleast in seeds (1.31 mg-g−1 DW). Antisaccharin property ofgymnemic acid A1 was greatly reduced on conversion into A2,while no activity was observed in case of A3 suggesting thatthe ester group in the genin portion of gymnemic acid im-parts the antisweet property to the triterpene saponins, thegymnemic acids. Gymnemic acids A2 and A3 possessed bothglucuronic acid and galactose in their molecular structureswhile glucuronic acid was found to be the only moiety in gymnemic acid A1 . Further, a series of gymnemic acids(gymnemic acid I, II, III, IV, V, VI, and VII) were isolated andcharacterized from the hot water extract of dry leaves of G.sylvestre**(11)**. The Gymnemic acids comprise of severalmembers designated as gymnemic acids I–VII, gymnemo-sides A–F, and gymnemasaponins Table 1. The derivatives ofgymnemic acids are several acylated tigloyl, methylbutyrylgroup substituted members, derived from deacylgymnemicacid (DAGA) which is a 3-O-β-glucuronide of gymnemagenin (3β, 16β, 21β, 22α, 23, 28-hexahydroxy-olean-12-ene).Gymnemic acid A comprises of gymnemic acids A1, A2, A3,and A4 and named gymnemagenin**(15)**.This constituent is a D-glucuronide of hexahydroxy-triterpene that esterifies with acids . Other five gymnemic acids, namely, VIII, IX, X, XI,and XII, were isolated and characterized later . Gymnemasaponins III, another antisweet compound, isolated fromG. sylvestre was found to consist of 23 hydroxylongispino-genin as the aglycone moiety glycosylated with either one ortwo glucose molecules at both the 23 or 28 hydroxyl groups. These compounds exhibited lesser antisweet effect thanthose of gymnemic acids. Gurmarin, an important 35 amino-acid peptide having a molecular weight of 4209, was isolated from G. sylvestre .The sugar suppression activity of this compound was determined electrophysiologically on the taste responses of rat.

The antisweet effect of this polypeptide is very specific tosweet taste on tongue, affected by the pH change. It has beenreported that the polypeptide exhibited maximum antisweet-ner property near its isoelectric point **(16)**. The hydrophobic,rather than the ionic, interaction plays a significant role inproper binding of gurmarin to the target molecules .The other important constituents isolated from leaves aregymnemasins A, B, C, and D and alkaloids . A number of saponins such as gymnemic acid, deacyl gymnemicacid, gymnemagenin , 23-

hydroxylnogispinogenin, andgymnestrogenin have been purifiedfrom G.sylvestre. The phytochemicals in leaf extract were also analyzed through gas chromatography coupled to mass spectrometry and identified for the presence of terpenoids, glycosides, saturated and unsaturated fatty acids, and alkaloids inthree different leaves extract, namely, petroleum ether, chloroform, and methanol as solvents used for extraction .The bioactive constituents present in the plant were found tobe mixture of diverse phytomolecules such as gymnemicacids, gymnemosides, gymnemasaponins, gurmarin, gymnemanol, stigmasterol, d-quercitol, β-amyrinrelated glycosides,anthraquinones, lupeol, hydroxycinnamic acids, and coumarols group**(13)** .

Table Number 1: Structures of gymnemic acids present in *Gymnema sylvestre*.R.Br:

1.GYMNEMIC ACID[9]



Gymnemic acid types	R1	R^2
Gymnemic acid l	Tigloyl	Ac
Gymnemic acid ll	2-methylbutyroyl	Ac
Gymnemic acid lll	2-methylbutyroyl	H
Gymnemic acid lV	Tigloyl	H

