



Indigenous plant medicines for health care: treatment of Diabetes mellitus and hyperlipidemia

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[ABSTRACT] Medicinal plants have played an important role in treating and preventing a variety of diseases throughout the world. Metabolic syndrome had become a global epidemic, defined as a cluster of three of five criteria: insulin resistance and glucose intolerance, abdominal obesity, hypertension, low high-density cholesterol, and hypertriglyceridemia. The current review focuses on Indian medicinal plant drugs and plants used in the treatment of diabetes and hyperlipidemia. Though there are various approaches to reduce the ill-effects of diabetes and hyperlipidemia and its secondary complications, plant-based drugs are preferred due to lesser side effects and low cost. The current review focuses on twenty-three medicinal plants used in the treatment of Diabetes mellitus and nine medicinal plants used in the treatment of hyperlipidemia. The wealth of knowledge on medicinal plants points to a great potential for research and the discovery of new drugs to fight diseases, including diabetes and hyperlipidemia.

[KEY WORDS] Diabetes mellitus; Hyperlipidemia; Medicinal plants; Treatment

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Introduction

In the last few decades eco-friendly, bio-friendly, cost-effective and relatively safe, plant-based medicines have moved from the fringe to the mainstream with the increased research in the field of traditional medicine^[1].

Plant-based medicine which uses medicinal plants as the first medicines is a universal phenomenon. Every culture on Earth, through written or oral tradition, has relied on the vast variety of healing plants for their therapeutic properties. The majority of medicinal plant products available today originated from the same traditional formulas or ingredients^[2]. The benefit of plant-based cures is that they are cheap and easily obtainable. They can get them directly from nature. Plant-based medicines are preferable as mainly non-toxic, having typically fewer side effects, better compatibility with physiological flora, and availability at affordable prices. The limitations of plant-based medicines are usually involved with

the treatment of more serious ailments like broken limbs. These situations require constant medical supervision and usage of more advanced medications and many patients are allergic to some plant-based medicines, making things worse once they take them in any form. Treatments are longer when a natural method is chosen^[1,3]. The World Health Organization (WHO) estimates that 4 billion people, 80% of the world's population, presently use plant-based medicine for some aspect of their primary health care^[2].

WHO has listed 21 000 plants, which are used for medicinal purposes around the world. Among these 2 500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world^[4]. The current review focuses on medicinal plants used in the treatment of Diabetes mellitus and hyperlipidemia, major crippling diseases in the world leading to huge economic losses.

Diabetes and Significance

Diabetes is a chronic disorder of carbohydrate, fat, and protein metabolism characterized by increased fasting and post-prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur

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in the developing countries. Studies conducted in India in the last decade have highlighted that the prevalence of diabetes is high, and that it is increasing rapidly in the urban population [5].

It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely to increase to 57.2 million by the year 2025. In traditional medicine, diabetes mellitus is treated with diet, physical exercise, and medicinal plants. More than 1200 plants are used around the world in the control of Diabetes mellitus, and approximately 30% of the traditionally-used antidiabetic plants were pharmacologically and chemically investigated [6].

Diabetes mellitus is a chronic metabolic disorder of multiple etiologies, and is mainly diagnosed by a blood glucose rise subsequent to insulin deficiency. Type I, insulin-dependent diabetes mellitus, is characterized when the body is totally short of the production of insulin. Diabetes patients of type I take daily doses of insulin. Type II, non-insulin-dependent Diabetes mellitus, is defined by failing to produce enough quantity, or appropriately use, insulin. This type constitutes the epidemic form of the disease [7].

Hyperglycemia can increase the oxidative stress by several mechanisms, including glucose auto-oxidation, non-enzymatic protein glycation, and activation of the polyol pathway. The rise in free radical activity is suggested to play an important role in lipid peroxidation and protein oxidation of cellular structures resulting in cell injury, and is implicated in the pathogenesis of vascular disease which are the main cause of morbidity and mortality in both type I and type II diabetes [8].

Mechanism of action of anti-diabetic agents

The aim of the treatment of diabetes is to reduce the blood glucose level. Anti-diabetic drugs can act in different ways, such as stimulation of beta-cell of pancreatic islet to release insulin, to resist the hormones which increase blood glucose, increase the number and sensitivity of insulin receptors, increase the glycogen content, enhance the use of organ glucose in the tissue, free radical scavenging, resist lipid peroxidation, correct the metabolic disorder of lipid and protein, and promote microcirculation in the body [7].

