Ilkogretim Online - Elementary Education Online, 2021; Vol 20 (Issue 1): pp. 6309-6325
http://ilkogretim-online.org
doi: 10.17051/ilkonline.2021.01.656

A Study Of An Applications Of Gymnema Sylvestre In Clinical Practice For The Treatment Of Diabetes Type 2 And Its Complications

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Abstract:

In this paper we explored the Diabetes mellitus, also known as Madhumeha, is one of the most common forms of metabolic condition that is seen in developing nations. It is distinguished by an elevated amount of sugar in the blood and is linked to both macrovascular and microvascular problems. Gymnema sylvestre (Asclepiadaceae) is revered as a potential antidiabetic herbal drug that has the capability of simultaneously regenerating beta cells and stimulating insulin secretion, and it is one of the herbs that are described for the management and treatment of diabetes mellitus in the Indian system of medicine known as Ayurveda.

In addition, Gymnema sylvestre has properties that make it effective against obesity and hyperlipidemia, as well as inflammation and cancer. This article provides an up-to-date assessment of the most recent findings from experimental research carried out on Gymnema sylvestre as a successful treatment for diabetes mellitus, as demonstrated by research carried out on both animals and humans. In addition to that, this study addressed the toxicity of Gymnema sylvestre as well as the potential obstacles that lie ahead in the development of a formulation for the prevention and management of diabetes.

KEYWORD: Diabetes Mellitus, Gymnema sylvestre, Anti-diabetic, Anti-hyperlipidemic, Anti-inflammatory, Anti-Cancerous

I. INTRODUCTION

As a source of medicine, plants have been practically utilized by every civilisation ever to ever exist. The World Health Organization (WHO) forecasts that roughly 80 percent of the population residing in poorer nations will use preparations derived from plants as medical treatments in the near future (1). Countries in Asia are recognized as important sources of information regarding the utilization of herbal species for the treatment of a wide variety of metabolic diseases (2). At least 25 percent of the medicines in today's pharmacopoeia come from plants. In the treatment of diabetes, Ayurveda, which is based on the Atharva Veda, recommends the utilization and effectiveness of herbal preparations. Hyperglycemia and disorders of carbohydrate, lipid, and protein metabolism are all symptoms of diabetes, which ultimately leads to inconsistencies either in the secretion of insulin or in its ability to do its job, or both. Diabetes is a cluster of inter-related metabolic anarchy symbolized by hyperglycemia (3). According to the World Health Organization, there were roughly 171 million individuals around the world suffering from diabetes in the year 2000, and it is anticipated that there would be 366 million by the year 2030. (4).

II Gymnema sylvestre: a Possible Treatment Derived from a Herbal Plant

One of the natural herbs that has been widely utilized in traditional medicine for the over two thousand years, Gymnema sylvestre, also known as Gurmar or Madhunashini, is one of such herbs.

It is a kind of woody plant that is indigenous to India, more specifically the woods of southern India. Additionally, it can be found in the tropical regions of Australia and Africa, as well as in the Asian countries of Malaysia, Japan, Vietnam, and Sri Lanka (5). The leaves and roots of the Gymnema sylvestre plant are the primary components of the plant that are utilized for medicinal purposes (6). The leaf powder is soft and yellow in color, and it has poor flow ability and compatibility with other substances (7). The herb gymnema has the ability to reduce blood sugar levels and preserve the liver (8, 9). The dried leaf and root of the gymnema plant have been used medicinally for a very long time to treat a variety of conditions, including cough, leprosy, skin illnesses, and wounds. It has been shown that a liquid extract obtained from the roots of the Gymnema plant can be used to treat nausea, vomiting, and diarrhea. Additionally, it has been found that a paste created from the plant and mixed with mother's milk can effectively treat mouth ulcers (10, 11).

This present review aims to provide the most recent developments on the pharmacological and clinical research that has been conducted to establish the hypoglycemic effect of the plant, unraveling its active hypoglycemic constituents in the treatment of diabetes. Specifically, the review will focus on the plant's ability to lower blood sugar levels. In addition, the study highlighted other uses of Gymnema sylvestre, such as its anti-bacterial, anti-cancer, and anti-arthritic properties.

Gymnema sylvestre has a wide range of potential uses.

Ayurvedic doctors have a strong preference for the use of gymnema sylvestre as an effective diabetes treatment and management tool. The activities of gymnema sylvestre that have been categorized as anti-diabetic, anti-hyperlipidemic, anti-obese, anti-oxidant, immunomodulatory, and wound healing are explained in this picture (Fig.1).

Based on research conducted on animals, gymnema sylvestre has been shown to have anti-diabetic properties.

The anti-diabetic potential of Gymnema sylvestre was investigated in diabetic rats by treating them with an alcoholic extract of the leaves at a dosage of 100 milligrams per kilogram per day for a duration of one month (20). In the rats that were given Gymnema sylvestre extract to treat their diabetes, after two weeks of treatment, the average blood glucose level dropped by a sizeable amount. It was concluded that possibly Gymnema sylvestre does not affect thyroid hormone-mediated type 2 diabetes mellitus as there was no effect of Gymnema sylvestre noted on the level of thyroxine even in corticosteroid induced diabetes mellitus rat. This was due to the fact that no effect of Gymnema sylvestre was noted on the level of thyroxine.