4.0 MOA of Gymnemic acid :-

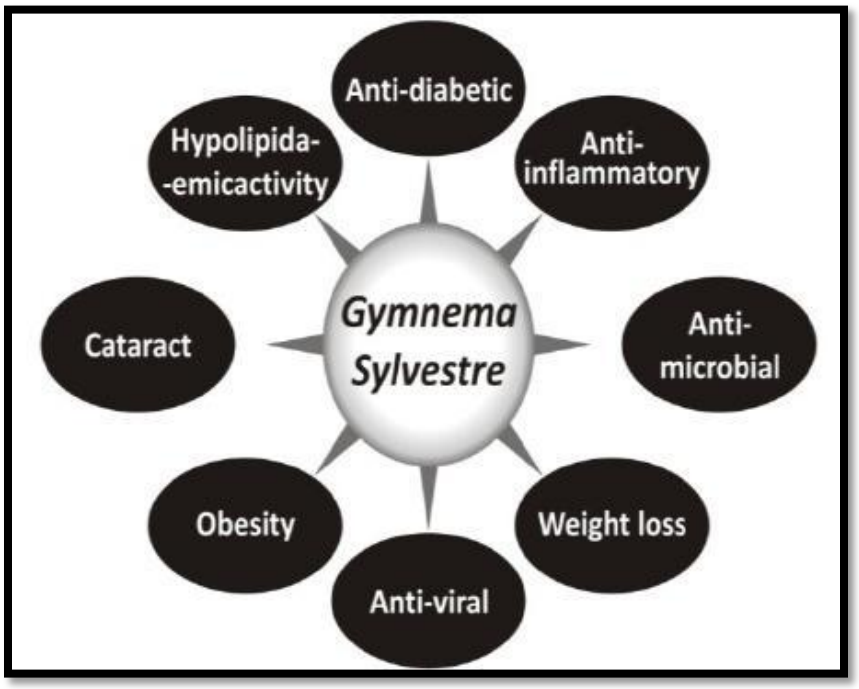
The gymnemic acids are the main constituents of gymnema and are amixture of at least 17 different saponins . The gymnemic acidshave been shown to have antidiabetic, antilipidemic and anti-inflammatoryproperties. The phytochemical delays the absorptionof glucose into the blood. The atomic arrangement of gymnemic acidmolecules is the same as that of glucose molecules. Therefore, gymnemicacids fill the receptors in the taste bud leading to a prevention of activatingthe sugar molecules that are present in consumed food. Additionally, theacids fill the receptors located in the absorptive external layers of theintestine so as to prevent the absorption of glucose by the intestine. This results in low blood sugar.In addition, the acids have been found to stimulate the pancreas to produce insulin which is required for glycemic control and treating adultonset diabetes mellitus**(17)**.The acids also increase theexcretion of cholesterol in faeces and can act as a laxative, coughsuppressant and a diuretic. The gymnemic acidshave been shown to interfere with the ability of the taste buds present onthe tongue to taste sweet or bitter. Researchers believe that the ability ofthe acids to inhibit the sweet taste means that it also inhibits the intake ofglucose. However, this has not been proved by research evidence. In summary, the mechanism by which thephytochemicalinduces antidiabetic responses include increasing the secretion of insulin,increasing glucose utilization, promoting the regeneration of pancreatic islet cells and inhibition of glucose absorption in the small intestines**(19)**. The gymnemic acids also have antioxidant properties capable ofscavenging reactive oxygen species and other free radical.

There are some possible mechanisms by which the leaves and especially Gymnemic acids from G. sylvestre exert its hypoglycemic effects are:

- It increases secretion of insulin
- It promotes regeneration of islet cells
- It increases utilization of glucose: It is shown to increase the activities of enzymes responsible for utilization of glucose by insulin-dependent pathways, an increase in of phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase and
- It causes inhibition of glucose absorption from intestine, the exact action being unknown. Itcould be involve one or more mechanisms**(14)**.

5.0 Pharmacological Aspect :-

G. sylvestre is one of the indispensable medicinal plants used in Ayurvedic system of medicine for the treatment of diverse diseases 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 . 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 **(20)** .

Figure 2 :- medicinal properties of *Gymnema sylvestre*

5.1 Antidiabetic activity

The primary clinical application for this botanical is as an antidiabetic agent. Gymnema has been the object of considerable research since the 1930s, with promising results for types 1 and 2 diabetes. The first scientific confirmation of its use in human diabetics came almost 80 years ago when it was demonstrated that the leaves of G. sylvestre reduced urine glucose in diabetics. In 1990 a series of published studies on G. sylvestre extract lifted this herb from interesting to revolutionary. It was shown that the administration of G. sylvestre extract to diabetic animals not

