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A systematic review of *Gymnema sylvestre* in obesity and diabetes management

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Abstract

The prevalence of obesity is associated with many health-related problems. Currently, more than 300 million people are considered to be obese. According to the World Health Organization (WHO), by 2030, 87 and 439 million people will be affected in India and the world, respectively. Today, herbal medicines are gaining interest in the treatment of obesity and diabetes, because of their minimal side effects. Gymnemic acid – an active component isolated from *Gymnema sylvestre* – has anti-obesity and antidiabetic properties, decreases body weight and also inhibits glucose absorption. Several components extracted from *Gymnema* prevent the accumulation of triglycerides in muscle and liver, and also decrease fatty acid accumulation in the circulation. In this paper, an attempt has been made to review the effects of various extracts from *Gymnema sylvestre* in the regulation of carbohydrate and lipid metabolism in both animal and clinical studies.

Keywords: *Gymnema sylvestre*; obesity; diabetes; metabolism

INTRODUCTION

Obesity is a worldwide epidemic and it is associated with many health-related problems, such as insulin resistance, type 2 diabetes mellitus (T2DM), ischemic heart disease, retinopathy, neuropathy and even cancer, which can lead to failure of several organs.[1–3] It is associated with the formation of mature adipocytes from preadipocytes with abundant accumulation of lipid droplets resulting increased fat cell size (hypertrophy) and number (hyperplasia).[4] It is also associated with copious levels of triglycerides (TG) in the adipose tissue. Excess accumulation of these triglycerides leads to increase circulatory free fatty acids (FFAs) and their further accumulation in tissue other than adipose tissue (e.g. muscle and liver) as a lipid burden hypothesis.[5] High concentration of fatty acids in adipose tissue leads to secretion of adipokines, and results in lowered vascularization, with development of hypoxia (low amounts of oxygen) and inflammation.[4] Adipokines, which are released from adipocytes, consist of adiponectin, leptin, PPARγ Peroxisome proliferator-activated receptor), resistin and other pro-inflammatory cytokines.[6,7] Currently, more than 1 billion people and 300 million people are considered to be overweight and obese, respectively.[8] Maintaining a proper energy balance, i.e. between intake and expenditure, and change in lifestyle are necessary for treatment of obesity. Weight loss procedures such as liposuction, bariatric surgery and Roux-en-Y gastric bypass were not much effective in preventing the body weight gain in humans. A recent pharmacological treatment for obesity is Orlistat, which inhibits pancreatic lipase and decreases the absorption of dietary fats, which are ultimately excreted in the feces.[3]

Progression of obesity contributes towards insulin resistance, in which the body is unable to respond to insulin to clear glucose from the circulation. Insulin resistance is a hallmark of type 2 diabetes.[9,10] T2DM is associated with increased glucose concentration in the circulation, along with insulin and free fatty acid levels. Moreover, activities of antioxidant enzymes, glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase are decreased in diabetic patients.[11] According to recent estimates, India has a rapidly exploding diabetes epidemic.[12] Unfortunately, India today leads the world with the largest number of diabetics. The World Health Organization (WHO) estimated that 32 million people were affected by this disease in India in 2000, which will increase to 87 million by the year 2030;[13] the prevalence of diabetes in the world is estimated at 439 million people by 2030.[14] Pharmacological drugs such as sulfonylureas, biguanides and thiazolidinediones are available for the treatment of T2DM.[15] The activity of these drugs will be reduced by prolonged usage because T2DM needs a long treatment duration, which emphasizes the importance of the long-term safety of these drugs.[16]

Today herbal medicines have been gaining much popularity for treating the above-mentioned diseases because of their safety and lack of side effects. In India, China and other countries herbal medicines have been used widely for treating various diseases since ancient times.[17] More than 800 traditional plants have been used for the treatment of obesity and diabetes.[18] Among them, a widely used herb such as *Gymnema sylvestre* and their preparations, and their role in treating obesity, diabetes and other metabolic syndromes in animal and human models, have been discussed in this review.

