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A Comprehensive Review on Role of Selected Traditional Herbs in the Treatment of Metabolic Syndrome

Javed Ahamad*

Department of Pharmacognosy, Faculty of Pharmacy, Ishik University, Erbil, Kurdistan Region, IRAQ.

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***Correspondence to:**

Dr. Javed Ahamad

Assistant Professor, Department of Pharmacognosy, Faculty of Pharmacy, Ishik University, Erbil, Kurdistan Region, IRAQ.

Email: jas.hamdard@gmail.com

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Abstract

Medicinal plants have been identified and used traditionally throughout the world from beginning of the human civilization. The term metabolic syndrome is characterized by a combination of obesity, diabetes and cardiovascular complications. In recent years' metabolic syndrome is major cause of deaths worldwide. Traditional herbs and natural products are claimed to be beneficial in controlling metabolic syndrome. Thus, in the present review, we reviewed traditional herbs like *Olea europaea* (Olives), *Momordica charantia* (Bitter-gourd), *Gymnema sylvestre* (Gurmar) and *Enicostema littorale* (Chota-chiretta) and their active components for treatment of metabolic syndrome. Metabolic syndrome represents a cluster of related metabolic abnormalities, including central obesity, hypertension, dyslipidemia, hyperglycemia and insulin resistance, with central obesity and insulin resistance in particular recognized as causative factors. Metabolic syndrome has shown significant impact on the health, quality of life and life expectancy of patients, as well as on the healthcare system. A literature review was conducted using PubMed, Science Direct and Google Scholar to search for *O. europaea* (Olives), *M. charantia* (Bitter-gourd), *G. sylvestre* (Gurmar) and *E. littorale* (Chota-chiretta) and their active components related to metabolic syndrome. Based on the evidence presented within the literature, the aforementioned traditional herbs and their active components could provide specific treatment for metabolic syndrome. Further research is encouraged to determine the efficacy of these traditional herbs in the clinical treatment of obesity, diabetes and cardiovascular complications.

Key words: Metabolic syndrome, *Olea europaea*, *Momordica charantia*, *Gymnema sylvestre* and *Enicostema littorale*.

INTRODUCTION

Metabolic Syndrome is not a distinct disease but a cluster of unfavorable metabolic factors and conditions, the presence of which cumulatively elevate the probability of developing cardiovascular disease and events, associated with decreased life expectancy and expediting mortality. Metabolic syndrome, formerly termed 'Syndrome X', is a disease of energy metabolism and storage.[1] The worldwide prevalence of metabolic syndrome in persons aged 18-30 has been estimated to be 5.2%.[2] Metabolic syndrome has been noted as measure cause of deaths worldwide in recent years.

Pathogenesis of metabolic syndrome is multi-facited and it includes a combination of multiple factors, such as sedentary lifestyle, unhealthy diet choice and genetic factors. Metabolic syndrome is highly prevalent and adversely affects the general population by elevating risk of cardiovascular complications, obesity and diabetes.[3] The pathogenesis of type 2 diabetes is considered a complex mixture of developments within the body and long-term obesity has long been recognized as a major pre-disposing factor to the emergence of a diabetic state.[4-6] Excessive adipose tissue, as seen in obesity, causes inflammation and is strongly linked to the development of type 2 diabetes.[7] Usually, the majority of individuals with type 2 diabetes are overweight[8] and overweight individuals without diabetes are already at a higher risk of developing a poor lipid profile and cardiovascular disease.[9]

Clinical studies reported that up to 19% of type 2 diabetes have hypertension, hyperlipidemia and obesity and 51% of that have some combination of hypertension, hyperlipidemia and obesity with another 5% having coronary artery disease plus hypertension and hyperlipidemia.[10] Alternative medicines and natural products are claimed to be beneficial in controlling diabetes, obesity and cardiovascular complications. Hence, in present review we summarized beneficial pre-clinical and clinical effects of *Olea europaea* (Olives), *Momordica charantia* (Bitter-gourd), *Gymnema sylvestre* (Gurmar) and *Enicostema littorale* (Chota-chiretta) and their active components in treatment of metabolic syndrome and this review helps for future researcher as tools for drug research.