only resulted in improved glucose homeostasis, this improvement was accompanied by a regeneration of β-cells in the pancreas . Scientific investigation of the biological effect of oral administration of the leaves powder revealed that G. sylvestre therapy also increased the activities of the enzymes affording the utilisation of glucose by insulin dependent pathways: it controlled phosphorylase levels, gluconeogenic enzymes and sorbitol dehydrogenase. This valuable herb appears to correct the metabolic derangements in diabetic rabbit liver, kidney and muscle . Oral feeding of powdered leaves of G. sylvestre (500 mg/rat) for 10 days significantly prevented intravenous beryllium nitrate induced hyperglycemia in rats and normalized it in 4 days in comparison to 10 days in untreated rats. However, no significant hypoglycemia was seen in normal rats that were daily fed with the leaves of G. sylvestre for 25 days . Oral administration of aqueous extracts of leaves of G. sylvestre (20 mg/day) for 20-60 days normalized blood sugar levels of STZ diabetic rats through β-cell regeneration . Single as well as chronic (32-35 days) oral administration of aqueous extract of G. sylvestre leaves (1g/kg) to 18-h fasted non-diabetic and STZ (30 mg/kg) induced mild diabetic rats showed significant reduction in blood glucose on OGTT (1 g/kg) without any significant effect on immuno-reactive insulin (IRI) levels . Oral administration of varying doses (50, 100, 200 and 500 mg/kg) of aqueous extract to normal and STZ diabetic rats showed significant dose–dependent hypoglycemic activity . However, (1995) reported no effect of G. sylvestre leaves extract (120 mg/kg/day PO) for 7 days on insulin resistance in STZ diabetic rats. Hypolipidemic effect is described in spontaneously hypertensive rats . Various hypoglycemic principles of G. sylvestre isolated from the saponin fraction of the plant are referred as gymnemosides and gymnemic acid . Its triterpene glycosides isolated from plant inhibited glucose utilization in muscles . Gymnemic fractions also inhibit glucose uptake in the intestine . Alcoholic extract also stimulate insulin secretion from the rat islets of Langerhans and several pancreatic beta cell lines in absence of other stimulus . However, triterpene glycosides exhibited little or no inhibitory activity against glucose absorption in OGTT conducted in rats. Gymnemic acid I and gymnema saponin V lacked antihyperglycemic effect**(5)**. Oral administration of aqueous leaf extract (50, 100, 200 and 400 mg/kg) to normal and STZ diabetic rats showed dose-dependent decrease in blood glucose level . In another study, water soluble fraction of alcoholic extract of the plant significantly lowered the hepatic glycogen content of the glucose fed rats . Beneficial effects of oral treatment of G. sylvestre leaves extract (400 mg) for 18-20 months plus conventional treatment showed beneficial effects in 22 NIDDM

patients. Results showed significant reduction in blood glucose, glycosylated haemoglobin and plasma proteins and lowering of conventional drug requirement. Five patients totally discontinued conventional drug therapy and maintained blood glucose homeostasis with plant extract alone. In addition, serum insulin levels were raised suggesting insulin-releasing effect . Oral administration of a water-soluble leaves extract of G. sylvestre (400 mg/day) to 27 IDDM patients on insulin therapy lowered fasting blood glucose, glycosylated haemoglobin (HbA1c), glycosylated plasma protein and insulin requirements but it remained higher than controls. In addition, it reduced serum lipid level to near normal levels . In a clinical observation of aqueous decoction of G. sylvestre leaves (2 gm thrice daily) to 10 healthy persons (10 days) and 6 diabetic patients (15 days) significantly reduced the fasting and OGTT glucose level in all the groups except OGTT in healthy group . The hypoglycemic effect of G. sylvestre was later studied in 16 normal subjects and in 43 mild diabetic patients. The results indicate that G. sylvestre leaf powder has a hypoglycemic effect comparable to tolbutamide. Serum triacylglycerol, free fatty acids and cholesterol levels was significantly decreased in diabetic patients **(12)**. The extended release tablet of the G. sylvestre as a supplementary treatment in about 65 patients also showed the positive results to reduce blood glucose, glycosylated hemoglobin and glycosylated plasma proteins, thereby reducing the complications of the diabetes . Experimental studies were conducted on rats fed on high carbohydrate diet for 15 days and later rendered hyperglycemic by injecting anterior pituitary extract 100 mg/kg subcutaneously daily for ten days. These animals were treated with ethanol extract of G. sylvestre at a dosage of 100 mg/kg orally. Results indicated insignificant reduction in blood sugar in normal rats, whereas significant reduction in anterior pituitary treated hyperglycemic rats. Effect of the drug was comparable to that of tolbutamide (50 mg/kg) in the hyperglycemic rats. The drug influenced the disturbed carbohydrate metabolism in hyperglycemic animals by limiting the carbohydrate turnover and thus inhibiting the vicious cycle of hyperglycemia . Further studies were conducted on albino rats to establish the antidiabetic activity of G. sylvestre, which was compared with other conventional indigenous oral antidiabetic drugs like Coccinia indica, Pterocarpus marsupium, Momordica charantia. The animals were subcutaneously injected with 100 mg/kg dose of the anterior pituitary extract, these animals were then fed with alcoholic extract of G. sylvestre and Coccinia indica (100 mg/kg each), aqueous infusion of Pterocarpus marsupium (20 ml/kg), extract of Momordica charantia (5 ml/kg) and tolbutamide (50 mg/kg) orally. Inhibition