During the trial with diabetic rabbits, Gymnema sylvestre showed improvements in glycogen synthesis, glycolysis, and gluconeogenesis, as well as increases in hepatic and muscle glucose absorption (21) and enhanced the formation of hemoglobin and protein glycosylation (23). Studies carried out by Srivastava and co-workers (1985) demonstrated the anti-hyperglycemic and life-prolonging effects of an aqueous extract of the dried leaves of Gymnema sylvestre. The extract was administered in four different single doses (of amounts 0.2 g, 0.4 g, 0.6 g, and 0.8 g respectively) to alloxan-induced diabetic rats with different ranges of blood glucose levels. The moderately diabetic rats given 0.6 grams of Gymnema sylvestre per day showed the greatest improvement in their blood glucose levels after receiving treatment with Gymnema sylvestre. This same group also had the highest life expectancy of any other group. Although the consumption of more than 0.6 grams of gymnema extract did not demonstrate any additional improvement in the control of blood glucose (24).

Gymnema sylvestre also possesses insulinotropic activity. The administration of Gymnema sylvestre has reduced the fasting glucose levels (at significant variation, P 0.001) along with a considerable lowering of serum lipid levels while concomitantly ameliorating serum protein levels. Gymnema sylvestre has also been shown to possess anti-inflammatory properties (25). The administration of the ethanolic excerpt (50 percent) of the leaves of Gymnema sylvestre (GS3, 20 mg/day/rat) and the processed residue of GS3 (GS4, 20 mg/day/rat) presented a 30 percent boost in the total -cells mass as well as in the numbers

of the islets (p 0.001) in a rat model of type 2 diabetes (26). The regeneration of pancreatic tissue was another factor that contributed to the successful management of the absolute levels of fasting sugar within 60 days in the GS3 group and 20 days in the GS4 group.

Because it increases the permeability of the cell membrane, the alcoholic extract of Gymnema sylvestre helps to promote the release of insulin from beta cells such as HIT-T15, MIN-6, and RINm5F. (27, 28). Based on the results of an exclusion test with trypan blue, it was determined that the extract increased the permeability of cells to dye due to its high saponin content in glycosides. Insulin is secreted as a result of an influx of calcium ions into beta cells, which is caused by a Ca++-sensitive component and is channel independent. Similar effects were observed by Liu et al. (29), who discovered that aqueous alcoholic extract (0.06-0.25 mg/ml conc.) caused MIN6 -cell line to release insulin. A higher concentration (more than 0.5 mg/ml) produces an enhanced absorption of trypan blue and leads to an increase in the Ca++ levels of beta cells. Through the regeneration of beta cells, the methanolic extract of Gymnema sylvestre leaf and callus also demonstrates anti-diabetic activity (30). The green compact callus that was obtained by in-vitro culture and then subjected to the stressful conditions of exposure to blue light with 2, 4-D (1.5 mg/L) and KN (0.5 mg/L) also demonstrated a considerable amount of beta-cell regeneration. According to research published in 2008 by Sujin et al., administration of greater doses (5, 10, 15, 20/g/25 days) of Gymnema sylvestre did not result in substantial mortality; however, behavioral abnormalities such as sluggish movements and hunger suppression were noted upon doses of 5 g and 20 g. (31). It is well known that gymnema sylvestre has the ability to inhibit the taste response in taste buds. The neural response of the murine chorda tympani towards sucrose was seen to be condensed by a compound that was isolated from the searing aqueous excerpt of the Gymnema sylvestre leaves. This matter was confirmed to be the peptide named Gurmarin, which comprised of 35 amino acids and had a molecular mass of 4,000 Dalton. After exposing the tongue to concentrations of the peptide greater than 1x10-6M, the inhibiting capability of the peptide on the experience of sweetness was determined (32). The inhibitory effect of gurmarin varies depending on the area of the tongue and the strain of mice (33).

An investigation into how rats respond to the taste of gurmarin found that the sweet taste receptors at the tip of the tongue are most likely engaged as a result of gurmarin's ability to connect to those receptors when the substance is consumed (34).

In diabetic rats, Kamble's colleagues investigated the pharmacokinetic and pharmacodynamic interaction following concurrent therapy with 400 mg/kg of Gymnema sylvestre extract and 0.8 mg/kg of glimepiride medication for a period of four weeks (35). The research showed that there was a positive pharmacodynamic interaction, which

resulted in a considerable increase in anti-hyperglycemic activities despite the fact that the pharmacokinetic parameters were not significantly altered.

The chitosan nanoparticle with Gymnema sylvestre extract was also evaluated against rats induced with streptozotocin, and it was discovered to decrease the fasting glucose level and glycosylated hemoglobin at the dose of 100 mg/kg body weight of the rats. This finding was made possible by the presence of the Gymnema sylvestre extract (36).