Free radicals are capable of damaging cellular molecules, DNA, proteins, and lipids leading to altered cellular functions. Many recent studies reveal that antioxidants capable of neutralizing free radicals are effective in preventing experimentally-induced diabetes in animal models, as well as reducing the severity of diabetic complications. For the development of diabetic complications, the abnormalities produced in lipids and proteins are the major etiologic factors. In diabetic patients, extra-cellular and long-lived proteins, such as elastin, laminin, and collagen are the major targets of free radicals. Due to the high level of sugar in the body, these proteins are modified and converted to glycoproteins. Modifications of proteins present in lens, vascular wall, and basement membranes are associated with the development of diabetes complications, such as cataracts, microangiopathy, atherosclerosis, and nephropathy. In Diabetes mellitus there are also multiple abnormalities in very low density lipoprotein (VLDL), low

density lipoprotein (LDL), and high density lipoprotein (HDL). Lipid peroxidation and AGEs are formed by the non-enzymatic glycosylation of proteins. AGEs tend to accumulate in tissues and cause abnormalities in cell and tissue functions. In addition, AGEs also bind to specific macrophage receptors and change vascular permeability. In nucleic acids and histones, AGEs cause mutations and alter gene expression [4].

There are various types of phytoconstituent present in plants belonging to different classes. Phytoconstituents like alkaloids may inhibit alpha-glucosidase and decrease glucose transport through the intestinal epithelium. Imidazoline alkaloids stimulate insulin secretion in a glucose-dependent manner. Polysaccharides increase the level of serum insulin, reduce the blood glucose level, and enhance tolerance to glucose. Flavonoids acts as antidiabetic agents by suppressing the glucose level, by reducing plasma cholesterol and triglycerides significantly, and by enhancing hepatic glucokinase activity, probably by enhancing the insulin release from pancreatic islets. Dietary fibers effectively adsorb glucose, retard glucose diffusion, and inhibit the activity of alpha-amylase, and may also be responsible for decreasing the rate of glucose absorption and concentration of postprandial serum glucose. Saponins stimulate the release of insulin and block the formation of glucose in the bloodstream, and ferulic acid stimulates insulin secretion [9].

Medicinal Plants as a Source of Anti Diabetics

Abelmoschus esculentus

Abelmoschus esculentus L. is a plant of the mallow family (Malvaceae). It is naturalized in all tropical countries and grows abundantly throughout India. The aqueous extract of fruits of *A. esculentus*, at a dose level of 300 mg/kg showed significant activity ($P < 0.001$) in adult albino Wistar rats. Fresh juice extract is mixed with a powder of *Pongamia pinnata* and is given to patients twice a day [10].

Abelmoschus moschatus

Abelmoschus moschatus (Malvaceae) is an aromatic medicinal plant, which is native to India. Myricetin [11] (Fig. 1), an active principle of *A. moschatus* improves insulin sensitivity through increased post-receptor insulin signaling mediated by enhancements in IRS-1-associated PI3-kinase and GLUT 4 activity in the muscles of obese Zucker rats. Myricetin might be used as a model substance for the development of antidiabetic compounds [12].

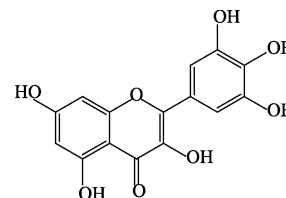


Fig. 1 Structure of myricetin

Aegle marmelos

Aegle marmelos (L.) Corrêa, (Rutaceae) is a popular me-

dicinal plant in the Ayurvedic and Siddha systems of medicine and in folk medicines used to treat a wide variety of ailments. The aqueous extract of *A. marmelos* seeds was administered orally at different doses (100, 250, and 500 mg·kg⁻¹) to normal, as well as sub (fasting blood glucose (FBG) normal; glucose tolerance abnormal) and mild (FBG 120–250 mg·dL⁻¹) diabetic rats. The dose of 250 mg·kg⁻¹ was found to be the most effective dose, and it decreases the blood glucose level (BGL) by 35.1% in normal healthy rats after 6 h of administration. The same dose also showed a marked reduction in BGL of 41.2% in sub and 33.2% in mild diabetic rats in a glucose tolerance test (GTT) after 2 h. Treatment of severely (FBG >250 mg·dL⁻¹) diabetic rats for 14 days with a dose of 250 mg·kg⁻¹ reduces the fasting blood glucose by 60.84% and urine sugar by 75% compared with their pretreatment levels. It also brought about a fall in total cholesterol (TC) level by 25.49%, with an increase of 33.43% in high density lipoprotein (HDL) and a decrease of 53.97% and 45.77% in low density lipoprotein (LDL) and triglycerides (TG), respectively [13]. Administration of an aqueous extract of the leaves improves digestion and reduces blood sugar, urea, and serum cholesterol in alloxanized rats as compared to control. Along with exhibiting hypoglycemic activity, this extract also prevented a peak rise in blood sugar at 1 h in an oral glucose tolerance test [14].