of the hyperglycemic response of the anterior pituitary extract at 6, 12 and 24 hours was most marked in tolbutamide and G. sylvestre. The inhibitory effect was highly significant in G. sylvestre when compared with Pterocarpus marsupium and Momordica charantia . The inhibitory effects of an extract of G. sylvestre and purified gymnemic acid on Gastric Inhibitory Peptide (GIP) release was studied in rats. The GIP release into the portal vein in response to duodenal infusion of D-glucose in presence of leaf extract of G. sylvestre at a dosage of 0.5 ml/kg. The results suggested that a glucose receptor which interacted with the leaf extracts of G. sylvestre and purified Gymnemic acid. The inhibition of GIP release by gymnemic acid observed was attributed to the interaction with the glucose receptor for GIP release which was similar in specificity to the active glucose transport system . In an animal study, (2000) have investigated the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnema saponin V) derived from the methanol extract of leaves of G. sylvestre in STZ diabetic mice. The saponin fraction (60 mg/kg) reduced blood glucose levels within 2-4 hour after the intraperitoneal administration. Gymnemic acid IV, not the other 4 glycosides at doses of 3.4-13.4 mg/kg reduced the blood glucose levels by 13.5-60.0% 6h after the administration comparable to the potency of glibenclamide, and did not change the blood glucose levels of normal mice. Gymnemic acid IV at 13.4 mg/kg dose increased plasma insulin levels in STZ diabetic mice . G. sylvestre extract suppressed neural responses to mixture of monosodium glutamate and disodium inosine monophosphate in rats **(4)**. Aqueous extract of G. sylvestre have been possess hypoglycemic activity . In vitro, the inhibitory effects of DPPH radicals and LDL oxidation were found with aqueous extract of G. sylvestre. Hypoglycemic and life prolonging properties of G. sylvestre leaf extract in diabetic rats have been proved by the literature . Cataract is the leading cause of blindness worldwide and Diabetes has been considered to be one of the major risk factors of cataract. Agents that can inhibit aldose reductase and prevent sorbitol accumulation may be helpful to combat sugar-induced cataract. In a recently conducted study, aldose reductase inhibitory activity of Diabecon (an herbal drug used for diabetes containing G. sylvestre) was studied together with its effect against sugar-induced lens opacity in organ culture. Diabecon aqueous extract showed potential inhibitory activity with an IC50 value of 10 µg/ml against rat lens aldose reductase. It was also demonstrated that most of these effects were mainly due to G. sylvestre . Research has shown that Gymnema sylvestre have significant antidiabetic activity by lowering the blood glucose, increasing the secretion of insulin

and protecting the pancreatic cells from damage by oxidative stress. oral administration of water-soluble leaves extract of Gymnema sylvestre to patients receiving insulin therapy lowered the fasting blood sugar and induced the secretion of insulin. Gymnema sylvestre supplementation increases the level of serum insulin suggesting that the phytochemical induces the regeneration of pancreatic beta cells in patients with type 2 diabetes. There is overwhelming scientific evidence that demonstrate the inhibitory effects of Gymnema extracts on the activity of the α-amylase confirming its anti-diabetic properties . The enzyme α-amylase usually catalyzes the hydrolysis of starch to glucose thereby increasing the blood glucose level which is a major problem in diabetic patients. Gymnema has also been shown to produce α-glucosidase inhibitors such as Gymnemic acids which cause a concentration-dependent non-competitive inhibition of the enzyme . The enzyme is usually involved in the hydrolysis of glucosides to glucose . Gymnema also produces proteins that interact with dipeptidyl peptidase forming a complex thereby inhibiting the activity of the dipeptidyl peptidase enzyme. Dipeptidyl peptidase is an enzyme that has been shown to play a role in the regulation of biological activities of the glucose-dependent insulinotropic polypeptide and Glucagon- like peptide-1 . Therefore, the inhibition of the dipeptidyl peptidase activity offers a new therapeutic approach for the management of type 2 diabetes**(9)** .