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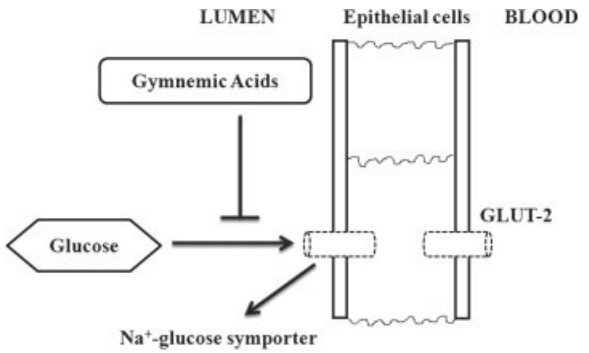

Figure 1. Possible mechanism for inhibition of glucose absorption in the small intestine by gymnemic acids.

GYMNEMA SYLVESTRE

Gymnema sylvestre is a medicinal plant belonging to the Asclepiadaceaea family. It is a slow-growing, perennial, medicinal woody climber found in central and southern India and tropical Africa. In the Ayurvedic system it is referred as 'Meshasringa', and it has potent anti-obesity and anti-diabetic activities. It is also used in homeopathic systems of medicine. *Gymnema* is further used in the treatment of asthma, eye complaints, inflammation, family planning and snakebite. Other uses for *Gymnema* leaf extract are as a laxative, diuretic and cough suppressant. In addition, it possesses antimicrobial, antihypercholesterolemic, hepatoprotective and sweet-suppressing activities.[19] Its leaves contain gymnemic acids: a mixture of at least 17 different saponins, acidic glycosides and anthroquinones.[20] Antidiabetic activity of gymnemic acids has been identified after their successful isolation and purification from the leaves of *G. sylvestre*.[21,22]

Mechanism of action of gymnemic acids

Gymnemic acids from *G. sylvestre* leaves have anti-obesity effects[23] and delay glucose absorption from the intestine into the blood.[24–26] The structure of gymnemic acid molecules is similar to that of glucose molecules. These molecules (gymnemic acid) bind to the receptor which is located on the taste buds of the tongue, thereby preventing their activation by sugar molecules, and suppress the uptake of sugar.[27] Similarly, a peptide called gurmarin isolated from *G. sylvestre* leaf also has the same effect in preventing intake of sugar-containing foods. Possible mechanisms for hypoglycemic effects of gymnemic acids from *G. sylvestre* leaves could be the secretion of more insulin from the pancreas, promoting the regeneration of islet cells, increasing glucose utilization by increasing enzyme activity, which is responsible for glucose utilization by an insulin-dependent pathway.[28] Gymnemic acid molecules can also bind the receptors (Na^+-glucose symporter) present in the intestine, thereby preventing absorption of glucose (Fig. 1). *Gymnema sylvestre* leaves have been found to cause lowering of blood glucose levels in animals and T2DM patients by increasing insulin secretion.[29] Moreover, a number of investigators have shown that cumarins, flavonoids, terpenoids and other secondary plant metabolites such as arginine and glutamic acid also have antidiabetic properties.[30]

HYPOGLYCEMIC AND ANTIHYPERLIPIDEMIC EFFECTS

Gymnema sylvestre was first documented in the late 1920s as a result of its hypoglycemic and hypolipidemic (lowering of blood glucose and lipids levels) activities.[31] Different *G. sylvestre* extracts have been used for treating obesity and diabetes in animal and human studies. Such preparations are well documented in the following sections. The effects of different extracts and their preparations on animal and clinical studies are listed in Tables 1 and 2, respectively. Although many studies utilized whole extracts rather than their individual active principles, a detailed list of active principles in these extracts (Table 2) have to be considered in future studies to explore the molecular roles of their hypoglycemic and hypolipidemic effects.