Alangium lamarckii

Alangium lamarckii Thwaites (Alangiaceae) is found commonly in the tropical forests of South India, and is occasionally grown in gardens. An alcoholic extract of the leaves of *A. lamarckii* was given to streptozotocin-nicotinamide-induced type-2 diabetic rats. *A. lamarckii* at two dosages, 250 and 500 mg·kg⁻¹, p.o. did not show any significant change in blood glucose level of normoglycemic rats ($P > 0.05$), whereas, an oral glucose tolerance test depicted a reduction in blood glucose level ($P < 0.05$). The streptozotocin-nicotinamide induced diabetic rats, significantly decreased the blood plasma glucose level ($P < 0.001$) comparable to glibenclamide (10 mg·mL⁻¹), restored the lipid profile, and showed improvement in liver glycogen [15].

Annona squamosa

Annona squamosa L. (Annonaceae), commonly known as custard apple, is cultivated throughout India, mainly for its edible fruit. Oral administration of *A. squamosa* (300 mg·dL⁻¹) aqueous leaf extract to diabetic rats for 30 days significantly reduced blood glucose, urea, uric acid, and creatinine levels, and increased the activities of insulin, C-peptide, albumin, albumin/globulin ratio, and restored all marker enzymes to near control levels [16].

Caesalpinia bonducella

Caesalpinia bonducella (L.) Fleming (Fabaceae) is widely distributed throughout the coastal region of India, and is used ethnomedically by the tribal people of India for controlling blood sugar. Both the aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic type II dia-

betic models. These extracts also increased glycogenesis thereby increasing liver glycogen content [17]. Two fractions BM 169 and BM 170 B could increase the secretion of insulin from isolated islets. The aqueous and 50% ethanolic extracts of *C. bonducella* seeds showed antihyperglycemic and hypolipidemic activities in streptozotocin (STZ)-diabetic rats [18].

Capparis decidua

Capparis decidua (Forssk.) Edgew. (Capparaceae) is found throughout India, especially in dry areas. Hypoglycemic effects were seen in alloxanized rats when the rats were fed with 30% extracts of *C. decidua* fruit powder for 3 weeks. This extract also reduced alloxan-induced lipid peroxidation significantly in erythrocytes, kidney, and heart. *C. decidua* was also found to alter superoxide dismutase and catalase enzyme levels to reduce oxidative stress [19].

Cassia sophera

Cassia sophera L. (Fabaceae), known as "Kasondi", is an important drug used in Unani medicine. Petroleum ether, chloroform, ethyl acetate, and methanolic extracts of *C. sophera* leaves were prepared, and each extract was given by the oral route at a dose of 200 mg·kg⁻¹ body weight for 14 days in alloxan-induced diabetic rats. The blood glucose levels were measured at 0, 2, and 4 h, and on the 7th and 14th day after treatment. The petroleum ether extract did not reduce the blood glucose level, however the chloroform, ethyl acetate, and methanol extracts significantly reduced ($P < 0.01$) the blood glucose level in the diabetic rats. Decreased levels of blood glucose and increased level of plasma insulin were observed, which indicates that the extracts of *C. sophera* stimulate insulin secretion from the remnant β cells or regenerated β cells [20].

Centratherum anthelminticum

Seeds of *Centratherum anthelminticum* (L.) Gamble (Asteraceae) have been used popularly in Ayurvedic medicine to treat diabetes and skin disorders. Folk medicine from Rayalaseema (Andhra Pradesh, India) reported widespread usage against diabetes. Hypoglycemic properties and the mechanism of the methanolic fraction of *C. anthelminticum* seeds (CAMFs) were investigated on the mouse β -TC6 pancreatic cell line and streptozotocin (STZ)-induced diabetic rat models. Oral administration of 100 and 50 mg·kg⁻¹ of CAMFs and 50 mg·kg⁻¹ of glibenclamide produced a significant reduction in blood glucose levels at weeks 1–4 when compared with untreated diabetic rats. In the final week of the study period, 100 mg·kg⁻¹ of CAMFs produced the maximal decrease of blood glucose level (51.40%) as compared to untreated diabetic rats, and 50 mg·kg⁻¹ of CAMFs caused a 46.47% decline, whereas the glibenclamide group achieved a 50% drop in blood glucose levels [21].