5.2 Hypolipidaemic Activity

In a study conducted on experimentally induced hyperlipidaemic rats the leaf extract at a dosage of 25-100 mg/kg administered orally for two weeks reduced the elevated serum triglyceride (TG), total cholesterol (TC), very low density lipoprotein (VLDL) and low density lipoprotein (LDL)—cholesterol in a dose dependent manner. The ability of the extract at 100mg/kg to lower TG and TC in serum and its antiatheroscelrotic potential were almost similar to that of a standard lipid lowering agent clifibrate . In another study a dose-dependent increase in fecal cholesterol and cholic acid-derived bile acid excretion has been demonstrated in rats . A 3-week study showed a decrease in apparent fat digestibility and an increase in excretion of neutral sterols and acidic steroids in rats receiving an extract of G. sylvestre leaves and either a normal or high-fat diet. Total serum cholesterol and triglycerides also were decreased significantly . After 10 weeks, plasma triglycerides were lower in Gymnema-fed rats than in controls, but the difference in plasma total cholesterol levels was no longer significant . An aqueous extract of the

leaf was effective in reducing serum lipids in 27 insulin dependent diabetic patients taking insulin only, when treated with 400 mg/day. Serum levels of lipids returned to near normal **(8)** .

5.3 Weight control:-

Gymnema helps to promote weight loss possibly through its ability to reduce cravings for sweets and control blood sugar levels. The peptide gurmarin, temporarily binds to the sweet and bitter receptors on the tongue, thereby blocking the taste sensation and thus reduces sweet cravings34. A standardized Gymnema sylvestre extract in combination with niacin-bound chromium and hydroxycitric acid 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 Gymnema sylvestre extract and hydroxycitric acid, niacin-bound chromium can serve as an effective and safe weight-loss formula that can facilitate a reduction in excess body weight and BMI, while promoting healthy blood lipid levels35. Use of a dietary supplement containing Gymnema sylvestre in combination with glucomannan, chitosan, fenugreek, and vitamin C was investigated in obese adults (body mass index 30 kg/m2 or more). These adults lost significantly body weight, and percentage of body fat and absolute fat mass were significantly reduced. Reduction in upper abdominal, waist, and hip circumferences also was demonstrated in this patients36. An increase in body weight was significantly suppressed in a long-term study of the administration of Gymnema sylvestre extract in rats fed a high-fat diet. However, in rats receiving a normal diet, no significant suppression of weight gain was observed**(4)** .

5.4 Anti-Obese Activity

Abdominal fat deposition is yet another pivotal criterion branded as the harbinger of diabetes. The increase in adipocytes lessens the quantity of insulin receptors on cells that are targets of insulin in our body. This substantially diminishes the requisite amount of insulin to be present in the circulation and potentially reduces its metabolic functions. An alarming 40-80 percentile of diabetics have been reported to be obese. The adipocytes secrete resistin hormone, a 12.5 kDa cysteine-rich protein . Studies in murine models have implicated that the prevalence of resistin in the blood circulation accentuates insulin resistance developed. Recent in vivo and in vitro

investigations have shown that resistin sways glucose metabolism. In murine models, the inclusion of resistin patently amplifies the creation of glucose from the liver and thus drops the hepatic insulin exploit . Pravenec and co-workers have shown that genetically modified rats which secrete more resistin than required have glucose intolerance and disrupted skeletal muscle glucose metabolism **(2)**.Gymnema sylvestre is shown to have very useful properties for the management of both obesity and diabetes. Administration of a supplement comprising of Gymnema sylvestre with glucomannan, fenugreek, vitamin C and chitosan to a patient with body mass Index 30 kg/m2 or more resulted in significant reduction in their weight and also the overall fat percentage. Administration of gymnemic acid increased the fecal excretion of steroids and cholesterol . Weight gain was eventfully curbed in rats treated with the extract . The hexane extract of Gymnema sylvestre leaves (150 mg/kg and 250 mg/kg body weight) sig-nificantly ($p<0.001$) reduced increased body weight in Sprague dawley rats . A separate study was undertaken to analyze the effect of a new extract of an immensely bio-available, calcium-potassium salt of (–)-hydroxycitric acid for weight loss. The same excerpt was also used along with a niacin-bound chromium compound and with Gymnema sylvestre extract achieved weight loss in mildly fat individuals. Weight loss was analyzed by evaluating body weight fluctuations, body mass index, appetite, serum triglyceride, total cholesterol, HDL, LDL, leptin and serotonin concentrations, the elimination of urinary fat metabolites was also noted . Gymnema sylvestre extract endorses weight loss as it trims down sweet cravings and thus manages the blood sugar concentrations **(11)** .