ANIMAL STUDIES

Effect of aqueous extract

Administration of water extract of *G. sylvestre* (62.5 g kg^{-1} body weight) via the diet to Otsuka Long–Evans Tokushima Fatty rats (OLETF, exhibiting multifactor syndrome including polyphagia, dislipidemia, hyperglycemia and increased body weight) showed reductions in body weight, serum triglycerides and cholesterol levels after a 3-week treatment period. In summary, *G. sylvestre* showed a decrease in intensity of the genetic multifactor syndrome symptoms mostly observed in diabetes.[32] Another study by Reddy *et al.*[3] demonstrated that feeding of aqueous extract of saponins rich in *G. sylvestre* R. Br (SGE, 100 mg kg^{-1}) for 8 weeks reduced body weight gain and organ weight such as liver, kidney and heart, as well as peritoneal and perirenal fat, of high-fat-diet (HFD) induced obese rats. However, a significant reduction in plasma lipids (total cholesterol-TC, triglyceride-TG, VLDL and LDL cholesterol levels) was observed in the case of the SGE-fed group compared to HFD animals. To conclude, anti-obesity properties of SGE included the lowering of organ weight and total plasma lipids and these observations are similar to the effects of Orlistat, which is a potent anti-obesity drug.

Effect of ethanol extract

Gymnema sylvestre R. Br (33 mg kg^{-1} body weight) administration in rats showed decrease in apparent fat digestibility and promoted the excretion of neutral sterol and acidic sterols in feces in both the normal and HFD fed groups. In addition, serum TC and TG levels were decreased, serum HDL-cholesterol and phospholipid levels were not affected, and blood lecithin cholesterol acyltransferase (LCAT) activity was increased by *G. sylvestre* administration. Intrahepatocellular lipid accumulation was also decreased, and no effect on organ weight (liver, mesenteric, epididymal fat and cecum) was observed. Administration of *G. sylvestre* extract showed a hypolipidemic effect and increased cholesterol ester synthesis by LCAT activity for HDL formation.[33]

Liu *et al.*[34] reported the insulinotropic activity of an extract of *G. sylvestre* (OSA: Om Santal Adivasi) in mouse MIN6 β-cells and human islets of Langerhans. Addition of OSA (0.06–2 mg mL^{-1}) to MIN6 β-cells showed a significantly stimulated insulin secretion in the presence of 2 mmol L^{-1} glucose and insulin secretion was further increased by the presence of 20 mmol L^{-1} glucose with incubation of 0.25–0.5 mg mL^{-1} OSA. After exposure of β-cells to trypan blue, more than 90% cells were alive at $\leq$0.25 mg mL^{-1} OSA at an incubation of 2 and 20 mmol L^{-1} glucose. OSA (0.1–0.2 mg mL^{-1}) also stimulated insulin secretion at 2 mmol L^{-1} glucose in the presence or absence of extracellular Ca^{2+} levels. However, both concentrations of OSA (0.03 and 0.06 mg dL^{-1}) are responsible for the increased $[Ca^{2+}]i$ levels in Fura-2-loaded MIN6 β-cells. In another report, OSA (0.125 mg mL^{-1}) also showed an

Table 1. Studies on the effect of *Gymnema sylvestre* preparations in animal and clinical studies

Gymnema sylvestre preparation	Model used	Dose (mg kg^{-1} body weight)[a]	Effect	Reference
Methanolic extract of gymnemic acids IV	Wistar rats and ddY mice	13.4	↓ Blood glucose levels ↑ Plasma insulin ↓ Glucose uptake	39
Hydrous alcohol extract	Wistar rats	33	↓ Apparent fat digestibility ↑ Excreted neutral and acid sterols in feces ↓ Serum TC, TG ↑ LCAT activity	33
GYM 250 extract	Humans	400	↓ Body weight, BMI ↓ Serum leptin levels ↓ Serum LDL, VLDL, TG ↑ Urinary MDA, ACT, FA, ACON	44
Aqueous extract	OLETF and LETO rats	62.5	↓ Body weight ↓ Serum TC, TC	32
Methanol extract	Wistar rats	200	↓ Plasma glucose ↓ Serum TC, VLDL, LDL ↑ Serum HDL	40
Aqueous extract of OSA	Mouse MIN 6 β-cells and Human islets	0.06–2 and 0.25–0.5 mg mL^{-1}	↑ Insulin release	34
Acetone extract of dihydroxy gymnemic triacetate	Wistar rats	20	↓ Plasma glucose, HbA1C ↑ Plasma insulin, muscle and liver glycogen ↓ Serum TC, VLDL, LDL	42
Methanol extract	Wistar rats	200	↑ Body liver and pancreas weights ↓ Plasma glucose ↓ Serum TC, VLDL, LDL ↑ Pancreatic granules of β-cells	41
OSA capsule	Humans and pancreatic islets	500 mg d^{-1}	↓ Fasting blood glucose ↓ Postprandial blood glucose ↑ Serum Insulin, C-peptide	43
Aqueous extract (SGE)	Wistar rats	100	↓ Body weight, organ weights ↓ Plasma TC, TG, VLDL, LDL-C	3
Ethanol extract	Sprague–Dawley rats	100	↓ Blood glucose ↓ Serum TG, LDL, TC ↑ Serum insulin ↓ Malonaldehyde in serum, liver and kidney ↑ Glutathione content ↑ GSH-Px, GST, catalase ↓ SGOP, SGPT	11
OSA capsule	ob/ob mice and ICR mice	500	↓ Blood glucose ↑ Preproinsulin expression and insulin secretion	36
OSA capsule	Mouse and human islets	0.25–1.0 mg mL^{-1}	↑ Insulin secretion ↑ Protein kinase activity ↓ cAMP levels	37
Ethanol extract (GSE)	Wistar rats	200	↓ Body mass index ↓ Serum TC, TG, LDL, VLDL cholesterol ↓ Serum leptin, insulin, glucose, LDH, apo-B ↑ Gpx, GR, GST, SOD, catalase ↓ Perirenal, mesenteric and epididymal fat mass	38