Phytochemistry and bioactive components with diabetes-fighting potential

The primary constituent of Gymnema sylvestre is known as gymnemic acid, which is a complex mixture of at least 17 distinct saponins (37), the majority of which belong to the oleanane and dammarene classes (39). The longispinogenin 3-O—D-glucopyranoside, which is also known as 3-O—D-glucuronopyranoside (1-6) -β-D-glucopyranosyloleanolic acid 28-O- β-Dglucopyranosyl ester, 21 β-benzoylsitakisogenin 3-O-βD-glucuronopyranoside 3-O-β-D-xylopyranosyl \s(1-6) -β-D-glucopyranosyl (1-6)-β-D-glucopyranosyl oleanolic acid 28-O-β -D-glucopyranosyl ester, oleanolic acid 3-O-β-D-xylopyranosyl(1-6) -βD-glucopyranosyl(1-6)-β-D-glucopyranoside and

3-O-β-D-glucopyranosyl (1-6)

-β-D-glucopyranosyl oleanolic acid 28-β -D-glucopyranosyl (1-6) The glycosides of oleanane-triterpene are referred to as —Dglucopyranosyl ester. These were deciphered through the use of hydrolysis, and then spectrophotometric analysis was performed. In the same manner, seven other unique dammarane-style saponins were isolated from a leaf fragment of Gymnema sylvestre; these saponins are referred to as gymnemasides I through VII. The gypenosides XXVIII, XXXVII, LV, LX11, and LXIII belong to the same category of saponins as those that were known previously.

Gymnemosides and gymnemic acid are the two saponin components of Gymnema sylvestre that are responsible for the plant's ability to lower blood sugar levels (40). The portion of the plant known as triterpene glycosides is responsible for preventing the intake of glucose by the muscles (41, 42). It was shown that the glucose absorption in rats could be blocked by the inhibitory effects of triterpene glycosides and different gymnemosides derived from Gymnema sylvestre (43). At a dose of 20 mg/kg, a novel compound known as dihydroxy gymnemic triacetate, which was isolated from acetone extract, decreased the level of sugar in the blood by 65 percent and glycosylated hemoglobin by 39.56 percent while simultaneously increasing the level of insulin in the plasma by 63 percent (44).

The effectiveness of glibenclamide (14.8 mg/kg body weight) and intravenous administration of gymnemic acid (13.5 mg/kg body weight) in reducing the sugar level was

comparable. The sugar level was reduced to 60 percent after gymnemic acid was administered (45). Recently, crystallographic analysis of gymnemagenin indicated that it gels well with the crystallographic constitution of the target protein (dipeptidyl peptidases, aldose reductases, glucokinase, fructose 1,6-bisphosphate, cytochrome 450, 11-hydroxysteroid dehydrogenase, tyrosine phosphatases, protein kinase B, glutamine fructose6-phosphate (46).

action directed against hyperlipidemia

The metabolic disorder known as diabetes mellitus is frequently linked to changes in lipid metabolism, which regulate levels of lipoproteins (47).

Lipoprotein abnormalities are the root cause of insulin resistance, which is caused by a variety of factors. Some of these factors can reduce the activity of lipoprotein lipase (LPL) and peroxisome-proliferator activated receptor (PPAR) gamma, while others can increase the activity of acyl-CoA synthetase and the transporter of microsomal triglyceride. When given orally to experimental rats for a period of two weeks, a dose ranging from 25 to 100 milligrams per kilogram of the leaf extract of Gymnema sylvestre showed a dose-dependent tectonic decline in the lipid profile. It was almost comparable to a standard lipid-lowering agent in terms of the effects that the extract of Gymnema sylvestre had on lowering serum triglycerides, total cholesterol, and atherosclerotic property when it was administered at 100 mg/kg (48).

Mall et al. examined the hypolipidemic activity of a higher dose of aqueous leaf extract (up to 800 mg/kg body weight for 30 days) in alloxan-induced diabetic rats. They found that the extract had a positive effect (49). The decrease was investigated at all dosages (400,600, and 800 mg/kg body weight), however the highest concentration showed a significant difference when compared to the other days that were observed. Although the administration of the excerpt demonstrated a significant reduction in the levels of serum lipids and fasting blood glucose, it also demonstrated a desirable increase in the levels of serum high-density lipoprotein (HDL)-cholesterol. Rachh et al. in 2010 obtained a similar significant decrease in the other lipid parameters and a significant increase (p 0.05) in HDL level when hydroalcoholic leaf extract (200 mg/kg body weight) of the plant was administered in the diet of high cholesterol-fed (2 percent cholesterol + 1 percent sodium cholate + 2 percent coconut oil) rats. This was achieved by administering the hydroalcoholic leaf extract of the plant in the diet of the rats (12).

When combined with chitosan and ascorbic acid in a ratio of 1:10:2, the herb gymnema sylvestre is able to provide protection against the condition known as hypercholesterolemia. At a dose of 4.68 g/kg diet, a significant reduction in serum triglyceride levels (35.87

percent), total cholesterol levels (43.89 percent), LDL cholesterol levels (54.00 percent), and atherogenic index (AI) (41.47 percent) was found (50).

It was discovered that feeding rats leaf extract led to a reduction in the perceptible breakdown of fat as well as an increase in the emission of neutral sterols and acidic steroids (51). The use of a novel dihydroxy gymnemic triacetate led to a reduction in total cholesterol, triglyceride, and LDL levels by 54%, 55%, and 40%, respectively, while at the same time an increase in HDL level of 38% was observed (44).

Efforts Made to Combat Obesity

The accumulation of fat around the abdomen is yet another important factor that is considered to be a predictor of diabetes. Because of the increase in adipocytes, the number of insulin receptors that can be found on the cells that are the targets of insulin in our bodies is reduced.