5.5 Antioxidant activity

As already discussed, there is research evidence to show that oxidative stress plays a significant role in the pathogenesis of diabetes and its complications. The process of glucose oxidation, non-enzymatic glycation of proteins, and the oxidative degradation of glycated proteins leads to the formation of free radicals. Therefore, a good antidiabetic drug should show some antioxidative property. Indeed, research has shown that Gymnema sylvestre has significant antioxidant activity. A study found that the phytochemical inhibits 2,2- diphenyl-1-picrylhydrazyl (DPPH), scavenges superoxide and hydrogen peroxide with an antioxidant capacity of 17.54 mg/g expressed as ascorbic acid. Similarly, another study also found that Gymnema sylvestre extracts showed moderate antioxidant activity and when combined with other phytochemicals had an

IC50 of 45 µg/ml. Research has when also demonstrated that Gymnema when used alone or in combination with another phytochemical protects animals from the effects of lipid peroxidation . This shows the ability of the phytochemical to inhibit lipid peroxidation thereby suggesting its antioxidant property **(21)** .

5.6 Wound Healing Activity

Diabetes exponentially reduces the wound healing capacity of the body, hence the recurrence of a severe, never-healing infection from a simple wound is always a major threat .In one of the recent studies, Carbopol gel was prepared from the hydroalcoholic extracts of Gymnema sylvestre and Tageteserecta Linn. to determine its wound healing activity in albino mice . In both, the models, a prominent decrease in the time required for the occurrence of epithelial tissues was evidently noticed and the combined gel exhibited hastening of the wound healing process. The hydro alcoholic extracts could possibly accentuate wound healing as they have antioxidant potential and the phyto-constituent (flavonoids) prevalent in it that fastens the process of wound healing**(13)** .

5.7 Antiarthritic Activity.

The leaf extract of G. sylvestre was examined for antiarthritic activity on albino rats. The water soluble and petroleum ether (40–60∘C) extract was found tobe significantly effective in controlling arthritis. It was also assumed that the most potent antiarthritic activity of the leaves may be due to the nature of triterpenoids, steroids, and saponin glycosides . Different extracts were suspended with 1% Tween 80, and the drug Diclofenac sodium was administered once daily through oral route and the effect was monitored for 21 days. It was observed that the rats developed swelling in multiple joints on induction with an adjuvant and exhibited inflammation in cells, bone destruction, and re shaping. The petroleum ether extract treated group showed significant reduction in paw swelling possibly due to inhibiting the response of inflammatory cells or blocking the release of mediators like cytokines (IL-Ib and TNF-a), GM CSF, interferons, and PGDF which are responsible for pain and disabilities arising due to destruction of bone and cartilage . The other possible mechanism of action suggested protection of the release of joint cartilage and bone destruction in chronic arthritic model.The multiple studies

employing use of polar solvents in extract preparations by investigators demonstrated the antiarthritic potential of the leaf extract**(3)**.

5.8 Treatment of Dental Caries.

Dental caries can be defined as infection of tooth, occurring due to various kinds of gram-positive cariogenic bacteria like S. aureus, S. mitis, and S.mutans, and fungus-like Candida albicans which attaches to the tooth surface through release of extracellular polysaccharides from sucrose and metabolize sugar to organic acid mainly lactic acid resulting in demineralization of the tooth enamel . The chloroform, petroleum ether, and methanolic leaf extracts of G. sylvestre at various concentrations of 25,50, and 100 mg/mL were tested against microbial dental infections and found to be significantly effective against these cariogenic bacteria particularly the methanolic extract which showed highest activity at minimum concentration.The good potential of the hydroalcoholic extract of the plant leads to the development and manufacture of gurmar tooth powdered marketed as "Gurmar Herbal tooth paste" and "Gurmar Herbal Tooth powder." These herbal formulations offer new prospects in the treatment of dental caries once clinically approved by the scientific community**(7)**.