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Traditional Herbs for Treatment of Metabolic Syndrome

Olea europaea (Olives)

Olea europaea Linn. (Oleaceae), commonly known as Olives and Zaytoon in Mediterranean region. Its fruits and oil are essential components of Mediterranean diets. Olive tree is a globally prevalent plant species and has been described as one of the most important cultivated crops.[11] The olive tree is particularly special to mankind due to its recurrent appearances throughout historical and religious texts and its incorporation into traditional herbal medicines.[12] The major phytoconstituents of Olive are belong to phenolics and lipids class. The phenolic compounds of olives classified on based of their chemical characteristics are mainly phenolic acids, phenolic alcohols, flavonoids and secoiridoids.[13] Olives beneficial effects may be attributed due to its phenolic constituents mainly oleuropein and related compounds. Oleuropein (Figure 1) is a secoiridoid type of phenolic compound abundantly present in Olive and it consists of three structural subunits: hydroxytyrosol, elenolic acid and a glucose molecule and it is reported as chemo-taxonomic marker of Olive.[14,15]

Role of *O. europaea* and Oleuropein in Metabolic Syndrome Treatment

Recent preclinical and clinical studies described the beneficial effects of olives and oleuropein on various human ailments including metabolic syndrome. Bodyweight and abdominal adipose tissue gain have been prevented by Oleuropein in animal models.[16-19] This occurs potentially by Oleuropein repressing mitochondrial activity during adipogenic differentiation and expression of the genes involved in adipogenesis. Santiago-Mora *et al.*[20] found that Oleuropein inhibited Proliferator-activated receptor gamma 2 (PPARγ2), the lipoprotein lipase (LPL) and the fatty acid-binding protein 4 (FABP-4) gene. PPAR-γ has been linked to adipocyte macrophage differentiation into their anti-inflammatory M2 form[21] which has been linked to metabolic health and better insulin sensitivity.[22,23] In a study by Drira *et al.*[24] on 3T3-L1 adipocytes, it was found that Oleuropein inhibits differentiation. Inhibition of transcription factors PPAR-γ, C/EBPα, SREBP-1c occurred after the addition of Oleuropein. In another study, presence of PPARγ, SREBP-1c and FAS as a result of a high cholesterol diet were significantly lower in Oleuropein fed mice. This sane study also found that Oleuropein increased AMPK phosphorylation in epididymal adipose tissue.[18]

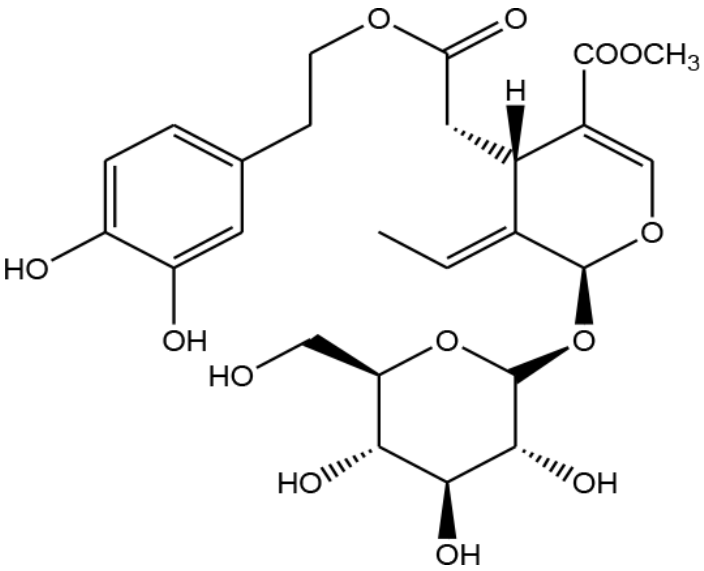


Figure 1: Chemical structure of Oleuropein.

Olive leaves infusion and/or decoctions have traditionally been used to treat diabetes.[25] In nicotinamide and streptozotocin induced co-diabetic hypertensive rats, daily dose of Oleuropein showed a significantly lower glucose levels in a glucose tolerance test,[26] reduced fasting blood glucose levels.[27] Oleuropein administered alone improved glucose tolerance[26,17] and reduced insulin resistance[28] or insulin sensitivity.[16] Oleuropein has been implicated to improve postprandial glycaemic profile via hampering Nox2-derived oxidative stress.[29] In a study by Hadrich *et al.*[30] found that Oleuropein and insulin co-administered led to an increase of phosphorylation of Akt and IRS which increased GLUT4 presence on C2C12 myoblasts. Oleuropein also reduced fasting blood glucose in high fat diet mice.[31] Hydroxytyrosol and oleuropein shows α-glucosidase and α-amylase enzyme inhibitory activities.[32]