[a] Studies used mg kg^{-1} body weight for dosage unless otherwise indicated.

increase in insulin release from human islets at 2 and 20 mmol L^{-1} glucose levels, in the presence or absence of extracellular Ca^{2+} levels. In summary, *G. sylvestre* extract is responsible for the *in vitro* stimulation of calcium influx into mouse and human pancreatic islets for the release of insulin secretion.

An ethanol extract of *G. sylvestre* (100 mg kg^{-1}) fed for 4 weeks to STZ diabetic rats showed reduction in body weight, slightly increased liver weight and no change in kidney weight. However, administration of *G. sylvestre* extract to diabetic animals for 7 weeks resulted in a decrease in blood glucose levels and serum triglycerides, LDL-cholesterol and total cholesterol, and an increase in serum insulin levels. Oral feeding of ethanolic extract of *G. sylvestre* showed a reduction in lipid peroxidation product (e.g. malonaldehyde) in serum by 31.7%, in liver by 9.9% and

Table 2. Chemical compounds present in different extracts of *Gymnema sylvestre*

Extract	Compounds	Reference
Aqueous	Alkaloids, saponins, proteins, phenols, glycosides, resins, tannins	45
	Alkaloids, phenols, tannins, flavonoids, saponin	46
	Sterols, triterpenoid, tannins	47
	Alkaloids, phytosterols, tannins, phenols	48
	Terpenoids, flavonoids, tannins	49
	Saponins	50
	Alkaloids, phenols, tannins, saponin	51
	Terpenoids, alkaloids, flavonoids, saponins, tannins, quinone	52
	Anthraquinones, tannins, saponins	53
Ethanol	Alkaloids, proteins, phenols, glycosides, resins, tannins	45
	Alkaloids, saponins, glycosides, tannins, flavonoids	54
	Alkaloids, phenols, tannins, flavonoids, saponin	46
	Sterols, triterpenoid, tannins	47
	Alkaloids, phytosterols, tannins, phenols	48
	Alkaloids, phenols, tannins, saponin	51
	Alkaloids, tannins, quinine	52
	Flavonoids, alkaloids, glycosides	53
Methanol	Alkaloids, phenols, tannins, flavonoids, saponin	46
	Flavonoids, phenols, saponins, tannins, triterpenes	55
	Terpenoids, tannins	49
	Anthraquinones, alkaloids, flavonoids, phenols, steroids, tannins, terpenoids	50
	Terpenoids, alkaloids, saponins, quinone	52
Chloroform	Alkaloids, phenols, tannins, flavonoids, saponin	46
	Flavonoids, phenols, triterpenes	55
	Steroids, terpenoids	56
	Tannins	49
	Phenols, steroids, tannins	50
Petroleum ether	Flavonoids, phenols, triterpenes	55
	Terpenoids, saponins	49
	Saponins, tannins and steroids	50