5.9 Antibiotic and 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 .The antibacterial activity of G. sylvestre and gymnemic acid was also studied against E. coli and B. cereus and the antimicrobial effect was significant against the microbes. L 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. In a similar study, the antimicrobial effect of ethanolic extract of G. sylvestre against Bacillus pumilus, B. subtilis, P.aeruginosa, and S. aureus showed promising antimicrobial effect . It can be inferred from the studies that the methanolic and ethanolic leaf extract of Gymnema sylvestre possesses

considerable antibiotic and antimicrobial activity**(8)**.

5.10 Immunomodulatory Activities

Several components of the immune system face discrepancies when inflicted with type 2 diabetes which lead to inflammation and glucose abnormalities. The cytokines are produced when the macrophages enter the adipocytes; these cytokines specifically cause the neighboring liver, muscle or fat cells to become insulin resistant. Several markers of inflammation such as C-reactive protein, fibrinogen, the interleukins and tumor necrosis factor-α (60) get elevated in diabetes. The extracts of Gymnema sylvestre restricted the histamine release in vitro . The leaf extract had significantly elevated the neutrophil chemotaxis that consequentially elevated neutrophils reduction of Nitro Blue Tetrazolium dye to form formazan thus ascertaining intracellular carnage aspect and a total increase in metabolic activity of phagocytosing neutrophils. This is perhaps due to the presence of tannins present in Gymenma leaves which have anti-inflammatory and immunomodulatory attributes . The methanolic extract of Gymnema sylvestre leaves showed a potential effect at 100µg/ml in nitric oxide and ROS generation in macrophage and 20µg/ml in lymphocyte proliferation leading to stimulation of myeloid and lymphoid elements of the immune system and thereby restoring the innate immunity **(9)**.

5.11 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 .The bioactive constituents inG. sylvestre known as tannins and saponins are responsible for the anti-inflammatory activity of the plant . 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 500 mg/kg with drug, phenylbutazone as standard. It was found that the gymnema aqueous extract at a concentration of 300 mg/kg significantly decreased the paw oedema volume by 48.5% within 4 hours of administration while the drug phenylbutazone 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**(1)**.

5.12 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 . 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 IC50 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 . With the rising percentage of cancer in people, the herbal formulation is a prospective medication in cancer therapy**(2)**.

5.13 Hepatoprotective Activity.

The hepatoprotective effect of hydro-alcoholic extract of G. sylvestre was evaluated by Srividya. The rat hepatocytes (freshly prepared) were subject to treatment with different concentration of hydroalcoholic extract prepared by the hot maceration process. The extract at a concentrations of 200, 400, and 600 μg/mL showed significant antihepatotoxicity against the D-galactosamine-induced hepatotoxicity, and the concentration of 800 μg/mL was found to be cytotoxic. The cells exhibited a significant restoration of the altered biochemical parameters towards the normal ($P<$ 0.001) when compared to D-galactosamine treated groups in a dose-dependent manner,when treated with the hydroalcoholic extract different extracts of G. sylvestre**(17)** .

6.0 Toxicology :-

Even in the long-term study, there was no report of any undesirable effect. However, hypoglycemia is one of the possibilities of its administration. High doses of Gymnema sylvestre leaves did not exhibit any adverse effect on the gastrointestinal mucosa; hence, it poses to be a harmless gastrotoxic anti-inflammatory response compared with other anti-inflammatory agents . While in an acute toxicity investigation in mice a negative behavioral changes, neurologic and autonomic upshots were evident. Safety ratio (LD50/ED50) in the diabetics was sixteen while in

the healthy rats it was eleven .Evidence regarding the toxicity of the plant or its parts on the human has been documented rather in patients with quotidian consumption of Gymnema sylvestre the serum urea, uric acid, and hemoglobin levels remain normal. However, it is suggested to avoid the administration of Gymnema sylvestre during pregnancy. Thus, Gymnema sylvestre is generally safe and devoid of side effect. The administration is recommended under the clinical supervision of the healthcare professional**(5)** .

7.0 Dosage:-

Pediatric Dose: No sufficient evidence is available on the use of Gymnema sylvestre in pediatric population. Thus, it is not recommended for pediatrics57.