High levels of LDL, TC and low HDL are associated with increased cardiovascular risk and development of atherosclerotic cardiovascular diseases and all-cause mortality.[33] Oleuropein has been shown to reduce serum LDL, TC and serum triglycerides whilst also increasing serum HDL.[18,34] In wild-type mice, Oleuropein caused reduction in serum TG and TC but when given to PPAR-α null mice, no effect was observed. This was shown to be due to activation and upregulation of PPAR-α mRNA with an increase in multiple PPAR-α target genes. Furthermore, an *in-silico* study showed that Oleuropein was a PPAR-α ligand which was corroborated with evidence of increased PPAR-α and RXR homodimerization. This same study also found that Oleuropein upregulated the LDL-R receptor in the Liver and increased the expression of other genes involved in synthesis, up-take, transport, metabolism and elimination of TGs.[35] This evidence suggests Oleuropein may have a similar mechanism of action for the commonly known class of lipid-lowering drugs, Fibrates, though potentially without the risk of associated adverse effects. It could be assumed that Oleuropein would have a beneficial or protective effect by improving the lipid profile, preserving β-cell function and reducing the risk of adverse events, progression of T2D, its complications and mortality related to it. A potent antioxidant effect has been observed with Olive oil and Olive oil extract.[36] Oleuropein reduced Thiobarbituric Acid reactive substances in tissues of the Heart, Liver, Kidneys, Aorta and increased Liver superoxide dismutase and catalase activity in mice.[37] In a study investigating Oleuropein's cardioprotective antioxidant effects, it was found that Oleuropein was such an effective antioxidant that it reduced oxidative stress related cardiac reperfusion injuries in isolated rat hearts. This was characterized by a significant reduction in Glutathione, Oxidized Glutathione and TBARS.[38]

Momordica charantia (Bitter gourd)

Momordica charantia Linn. (Cucurbitaceae) is used in many Asian countries as a traditional functional food and medicine, especially for the treatment of diabetes mellitus. Cucurbitane-typetriterpenoids are the main active constituents of *M. charantia* and have a number of potential biological and pharmacological activities including antidiabetic, anti-obesity, anticancer and anti-HIV activities.[39]

Role of *M. charantia* and Charantin in Metabolic Syndrome Treatment

Lotlikar and Rajarama,[40] reported that charantin (Figure 2) produces gradual but significant fall in blood sugar level in normal rabbits. He also found that the effects of charantin were more erratic. In alloxan diabetic rabbits. Khanna *et al.*[41] isolated Polypeptide-*p* from the fruits and seeds of bitter gourd and it shows potent hypoglycaemic effect when administered subcutaneously

to gerbils and humans. *M. charantia* aqueous extract from unripe fruits stimulate insulin release from isolated β-cell of obese-hyperglycaemic mice.[42] Handa *et al.*[43] reported that vicine from the seeds of *M. charantia* shows hypoglycaemic response in normal fasting albino rats.

The fruit juice of *M. charantia* significantly increased the number of β-cells in treated animals when compared with untreated diabetic rats.[44] Anun *et al.*[45] reported that protein extract from *M. charantia* significantly increased insulin secretion and increased glucose uptake in adipocytes. Acetone extract of whole fruit powder of *M. charantia* lowered the blood in alloxan-induced diabetic albino rats. Histological observations with acetone extract showed different phases of recovery of β-cells of the islets of Langerhans of pancreas.[46] Cucurbitane-type triterpene glycosides, charantosides A-C and momordicoside A has been isolated from a methanolic extracts of *M. charantia* fruits and these above compounds showed moderate inhibitory activity against α-glucosidase enzyme.[47]

Oral administration of acetone extract of *M. charantia* fruit powder causes reduction in the blood sugar and serum cholesterol levels in alloxan-induced diabetic rats.[48] Biter gourd capsules (2000 mg/day), causes significant improvement in fasting blood glucose as well as 2-hr postprandial blood glucose.[49]