in kidney 9.1% in diabetic rats. Moreover, the extract increased glutathione content by 27.29 µg mL^{-1} and also increased the activity of enzymes such as glutathione peroxidase (GSH-Px) by 78.7%, glutathione-*S*-transferase (GST) by 23.1% and catalase by 55.94% in rat liver. In contrast, decreases in serum glutamate oxaloacetate transaminase (GOP) by 30.9% and glutamate pyruvate transaminase (GPT) by 32.6% were shown in the diabetic group treated with *G. sylvestre*. Diabetes mellitus is associated with increased oxidative damage to the tissues. Administration of *G. sylvestre* extract to diabetic rats exhibited potent antioxidant properties and also increased oxidative enzyme activity.[35]

A recent study by Al-Romaiyan *et al.*[36] demonstrated that oral administration of OSA (500 mg kg^{-1}) isolated from *G. sylvestre* showed a reduction in blood glucose levels at 90 and 120 min in ob/ob mice, while *in vitro* study showed that OSA (0.25 mg mL^{-1}) was responsible for the insulin secretion from isolated mouse islets upon incubation with 2 and 20 mmol L^{-1} glucose. However, preproinsulin (PPI) expression was increased when OSA (0.125 mg mL^{-1}) was incubated with pancreatic islets. Further, an increase in PPI gene expression levels was observed with increased concentration of OSA (0.25 mg mL^{-1}), but these levels were significantly lower compared to 20 mmol L^{-1} glucose. Meanwhile, insulin content of mouse islets was maintained at normal levels in the case of both OSA and 20 mmol L^{-1} glucose. In conclusion, OSA showed insulin secretion from the pancreas to maintain normal blood glucose levels and was also responsible for preproinsulin (PPI) biosynthesis, which ultimately activates insulin synthesis.

Al-Romaiyan *et al.*[37] reported that when a novel component of *G. sylvestre* extract (OSA 0.25 and 1.0 mg mL^{-1}) was incubated with MIN6 β-cell monolayers for 30 min, an increase in insulin secretion was shown in the presence of influx of extracellular calcium ions and 2 mmol L^{-1} glucose. However, removal of extracellular calcium from MIN6 β-cells did not show any effect on insulin secretion with OSA at 1.0 mg mL^{-1}, but insulin secretion was reduced in the presence of voltage-gated calcium channel (VGCC) blocker nifedipine at 10 µmol L^{-1}. In contrast, OSA (0.03 mg mL^{-1}) also elevated intracellular calcium ions in β-cells, with no change in the K_{ATP} conductance. OSA (0.25 mg mL^{-1}) was responsible for the activation of protein kinase (serine–threonine kinase) in mouse and human islets to release insulin in the presence of 2 mmol L^{-1} glucose. Inhibitors for diacyglycerol-sensitive protein kinase C and calcium modulin kinase II (CAMK II) prevented insulin release from mouse and human islets in the presence of OSA. In the presence of 50 nmol L^{-1} calcium, permeabilized MIN6 pseudoislets (using an electric field of 3.4 kV cm^{-1}) were responsible for the insulin secretion at 0.25 mg mL^{-1} OSA. Phosphodiesterase inhibitor (3-isobutyl-1-methylxanthine-IBMX) increased the levels of intracellular cAMP, thereby increasing the release of insulin secretion in mouse and MIN 6 β-cells, but incubation with 0.25 mg mL^{-1} OSA decreased intracellular cAMP levels in both mouse and MIN 6 β-cells. In summary, OSA isolated from *G. sylvestre* was responsible for the secretion of insulin from pancreatic β-cells of both mouse and humans under *in vitro* conditions by means of protein kinase (serine–threonine kinase) activation.