Adult Dose: The adult dosage for Gymnema sylvestre liquid extract is 25 to 75 ml per week 47.In Type 1 or 2 DM patients, 200mg extract GS4 orally twice daily (or 2ml of an aqueous decoction [10g of powdered leaves per 100ml] three times daily) to be taken in conjunction with other hypoglycemic agents is recommended58. Currently available medical and scientific literature indicates that the dietary supplement should be standardized to 25% gymnemic acids per dose and most common dose is standardized extract of 250 mg twice a day**(20)** .

8.0 Contraindications/ allergies:-

Allergy: People allergic to plants in the Asclepiadaceae (milkweed) family may be allergic toGymnema sylvestre58. When used in appropriate dosages, gymnema appears to be fairly safe, althoughextensive studies have not been performed. One obvious risk is that if gymnema is successful, it may lower blood sugar levels too far, causing a dangerous hypoglycemic reaction. For this reason, medical supervision is essential.59 Hence; Gymnema sylvestre should be used cautiously diabetic patients on hypoglycemic medications. However hypoglycemia may also occur in non-diabetic patients58. Pregnancy and Lactation: To date, the medical literature has notreported any adverse effects related to fetal development during pregnancy or to infants who are breast-fed. Therefore it is not recommended due to insufficient safety information **(19)**.

9.0 Interactions:-

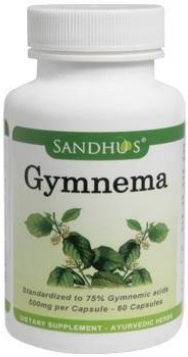
Interactions with other herbs: Since Gymnema sylvestre may decrease blood sugar levels, taking it with other blood sugar-lowering herbal products may result in hypoglycemia—blood sugar that is too low. Herbals that may reduce blood sugar include:

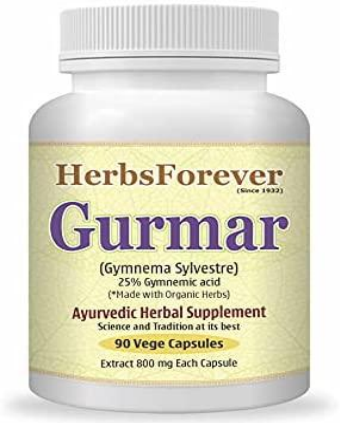
- Eleuthero
- Fenugreek
- Ginger (in high amounts)
- Kudzu
- Panax Ginseng**(3)**

10.0 Market Formulations :-

MERLION Naturals Gymnema sylvestre Dietary supplements 120 Tablets	
Madhuvijay Gymnema sylvestre For Healthy Blood Sugar Support 500 mg Herbal Supplement 60 Capsule	

SWANSON Gymnema sylvestre leaf Blood Sugar Support 400mg Herbal supplement 100 Capsule	

JIVA Botanicals Gymnema sylvestre All natural Ingredients Advanced extract formula Dietary supplements 600mg 90 Capsule	
SANDHUS Gymnema Standardized to 75% Gymnemic acids 500 mg per capsule 60 capsule	

Herbs Forever GURMAR Extract 800 mg each capsule Gymnema sylvestre 25% Gymnemic acid 90 vege capsule	

Conclusion :-

Diabetes mellitus is the most common metabolic disorder affecting human beings and is characterized by chronic hyperglycemia. The prevalence of diabetes is rising and aggravating all over the world is being associated with an increase in financial burden, a decrease in quality of life, morbidity and mortality. In the past few years, Gymnema sylvestre has emerged as a cost-effective and potential intervention by targeting the etiological factors connected with diabetes. It functions as a blood sugar lowering agent, insulin stimulator, β-cell regenerator, facilitator of anti obesity and an anti-inflammatory agent. It produces not only blood glucose homeostasis but also showed anti-cancerous, anti-microbial, anti-arthritic activities. Gymnema sylvestre holds a definite promise in the management of diabetes mellitus. This review has updated the pharmacological, toxicological and clinical evaluation of this plant for treatment of diabetes and its associated abnormalities. The ethnomedical approach for diabetes using Gymnema sylvestre is practical, logical and economically worthwhile. But still, it requires scientific and technological validation, standardization for justification of its wide acceptability among a modern system of medicine. One can look toward to an integrated approach to future medicine using this traditional drug.

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