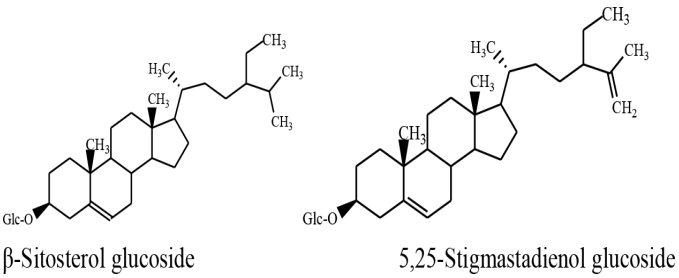
Perumal *et al.*[50] evaluated changes in urinary metabolite profile of the STZ-induced type 1 diabetes rats using *M. charantia* extract (100 and 200 mg/kg b. wt.). The results indicated that *M. charantia* was effective in lowering blood glucose level and also regulate the altered metabolic processes. Xu *et al.*[51] isolated a water-soluble polysaccharide (MCP) from the fruits of *M. charantia* and the hypoglycemic effects of MCP was evaluated in alloxan-induced diabetic mice at 100, 200 and 300 mg/kg body weight for 28 day. Results showed that fasting blood glucose level (BGL) was significantly decreased, whereas the glucose tolerance was marked improvement in alloxan-induced diabetic mice.

Enicostemma littorale (Chota-chiretta)

Enicostemma littorale (Gentianaceae) locally known as *Chota-chiretta* in India, is a commonly used Ayurvedic medicine for treatment of diabetes. Swertiamarin (Figure 3) is a secoiridoid glycoside derived from loganic acid through mevalonic acid pathway.[52] It is distributed predominantly among the members of Gentianaceae, mainly *E. littorale* and *Swertia chirata* Roxb. Some specific activities have been reported for swertiamarin such as anticholinergic, antihyperlipidemic, insulinotropic, antinociceptive, antioxidant and hepatoprotective.[53]

Role of *E. littorale* and Swertiamarin in Metabolic Syndrome Treatment

Ahamad *et al.*[54] reported that swertiamarin isolated from aerial parts of *E. littorale* shows glucose homeostasis via inhibition of carbohydrate metabolizing enzymes in *in-vitro* and *in-vivo* studies. Swertiamarin shows dose dependent inhibition of α-amylase and α-glucosidase (IC_{50} 1.29±0.25 mg/mL and 0.84±0.11 mg/mL) respectively. Erythrocentaurin isolated from the ethyl acetate fraction of *E. littorale,* exhibited a concentration-dependent α-amylase inhibition (IC_{50} 1.67 ± 0.28 mg/mL).[55] Dhanavathy,[56] reported that swertiamarin significantly causes reduction in fasting blood glucose, glycated hemoglobin (HbA1c), total cholesterol, triglycerides, LDL and increased the plasma insulin, HDL levels and body weight as compared to STZ-induced diabetic rats. Phoboo *et al.*[57] reported that swertiamarin showed moderate-to-high positive correlation between antioxidant activity and total phenolic content and



β-Sitosterol glucoside 5,25-Stigmastadienol glucoside

Figure 2: Chemical structure of Charantin (β-Sitosterol glucoside and 5,25-Stigmastadienol glucoside).

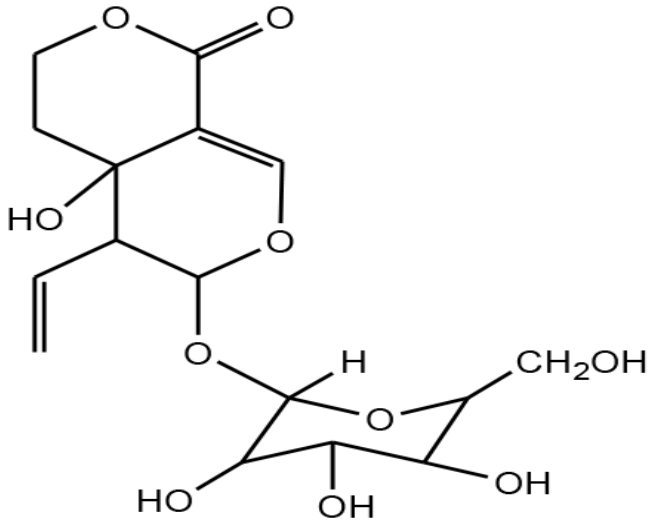


Figure 3: Chemical structure of Swertiamarin.

moderate-to-high α-glucosidase inhibitory activity. Swertiamarin has shown to modulate 5-HT_2 receptor and hypolipidemic potential in animal models of depression, diabetes and obesity.[58] Vaidya *et al.*[59] reported in *in-silico* studies performed that swertiamarin possess antidiabetic activity through inhibiting glycogen phosphorylase-a at pyridoxal phosphate binding site with its docking energy of -7.01 kcal/mol. Maroo *et al.*[60] reported dose dependent blood glucose lowering effect of the aqueous extract of *E. littorale* in alloxan induced diabetic rats.