This results in a significant reduction in the amount of insulin that must be present in the circulation and may also inhibit the metabolic tasks that insulin normally performs. Obesity is reported to affect 40–80 percent of diabetics, which is an alarmingly high percentage.

A protein with a high cysteine content and a molecular weight of 12.5 kDa is produced by adipocytes (52). Studies conducted on murine models have led researchers to conclude that the presence of resistin in the blood circulation plays a significant role in the progression of insulin resistance. Recent studies in vivo and in vitro have demonstrated that resistin influences glucose metabolism in a variety of ways. The presence of resistin demonstrably increases the amount of glucose that is produced by the liver in murine models, which results in a decrease in the amount of glucose that is exploited by hepatic insulin (53). It has been demonstrated by Pravenec and colleagues (2003) that genetically modified rats that secrete more resistin than is required suffer from glucose intolerance and have disruptions in the glucose metabolism of their skeletal muscles (54).

There is evidence that the herb gymnema sylvestre possesses characteristics that make it particularly effective for the control of both diabetes and obesity. When a patient with a body mass index of 30 kg/m2 or more was given a supplement that included Gymnema sylvestre along with glucomannan, fenugreek, vitamin C, and chitosan, the patient had a considerable drop in both their weight and their overall fat percentage.

The administration of gymnemic acid led to an increase in the amount of steroids and cholesterol excreted in the feces (55). Rats given the extract had a significant reduction in their rate of weight gain (56). The hexane extract of Gymnema sylvestre leaves significantly (p 0.001) decreased increasing body weight in Sprague dawley rats. The doses used were

150 mg/kg and 250 mg/kg (13). A separate trial was conducted to investigate the efficacy of a recently developed extract of a highly bioavailable calcium-potassium salt of (–)-hydroxycitric acid in assisting with weight reduction. In addition, the same extract was utilized in conjunction with a niacin-bound chromium compound and with Gymnema sylvestre extract to accomplish weight loss in persons who were just moderately overweight. Analyses of body weight fluctuations, body mass index, hunger, serum triglyceride, total cholesterol, HDL, LDL, leptin, and serotonin concentrations, as well as the clearance of urine fat metabolites, were performed on individuals who had lost a significant amount of weight (57). The elimination of cravings for sweet foods and beverages and the subsequent regulation of blood sugar levels are the two primary mechanisms by which gymnema sylvestre extract contributes to weight loss.

Activity Inhibiting Oxidation

The presence of diabetes circumstances results in the production of oxidative stress, which is responsible for the development of secondary problems. Under these conditions, a glycation reaction that takes place in a variety of tissues and plays a detrimental role in the diabetes secondary complications produces reactive oxygen species (ROS) (58). Further formation of free radicals, non-enzymatic protein glycosylation, glucose auto-oxidation, changes of antioxidant enzymes, and a rise in lipid peroxidation all lend credence to the hypothesis that oxidative stress contributes to the progression of diabetes (59).

The risk of diabetes complications can be significantly mitigated by antioxidant supplementation. Antioxidants, such as vitamin C, glutathione, and vitamin E, have been shown by a number of studies to be effective in reversing insulin resistance in individuals suffering from type 2 diabetes and cardiovascular disease. These patients had previously been diagnosed with insulin resistance. It has been observed that the alcoholic extract of Gymnema sylvestre can inhibit 1, 1-Diphenyl-2-picrylhydrazyl (DPPH), as well as clean up superoxide and hydrogen peroxide. This potential to decrease radicals has also been demonstrated in the ferric reducing prototype, in which the antioxidant capability was measured to be 17.54 mg/g when expressed in terms of ascorbic acid (14). The administration of a mixture (4.68 g/kg diet) of chitosan, vitamin C, and Gymnema sylvestre (10:2:1) resulted in a significant decrease (19.27 percent) (p0.05) in the plasma alanine aminotransferase potentiality (50).

Activities That Modulate the Immune System

When a person has type 2 diabetes, several different components of their immune system experience disparities, which ultimately lead to inflammation and glucose irregularities.

When macrophages infiltrate adipocytes, they create cytokines, and it is these cytokines that specifically induce the adjacent liver, muscle, or fat cells to become insulin resistant. Diabetes is associated with an increase in the levels of several inflammatory indicators, including C-reactive protein, fibrinogen, the interleukins, and tumor necrosis factor- (60).

In vitro testing showed that extracts of Gymnema sylvestre were able to inhibit the production of histamine (21). The leaf extract had a significant elevating effect on neutrophil chemotaxis, which in turn led to an elevating effect on neutrophils' reduction of Nitro Blue Tetrazolium dye to form formazan, thereby establishing an intracellular carnage aspect and a general elevating effect on the metabolic activity of neutrophils that were phagocytosing.

This could be because the leaves of the gymnema tree contain tannins, which are known to have anti-inflammatory and immunomodulatory effects (16). The methanolic extract of Gymnema sylvestre leaves showed a potential effect at 100 micrograms per milliliter in nitric oxide and reactive oxygen species generation in macrophage and at 20 micrograms per milliliter in lymphocyte proliferation, leading to stimulation of myeloid and lymphoid elements of the immune system and, as a result, restoring the innate immunity (61).