Kumar *et al.*[38] reported that ethanolic extract of *G. sylvestre* (GSE 200 mg kg^{-1}) for 28 days showed a decrease in body mass index (BMI) and hemodynamic parameters such as systolic, diastolic, mean arterial blood pressure and heart rate in HFD rats. However, a significant decrease in serum lipids (TC, TG, LDL-cholesterol and VLDL-cholesterols levels), serum leptin, insulin, glucose, lactate dehydrogenase (LDH) and apolipoprotein-B, and increased apolipoprotein-A1 levels were observed with GSE. After 4 weeks of HFD treatment, Na–K-ATPase levels in heart and liver tissues were decreased, but these levels reverted back to normal. In the GSE-fed group, antioxidant enzymes glutathione (GPx, GR, and GST), SOD and catalase levels in cardiac tissue were significantly increased in HFD rats. After administration of GSE, organ weights of visceral fat pad weights (perirenal fat, mesenteric and epididymal fat) were significantly decreased as compared with those of the HFD group. The above study concluded that *G. sylvestre* extract showed suppression of serum leptin, insulin and visceral fat pad weights, and further protected from myocardial tissue damage in HFD-fed obese rats.

Effect of methanol extract

Crude saponin fractions from the methanol extract of gymnemic acids I, II, III and IV from *G. sylvestre* dried leaves showed a significant decrease in blood glucose levels and an increase in

plasma insulin concentration of diabetic mice, with gymnemic acid IV at 13.4 mg kg^{-1}. In addition, gymnemic acid IV is also responsible for the inhibition of glucose uptake with anti-sweet activity. Among the different gymnemic acids, fraction IV had potent anti-obesity and antidiabetic properties. Hence it can be used as a prodrug for clinical applications.[39]

In another report, *in vivo* leaf and *in vitro* callus derived from *G. sylvestre* were evaluated for anti-diabetic activity by monitoring blood glucose and lipid profile in Wistar rats. Administration of extracts (200 mg kg^{-1} d^{-1}) from leaf and callus resulted in a significant decrease in plasma glucose and blood lipid profiles such as cholesterol, TG, VLDL and LDL level, and increased HDL levels compared to diabetic rats.[40] In conclusion, both leaf and callus extracts showed hypoglycemic and hypolipidemic effects in diabetic rats.

On the other hand, *in vitro* and *in vivo* experiments showed that *G. sylvestre* (200 mg kg^{-1}) leaf extract stimulated β-cell regeneration and reduced whole body, liver and pancreas weight in type 1 diabetic rats. Oral administration of *Gymnema* leaf and callus extracts significantly increased and maintained body, liver and pancreas weight and liver glycogen. Blood sugar and lipid profiles such as cholesterol, TG, HDL, LDL and VLDL were reduced. Electron microscopic analysis showed a significant increase in the secretary granule of β-cells, which showed that gymnemic acid prevented pancreatic damage.[41] In summary, both *in vivo* and *in vitro* leaf and callus extracts of *G. sylvestre* stimulated insulin secretion in type 1 diabetic animals induced by alloxan treatment and restored pancreatic β-cell function.

Effect of acetone extract

Daisy *et al.*[42] studied a novel component of *G. sylvestre* leaves, namely dihydroxy gymnemic triacetate ($C_{24}H_{30}O_9$), which was isolated by acetone extract. It is derived from the basic structure of gymnemic acid. Acetone extract of *Gymnema* showed a significant decrease in plasma glucose levels of STZ diabetic rats, when compared with other crude extracts like hexane and methanol. Oral administration of dihydroxy gymnemic triacetate (20 mg kg^{-1} body weight) was also shown to reduce plasma glucose concentrations by more than 50% and HbA1C by 40%, and increased body weight by 29% compared to diabetic animals. Serum lipids and plasma enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and acyl carrier protein (ACP) were brought back to normal levels in diabetic rats. Plasma insulin (50%), muscle glycogen (77%) and liver glycogen (60%) content were also increased with dihydroxy gymnemic triacetate. These results indicated that the novel component dihydroxy gymnemic triacetate with acetone extract from *G. sylvestre* showed a decrease in plasma glucose, marker enzymes and insulin levels in STZ diabetic rats compared to other crude extracts.