Upadhyay and Goyal,[61] demonstrated the efficacy of *E. littorale* twice a day for 3 months in preventing various complications arising in type 2 diabetic patient (*n*=84). At the end of the treatment, blood glucose and serum insulin levels of type 2 diabetic patients were significantly reduced. This study also significantly reduced urine sugar, systolic blood pressure as well as pulse rate. In addition, treatment significantly reduced serum creatinine, cholesterol and triglyceride levels along with a significant increase in serum HDL levels. Aqueous extract of *E. littorale* showed a significant decline in fasting blood sugar, postprandial blood sugar, serum cholesterol, triglyceride, LDL, VLDL levels and significant increase in HDL levels in clinical study.[62] Swertiamarin has been reported to have high anti-atherogenic, cholesterol lowering potential and inhibition of HMG-Co-A reductase.[63] Swertiamarin causes reduction in serum cholesterol levels and the oxidation of LDL. In addition, swertiamarin has also shown to have the ability in increasing the HDL levels and reduction in the ratio of LDL/HDL cholesterol.[64] Swertiamarin at 50 mg/kg, *i.p.* dose level once a day for 6 weeks resulted in significant reductions in serum triglycerides, cholesterol

and low-density lipoprotein levels in diabetic animals. Serum fasting glucose was significantly decreased.[65] The aqueous extract of *E. littorale* showed cardioprotective and antihypertensive effect in fructose-fed rats. High fructose fed rats treated with *E. littorale* showed improved insulin resistance, along with reduced hypertriglyceridemia, hypertension, platelet agreeability, blood coagulation, serum enzymes (CK-MB, SGOT, LDH and SGPT) and vascular reactivity.[66] In an *in-vitro* study, swertiamarin showed antioxidant activity by scavenging hydroxy radicals, H_2O_2 superoxide radicals and inhibiting lipid peroxidation and nitric oxide radical.[67]

Gymnema sylvestre (Gurmar)

Gymnema sylvestre R.Br. (Asclepiadaceae) is a herb native to the tropical forests of southern and central India and Sri Lanka. Chewing the leaves suppresses the sensation of sweet taste. It has been used as traditional medicine for the treatment of diabetes. The major bioactive constituents of *G. sylvestre* are a group of oleanane type triterpenoid saponins known as gymnemic acids. The chemical structures of phytoconstituents isolated from *G. sylvestre* are presented in Figure 4. Triterpenoid saponins of gymnemic acid A, B, C and D with sugar residues such as glucuronic acid, galacturonic acid, ferulic and angelic acids attached through carboxylic acids.[68]

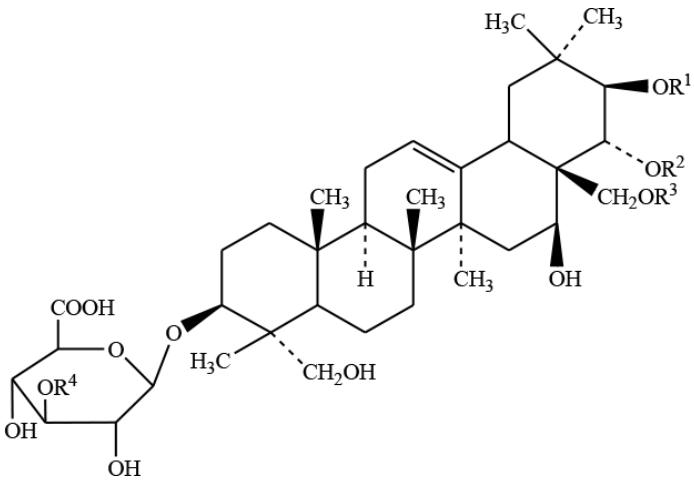


Figure 4: Chemical structures of different types of Gymnemic acids.

Gymnemic acids	R^1	R^2	R^3	R^4
I	-tga	-H	-Ac	-H
II	-mba	-H	-Ac	-H
III	-mba	-H	-H	-H
IV	-tga	-H	-H	-H
V	-tga	-tga	-H	-H
VIII	-mba	-H	-H	-OG
IX	-tga	-H	-H	-OG
X	-H	-H	-Ac	-H
XI	-tga	-H	-tga	-H
XII	-tga	-H	-Ac	-glu
XIII	-H	-H	-mba	-H
XIV	-H	-H	-tga	-H

(where: -Ac = acetyl; -Glu = glucose; -OG = β-arabino-2-hexulopyranosyl, tga = tigloyl, mba = 2-methyl butyroyl).