Activity in the Healing of Wounds

Because diabetes drastically impairs the body's ability to heal wounds, even minor cuts and scrapes pose a significant risk of developing a chronic infection that will never go away while diabetes is present (18).

Carbopol gel was made from the hydroalcoholic extracts of Gymnema sylvestre and Tageteserecta Linn in one of the more recent experiments to test the wound healing activities of the gel in albino mice (62). The mixed gel showed signs of speeding up the process of wound healing, and both of the models showed a significant reduction in the amount of time needed for the formation of epithelial tissues. The hydro alcoholic extracts have antioxidant potential, and the phytoconstituents (flavonoids) that are prevalent in it speed up the process of wound healing. Therefore, it is possible that the hydro alcoholic extracts will enhance the process of wound healing. In individuals who were only moderately overweight, the use of cerpt, in conjunction with a niacin-bound chromium compound and Gymnema sylvestre extract, resulted in significant weight loss. Analyses of body weight fluctuations, body mass index, hunger, serum triglyceride, total cholesterol, HDL, LDL, leptin, and serotonin concentrations, as well as the clearance of urine fat metabolites, were performed on individuals who had lost a significant amount of weight (57). The elimination of cravings for sweet foods and beverages and the subsequent regulation of blood sugar levels are the two primary mechanisms by which gymnema sylvestre extract contributes to weight loss.

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III Human Subjects in Clinical Studies and Experiments

In the clinical trials, the use of gymnema sylvestre as an anti-diabetic medication was proven to be successful. Gymnema sylvestre was found to have insulinotropic properties when it was given to adult human participants in the age range of 25 to 40 years old at a dosage of 2 grams per day split between two doses (25). When a water-based extract of Gymnema sylvestre leaves was given at a dosage of 2 gm thrice daily to 10 normal individuals over a period of ten days and in 6 diabetics for fifteen days, there was a potential for a reduction in the glucose intensity of the fasting and oral glucose tolerance test (OGTT). The only exception to this was the OGTT in the normal cluster (63). It has been shown that reducing the amount of glycosylated hemoglobin (HbA1C) in diabetics with the twice-daily use of a leaf extract of Gymnema sylvestre containing 400 milligrams is effective (64).

Multiple studies have demonstrated that Gymnema sylvestre is effective in treating diabetes of either type 1 or type 2, making it a potentially useful treatment option for diabetics. In one of the experiments, the participants (all of whom had type 2 diabetes) were given a daily dose of 400 milligrams of GS4 to see how well it worked (65).

During the 18–20 month evaluation period, it was found that Gymnema sylvestre significantly reduced plasma glucose (p 0.001), HbA1c (p 0.001), and glycosylated plasma protein (GPP) levels. Another individual study looked at the efficacy of the Gymnema sylvestre extract on 27 people who had type 1 diabetes over a period of time ranging from six months to thirty months (66). It was found that Gymnema sylvestre significantly

decreased the levels of GPP in the blood within the first six to eight months, and then it reduced serum amylase (p 0.001) within the 16–18 months after that. In comparison to insulin therapy (n=37), Gymnema sylvestre produced a statistically significant and clinically meaningful increase in blood C-peptide concentration after 16–18 months (p 0.001).

Paliwal et al. conducted a study in 2009 to determine what effect the administration of the leaf powder of Gymnema sylvestre had on the plasma glucose concentration of twenty type 2 diabetic women who were between the ages of 40 and 60 and lived in the city of Udaipur in the Indian state of Rajasthan (67). In addition to receiving 3 divided doses of 6 grams of Gymnema sylvestre leaf powder each day, the test subjects also participated in a dietary survey that utilized a method that required them to recall their eating habits for a period of 24 hours. Because the intervention's results showed that the powder worked effectively on lowering sugar levels without causing any unpleasant side effects, we can conclude that it is both an efficient remedy and a therapeutic agent in the process of lowering sugar levels.

The polyherbal formulation that was developed from Gymnema sylvestre (GSPF kwath; a mixture of ten herbs) exerted a considerable reduction in blood glucose (23.5% and 26.7%, respectively, for fasting and postprandial glucose level), as well as glycosylated hemoglobin (11.7 percent). After receiving GSPF treatment for 6 months, blood levels of cholesterol (14.4% lower), triglycerides (21.7%), LDL (26.8% lower), and very low density lipoprotein (VLDL) (21.7%) were reduced. In addition to this, there was a discernible rise in the levels of the molecular marker for oxidative stress (68). In a different trial, the short-term supplementation of G-400, which is a polyherbal formulation (1000 mg per day for eight weeks), was employed to attenuate the hyperglycemia and hyperlipidemia in the patients (69). In their study on Gymnema sylvestre as a potential herbal medicine for type 2 diabetes, Yadav et al. looked at both the preventive and therapeutic features of the plant (70).

IV. CONCLUSION

Diabetes mellitus, which is defined by chronic hyperglycemia, is the metabolic illness that affects humans the most frequently and is the most common form of the disease. The growing and worsening prevalence of diabetes around the world is being linked to a rise in the financial burden, a decline in quality of life, as well as morbidity and mortality. In the most recent few years, Gymnema sylvestre has emerged as a promising and cost-effective intervention for the treatment of diabetes by targeting the etiological variables associated with the disease. It acts as both an anti-inflammatory agent and a blood sugar reducing agent, as well as a regenerator for beta cells, a facilitator of anti-obesity, and a blood sugar lowering agent. Not only does it bring about homeostasis in blood glucose levels, but it has also been shown to have anti-cancer, anti-microbial, and anti-arthritic effects.