CLINICAL STUDIES

Effect of ethanol extract

In another study, a novel *G. sylvestre* extract was used to stimulate insulin secretion from human islets *in vivo* and *in vitro*. Oral administration of OSA capsules (500 mg d^{-1}) for 60 days showed a significant reduction of fasting blood glucose levels from 162 to 119 mg dL^{-1} and of postprandial blood glucose levels from 291 to 236 mg dL^{-1}, but no effect on body weight. Moreover, treatment with OSA capsules improved glycemic control, with increased circulating levels of serum insulin levels (from 24 to 32 μU mL^{-1}) and serum C-peptide concentration (from 298 to 447 pmol L^{-1}). Perfusion of isolated human islets with 0.125 mg mL^{-1} OSA at a concentration of 2 mmol L^{-1} glucose showed an increase in insulin secretion to 217%, and a further increase in insulin secretion was observed with 20 mmol L^{-1} glucose.[43]

In conclusion, data from the above study demonstrated that OSA isolated from GS leaf extract was effective in reducing blood glucose and increasing serum insulin and C-peptide levels in humans. On the other hand, *in vitro* studies suggested that incubation of OSA with isolated human islets of Langerhans β-cells stimulated insulin secretion.

Preuss *et al.*[44] reported that hydroxycitric acid (HCA) resulted in a decrease in body weight gain, reduced feed intake and *de novo* lipogenesis. Administration of HCA (60% HCA containing 2800 mg d^{-1}) combined with *G. sylvestre* extract (HCA + GSE 400 mg) to patients showed a decrease in body weight of approximately 2.35 and 4.53 kg in the HCA group, and approximately 2.74 and 5.69 kg of body weight reduction in the HCA + GSE group at the end of 4 and 8 weeks, respectively. Moreover, BMI of HCA and HCA + GSE groups showed a 5% and 6.1% reduction at 8 weeks, respectively, compared to the placebo group, having only 2% reduction in BMI. In addition, after 8 weeks' treatment, serum leptin levels decreased to 39.2% (HCA) and 44.3% (HCA + GSE), respectively, compared to the placebo (2.0%) group. Food intake was also decreased in the case of both HCA (15.6%) and HCA + GSE (21.2%) groups after 8 weeks. At the end of the experiment, a significant reduction in lipid profiles, such as LDL levels (13.2% and 19.1%), triglycerides (5.9% and 20.2%), total cholesterol (7.2% and 9.5%) and no change of VLDL levels was observed with HCA and HCA + GSE groups, respectively. Biomarkers of fatty acid oxidation compounds like malondialdehyde (MDA), acetaldehyde (ACT), formaldehyde (FA) and acetone (ACON) were determined in urinary fat metabolites of all groups. After treatment with HCA and HCA + GSE, increases in MDA, ACT, FA & ACON (1.9, 1.8, 2.1 and 1.4-fold, and 2.3, 1.9, 2.0 and 1.6-fold, respectively) compared to placebo group (1.2, 1.1, 1.2 and 1.1-fold) were observed at the end of the experiment. The study showed that HCA and the combination of HCA + GSE administration significantly reduced body weight gain, BMI and blood lipid levels, and increased the biomarker levels of fatty acid oxidation compounds compared to the placebo group.

CONCLUSIONS

Several herbal medicines are available in developing countries for treating obesity, diabetes and other metabolic disorders as alternative therapeutics. Among several herbs, different extracts (aqueous, methanol, ethanol and acetone) of *Gymnema sylvestre* have a role in the treatment of body weight gain, plasma glucose levels and accumulation of lipids in epididymal fat tissue, liver and muscle. The details of these effects for *G. sylvestre* and their supporting animal and clinical studies have been discussed in this review.

FUTURE PROSPECTS

Today, obesity and diabetes are considered major chronic diseases. Current treatments are not effective, because people are regaining their body weight even after successful weight loss, resulting in other metabolic disorders. Herbal ingredients (e.g. *G. sylvestre*) which have been used since ancient times, have a major role in treating the above-mentioned diseases. Active components

like gymnemic acid and dihydroxy gymnemic triacetate, isolated from *G. sylvestre*, have anti-obesity and anti-diabetic effects in animal models. However, little information has been recorded in human clinical studies. In contrast, the active components extracted from *G. sylvestre* have been used for treating several metabolic disorders, although their exact mechanism of action is not yet fully understood at the molecular level. Thus there is a great relevance in studying the mechanism of action of active components in animal and human studies.

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