Role of *G. sylvestre* and Gymnemic acids in Metabolic Syndrome Treatment

The ethanolic extract of *G. sylvestre* causes reduction in blood sugar in normal rats as well as in anterior pituitary extract induced hyperglycaemic rats.[69] Fushiki *et al.*[70] reported that Gurmar extracts and purified gymnemic acid shows inhibitory effects on Gastric Inhibitory Peptide release in rats. The alcoholic extract of *G. sylvestre* stimulated insulin release from HIT-T15, MIN6 and RINm5F β-cells and from islets in the absence of any other stimulus.[71] Sugihara *et al.*[72] reported the antihyperglycemic action of a crude saponin fraction and triterpenic glycosides (gymnemic acids I-IV and gymnemasaponin V) derived from the methanolic extract from the leaves of *G. sylvestre* in STZ-induced diabetic mice. The saponin fraction causes reduction in blood glucose levels. In this study, gymnemic acid IV also significantly causes reduction in the blood glucose level. Kang *et al.*[73] reported hypoglycemic activity of *G. sylvestre* extracts on oxidative stress and antioxidant status in diabetic rats. The *G. sylvestre* extracts exhibited strong antioxidant activity in the assays, including TBA (56%), SOD-like (92%) and ABTS (54%). Alkefai *et al.*[74] isolated arylated gymnemic acids and evaluated *in-vitro* α-glucosidase inhibition. The isolated compounds show dose dependent inhibition of α-glucosidase enzyme.

CONCLUSION

This review article summarised (Table 1) beneficial effects of *O. europaea*, *M. charantia*, *G. sylvestre* and *E. littorale* and their active components in metabolic syndrome including high blood pressure, high fat, high blood glucose and overweight. The results of most relevant preclinical and clinical studies showed the potential use of these traditional herbs in metabolic syndrome. This study discovered the clinical uses of *O. europaea*, *M. charantia*, *G. sylvestre* and *E. littorale* and their bioactive components can be beneficial for the treatment of metabolic syndrome. This study will help the researchers to uncover the critical areas of metabolic syndrome treatment by using traditional herbs that many researchers were not able to explore. Thus, the present work help researcher's in better treatment of metabolic syndrome by using these traditional herbs and their bioactive phytoconstituents.

Table 1: Role of Traditional Herbs in Treatment of Metabolic Syndrome.

Herbs and bioactive components	Results/ MOA	Reference
Olive and oleuropein	Inhibits PPARγ2, LPL) and FABP-4 gene	[20]
	Inhibits 3T3-L1 adipocytes and also PPAR-γ, C/EBPα, SREBP-1c	[24]
	↓ Leptin concentration	[19]
	↓ insulin resistance	[28]
	↓ fasting blood glucose levels	[27, 31]
	Improved glucose tolerance	[26]
	Promotes translocation of GLUT4 into the cell membrane via AMPK activation	[30, 31]
	↓ in serum TG and TC due to activation and upregulation of PPAR-α	[35]
	Scavenge ABTS radicals	[37]
	Inhibits induction of ICAM-1 and formation of plaque	[28]
***M. charantia*, charantin and peptides**	↑ insulin secretagogue and insulinomimetic activities.	[45]
	Inhibits α-glucosidase enzyme	[75]
	↓ insulin resistance	[76,77]
***E. littorale* and swertiamarin**	Shows insulinotropic action	[78]
	↑ hexokinase activity	[79]
	Shows antihyperlipidemic activity	[63]
G. *sylvestre* and gymnemic acids	↑ serum insulin levels provided by repair/ regeneration of the endocrine pancreas.	[80]
	↑ insulin release	[71]
	Inhibits glucose absorption	[81]
	Inhibits α-glucosidase enzyme	[74]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AMPK: 5' adenosine monophosphate-activated protein kinase; **FABP-4:** Fatty acid-binding protein 4; **HDL:** High-density lipoprotein; **IRS:** Insulin receptor substrate; **LPL:** Lipoprotein lipase; **LDL:** Low-density lipoprotein; **PPAR-α:** Peroxisome proliferator-activated receptor-alpha; **SREBP-1c:** Sterol regulatory element-binding transcription factor 1-c; **SGOT:** Serum glutamic-oxaloacetic transaminase; **SGPT:** Serum glutamic pyruvic transaminase; **T2D:** Type 2 diabetes; **TBARS:** Thiobarbituric acid reactive substances; **TC:** Total cholesterol; **VLDL:** Very low density lipoprotein.

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