In the treatment of diabetes, gymnema sylvestre shows strong promise as a potential treatment option. The pharmacological, toxicological, and clinical examination of this plant for the treatment of diabetes and the abnormalities that are linked with it have been brought up to date by this review. The ethnomedical treatment for diabetes that makes use of Gymnema sylvestre is one that is useful, makes sense, and is financially viable. In spite of this, it is necessary to obtain scientific and technological validation, as well as standardization, in order to justify its widespread adoption inside a contemporary medical system. One can have hope for an integrated method of treating future medical conditions by making use of this traditional medicament.

REFERENCES

1. Shelar DB, Shirote PJ. Natural product in drug discovery: back to future. J Pharm Res 2010; 3: 2007-8.
2. Kala CP, Farooquee NA, Dhar U. Prioritization of medicinal plants on the basis of available knowledge, existing practices and use value status in Uttaranchal, India. Biodivers Conserv 2004; 13: 453-69.
3. Shah D, Agarawal V, Parikh R. Noninvasive insulin delivery system: a review. Int J Appl Pharm 2010; 2: 35-40.
4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53.
5. Pham HTT, Hoang MC, Ha TKQ et al. Discrimination of different geographic varieties of Gymnema sylvestre, an anti-sweet plant used for the treatment of type 2 diabetes. Phytochemistry 2018; 150: 12-22.
6. Yadav D, Tiwari A, Mishra M et al. Anti-hyperglycemic and anti-hyperlipidemic potential of a polyherbal preparation “Diabegon” in metabolic syndrome subject with type 2 diabetes. Afr J Tradit Complement Altern Med 2014; 11: 249-56.
7. Singh SP, Patra CN, Dinda SC. A comparative evaluation of the flow and compaction characteristics of Gymnema sylvestre leaf powder. . J Adv Pharm Res 2010; 1: 1-11.
8. Hajare R. Comparing Modified and Relationship Study of Gymnema Sylvestre Against Diabetes. SF J Pub Health 2018; 2.
9. Smruthi G, Mahadevan V, Sahayam S, Rajalakshmi P, Vadivel V, Brindha P. Anti-Diabetic Potential of Selected Indian Traditional Medicinal Plants-An Updated Review. Journal of Pharmaceutical Sciences and Research 2016; 8: 1144.
10. Ekka NR, Dixit VK. Ethno-pharmacognostical studies of medicinal plants of jashpur district (Chhattisgarh). Int J Green Pharm 2007; 1.
11. Meena AK, Bansal P, Kumar S. Plants-herbal wealth as a potential source of ayurvedic drugs. Asian J Tradit Med 2009; 4: 152-70.

12. Rachh PR, Rachh MR, Ghadiya NR et al. Antihyperlipidemic activity of Gymenma sylvestre R. Br. leaf extract on rats fed with high cholesterol diet. Int J Pharmcol 2010; 6: 138-41.
13. Manish K, Aditi K, Renu A, Gajraj S, Poonam M. Antiobesity property of hexane extract from the leaves of Gymnema sylvestre in high fed cafeteria diet induced obesity rats. International Research Journal of Pharmacy 2011; 2: 112-6.
14. Rachh PR, Patel SR, Hirpara HV et al. In vitro evaluation of antioxidant activity of Gymnema sylvestre r. br. leaf extract. Romanian J Biology Plant Biol 2009; 54: 141-8.
15. Arunachalam KD, Arun LB, Annamalai SK, Arunachalam AM. Potential anticancer properties of bioactive compounds of Gymnema sylvestre and its biofunctionalized silver nanoparticles. Int J Nanomedicine 2015; 10: 31.
16. Malik JK, Manvi FV, Nanjwade BK, Alagawadi KR, Sinsh S. Immunomodulatory activity of Gymnema sylvestre R. Br.. leaves on in vitro human neutrophils. J Pharm Res 2009; 2: 1284-6.
17. Satdive RK, Abhilash P, Fulzele DP. Antimicrobial activity of Gymnema sylvestre leaf extract. Fitoterapia 2003; 74: 699-701.
18. Meyer JS. Diabetes and wound healing. Crit Care Nurs Clin North Am 1996; 8: 195-201
19. Malik JK, Manvi FV, Nanjware BR, Dwivedi DK, Purohit P, Chouhan S. Anti-arthritic activity of leaves of Gymnema sylvestre R. Br. leaves in rats. Pharm Lett 2010; 2: 336-41.
20. Gupta SS, Seth CB. Experimental studies on pituitary diabetes. II. Comparison of blood sugar level in normal and anterior pituitary extract-induced hyperglycaemic rats treated with a few Ayurvedic remedies. Indian J Med Res 1962; 50: 708.
21. Porchezhian E, Dobriyal RM. An overview on the advances of Gymnema sylvestre: chemistry, pharmacology and patents. Pharmazie 2003; 58: 5-12.
22. Shanmugasundaram KR, Panneerselvam C, Samudram P, Shanmugasundaram ERB. Enzyme changes and glucose utilisation in diabetic rabbits: the effect of Gymnema sylvestre, R. Br. J Ethnopharmacol 1983; 7: 205-34.
23. Shanmugasundaram ERB, Venkatasubrahmanyam M, Vijendran N, Shanmugasundaram KR. Effect of an isolate from Gymnema sylvestre, R. Br. in the control of diabetes mellitus and the associated pathological changes. Anc Sci Life 1988; 7: 183.
24. Srivastava Y, Nigam SK, Bhatt HV, Verma Y, Prem AS. Hypoglycemic and life-prolonging properties of Gymnema sylvestre leaf extract in diabetic rats. Isr J Med Sci 1985; 21: 540.
25. Shanmugasundaram KR, Panneerselvam C, Samudram P, Shanmugasundaram E. The insulinotropic activity of Gymnema sylvestre, R. Br. An Indian medical herb used in controlling diabetes mellitus. Pharmacol Res Commun 1981; 13: 475-86.
26. Shanmugasundaram ERB, Gopinath KL, Shanmugasundaram KR, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. J Ethnopharmacol 1990; 30: 265-79.
27. Persaud SJ, Al-Majed H, Raman A, Jones PM. Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability. J Endocrinol 1999; 163: 207-12.

28. Sheoran S, Panda BP, Admane PS, Panda AK, Wajid S. Ultrasound-assisted extraction of gymnemic acids from Gymnema sylvestre leaves and its effect on insulin-producing RINm-5 F β cell lines. Phytochem Anal 2015; 26: 97-104.
29. Liu B, Asare-Anane H, Al-Romaiyan A et al. Characterisation of the insulinotropic activity of an aqueous extract of Gymnema sylvestre in mouse β-cells and human islets of Langerhans. Cell Physiol Biochem 2009; 23: 125-32.
30. Ahmed ABA, 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: 1033-9.
31. Sujin RM. Anti-diabetic effect of Gymnema sylvestre (asclepiadaceae) powder in the stomach of rats. Ethnobot Leafl 2008; 2008: 153.
32. Imoto T, Miyasaka A, Ishima R, Akasaka K. A novel peptide isolated from the leaves of Gymnema sylvestre—I. Characterization and its suppressive effect on the neural responses to sweet taste stimuli in the rat. Comp Biochem Physiol A Comp Physiol 1991; 100: 309-14.
33. Shigemura N, Nakao K, Yasuo T et al. Gurmarin sensitivity of sweet taste responses is associated with co-expression patterns of T1r2, T1r3, and gustducin. Biochem Biophys Res Commun 2008; 367: 356-63.
34. Miyasaka A, Imoto T. Electrophysiological characterization of the inhibitory effect of a novel peptide gurmarin on the sweet taste response in rats. Brain Res 1995; 676: 63-8.
35. Kamble B, Gupta A, Moothedath I et al. Effects of Gymnema sylvestre extract on the pharmacokinetics and pharmacodynamics of glimepiride in streptozotocin induced diabetic rats. Chem Biol Interact 2016; 245: 30-8.
36. Venkatachalam P, Thiyagarajan M, Sahi SV. Fabrication of bioactive molecules loaded chitosan nanoparticles using Gymnema sylvestre leaf extracts and its antidiabetic potential in experimental rat model. J Bionanosci 2015; 9: 363-72.
37. Yoshikawa K, Kondo Y, Arihara S, Matsuura K. Antisweet natural products. IX. Structures of gymnemic acids XVXVIII from Gymnema sylvestre R. Br. V. Chem Pharm Bull (Tokyo) 1993; 41: 1730-2.
38. Ye WC, Zhang QW, Liu X, Che CT, Zhao SX. Oleanane saponins from Gymnema sylvestre. Phytochemistry 2000; 53: 893-9.
39. Yoshikawa K, Arihara S, Matsuura K, Miyaset T. Dammarane saponins fromGymnema sylvestre. Phytochemistry 1992; 31: 237-41.
40. Murakami N, Murakami T, Kadoya M, Matsuda H, Yamahara J, Yoshikawa M. New hypoglycemic constituents in “gymnemic acid” form gymnema sylvestre. Chem Pharm Bull (Tokyo) 1996; 44: 469-71.
41. Shenoy RS, Prashanth KVH, Manonmani HK. In Vitro Antidiabetic Effects of Isolated Triterpene Glycoside Fraction from Gymnema sylvestre. Evid Based Complement Alternat Med 2018; 2018: 7154702.

42. Bnouham M, Ziyyat A, Mekhfi H, Tahri A, Legssyer A. Medicinal plants with potential antidiabetic activity-A review of ten years of herbal medicine research (1990-2000). Int J Diabetes Metab 2006; 14: 1.
43. Yoshikawa M, Murakami T, Matsuda H. Medicinal foodstuffs. X. Structures of new triterpene glycosides, gymnemosides-c,-d,-e, and-f, from the leaves of Gymnema sylvestre R. Br.: influence of gymnema glycosides on glucose uptake in rat small intestinal fragments. Chem Pharm Bull (Tokyo) 1997; 45: 2034-8.
44. Daisy P, Eliza J, Farook KAMM. A novel dihydroxy gymnemic triacetate isolated from Gymnema sylvestre possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. J Ethnopharmacol 2009; 126: 339-44.
45. 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. J Asian Nat Prod Res 2000; 2: 321-7.
46. Rathore PK, Arathy V, Attimarad VS, Kumar P, Roy S. Insilico analysis of gymnemagenin from Gymnema sylvestre (Retz.) R. Br. with targets related to diabetes. J Theor Biol 2016; 391: 95-101.
47. Omae T, Shimamoto C, Hiraike Y et al. Hyperlipidemia and fat absorption in model rats with type 2 diabetes mellitus. Bull Osaka Med Coll 2006; 52: 45-58.
48. 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. Phytother Res 1994; 8: 118-20. 49. Mall GK, Mishra PK, Prakash V. Antidiabetic and hypolipidemic activity of Gymnema sylvestre in alloxan induced diabetic rats. Global J Biotechnol Biochem 2009; 4: 37-42.
50. Osman M, Fayed SA, Ghada IM, Romeilah RM. Protective effects of chitosan, ascorbic acid and gymnema sylvestre against hypercholesterolemia in male rats. Aust J Basic Appl Sci 2010; 4: 89-98.
51. Shigematsu N, Asano R, Shimosaka M, Okazaki M. Effect of administration with the extract of Gymnema sylvestre R. Br leaves on lipid metabolism in rats. Biol Pharm Bull 2001; 24: 713-7.
52. Steppan CM, Bailey ST, Bhat S et al. The hormone resistin links obesity to diabetes. Nature 2001; 409: 307-12.
53. Rajala MW, Obici S, Scherer PE, Rossetti L. Adipose-derived resistin and gut-derived resistin-like molecule–β selectively impair insulin action on glucose production. J Clin Invest 2003; 111: 225-30.
54. Pravenec M, Kazdová L, Landa V et al. Transgenic and recombinant resistin impair skeletal muscle glucose metabolism in the spontaneously hypertensive rat. J Biol Chem 2003; 278: 45209-15.
55. 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. J Nutr 1999; 129: 1214-22.

56. Shigematsu N, Asano R, Shimosaka M, Okazaki M. Effect of long term-administration with Gymnema sylvestre R. BR on plasma and liver lipid in rats. Biol Pharm Bull 2001; 24: 643-9.
57. Preuss HG, Bagchi D, Bagchi M, Rao CVS, Satyanarayana S, Dey DK. Efficacy of a novel, natural extract of (–)-hydroxycitric acid (HCA-SX) and a combination of HCASX, niacin-bound chromium and Gymnema sylvestre extract in weight management in human volunteers: A pilot study. Nutr Res 2004; 24: 45-58.
58. Kaneto H, Kajimoto Y, Miyagawa J et al. Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity. Diabetes 1999; 48: 2398-406.
59. Moussa SA. Oxidative stress in diabetes mellitus. Romanian J Biophys 2008; 18: 225-36.
60. Rizvi AA. The role of inflammation in diabetes and its complications. South Med J 2006; 99: 8-10.
61. Singh VK, Dwivedi P, Chaudhary BR, Singh R. Immunomodulatory Effect of Gymnema sylvestre (R. Br.) Leaf Extract: An In Vitro Study in Rat Model. PLoS One 2015; 10: e0139631.
62. Kiranmai M, Kazim SM, Ibrahim M. Combined wound healing activity of Gymnema sylvestere and Tagetes erecta Linn. Int J Pharm Appl 2011; 1: 135-40.
63. Khare AK, Tondon RN, Tewari JP. Hypoglycaemic activity of an indigenous drug (Gymnema sylvestre,'Gurmar') in normal and diabetic persons. Indian J Physiol Pharmacol 1983; 27: 257. 64. Joffe DJ, Freed SH. Effect of extended release gymnema sylvestre leaf extract (Beta Fast GXR) alone or in combination with oral hypoglycemics or insulin regimens for type 1 and type 2 diabetes. Diabetes Control Newslett 2001; 76.
65. Baskaran K, Ahamath BK, Shanmugasundaram KR, Shanmugasundaram ERB. Antidiabetic effect of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. J Ethnopharmacol 1990; 30: 295-305.
66. Shanmugasundaram ERB, Rajeswari G, Baskaran K, Kumar BRR, Shanmugasundaram KR, Ahmath BK. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol 1990; 30: 281-94.
67. Paliwal R, Kathori S, Upadhyay B. Effect of Gurmar (Gymnema sylvestre) powder intervention on the blood glucose levels among diabetics. Stud Ethno-Med 2009; 3: 133-5.
68. Mahajan S, Chauhan P, Subramani SK et al. Evaluation of "GSPF kwath": A Gymnema sylvestre-containing polyherbal formulation for the treatment of human type 2 diabetes mellitus. Eur J Integr Med 2015; 7: 303-11.
69. Kurian GA, Manjusha V, Nair SS, Varghese T, Padikkala J. Short-term effect of G-400, polyherbal formulation in the management of hyperglycemia and hyperlipidemia conditions in patients with type 2 diabetes mellitus. Nutrition 2014; 30: 1158-64.
70. Yadav D, Cho K-H. Preventive and therapeutic aspects of selected herbal medicines in diabetes mellitus. Progress in Nutrition 2017; 19: 117-26.