Chaenomeles sinensis

Chaenomeles sinensis (Thouin) Koehne (Rosaceae) fruits are reported to be rich in dietary fiber, organic acids, and bioactive triterpenes, such as oleanolic acid and ursolic acid. They also contain high levels of bioactive phenolic acids and

vitamins. Flavonoids are also reported to be one of the main phytochemical constituents present in *Chaenomeles* fruits, which have been proven effective in preventing free radical-caused oxidative damage. The antihyperglycemic, antihyperlipidemic, and antioxidant properties of *C. sinensis* fruit extract (CSFE) were investigated in streptozotocin (STZ)-induced (55 mg·kg⁻¹ body weight) diabetic rats. The results showed that CSFE significantly inhibited the progression of diabetes induced by STZ, and the inhibitory effect of CSFE on diabetes might be associated with its hypoglycemic effect, modulation of lipid metabolism, and its ability to scavenge free radicals [22].

The ethyl acetate fraction of *C. sinensis* was examined for effects of the supplementation of the α -glucosidase, α -amylase, and lipase inhibitory ethyl acetate (CSE) fraction from the fruits of *C. sinensis* on blood glucose (BG), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), acetylcholinesterase (AChE), and antioxidant levels. The diabetic rats were treated orally with CSE at the doses of 50 and 100 mg·kg⁻¹ bw for 14 days. BG, TC, TG, HDL-C, ALT, AST, and AChE levels were significantly reduced; whereas antioxidant levels were significantly increased in the treated groups. These observations suggest the protective effects of CSE against STZ-induced diabetic dementia model [23].

Dillenia indica

Dillenia indica L. belongs to the family Dilleniaceae, and is commonly called dillania. A methanolic extract of the leaves of *D. indica* was administered orally in alloxan-induced diabetic rats at a dose 250 and 500 mg·kg⁻¹. It showed a beneficial effect on blood glucose levels, as well as improving kidney and liver function, and hyperlipidemia due to diabetes. Extract treatment was also shown to enhance serum insulin levels and the body weight of diabetic rats as compared to the diabetic control group [24].

Ficus religiosa

Ficus religiosa L. (Moraceae) is prescribed for the treatment of Diabetes mellitus. In the present study, the antidiabetic effect of aqueous extract of *F. religiosa* bark (FRAE) was investigated in normal, glucose-loaded hyperglycemic and streptozotocin (STZ)-induced diabetic rats. The three doses caused significant reduction in blood glucose levels in all of the models. The effect was more pronounced at 50 and 100 mg·kg⁻¹, than at 25 mg·kg⁻¹. FRAE also showed a significant increase in serum insulin, body weight, and glycogen content in the liver and skeletal muscle of STZ-induced diabetic rats, while there was a significant reduction in the levels of serum triglyceride and total cholesterol. FRAE also showed significant anti-lipidperoxidative effects in the pancreas of STZ-induced diabetic rats. The antidiabetic effect of *F. religiosa* was compared with glibenclamide, a well-known hypoglycemic drug. The results indicate that FRAE possesses significant antidiabetic activity [25].

Gymnema sylvestre

Gymnema sylvestre (Retz.) R.Br. ex Schult. (Apocynaceae) is native to the tropical forests of southern and central India. *G. sylvestre* has been used in traditional medicine as a treatment for diabetes. The effect of *G. sylvestre* was investigated in both normal and alloxan-induced diabetic rats. The aqueous leaf extract of *G. sylvestre* at the dose of 400, 600, and 800 mg·kg⁻¹ body weight was administered orally once a day to the groups for 30 days. The study revealed that *G. sylvestre* has significant antidiabetic activity and hypolipidemic activity in alloxan-induced and normal fasting rats [26]. Most *G. sylvestre* supplements are standardized to a minimum of 25% gymnemic acid [9] (Fig. 2) (Table 1), the active ingredient in the leaves and root. The effectiveness of the extract from the leaves of *G. sylvestre* (GS4), in controlling hyperglycaemia was investigated in twenty-two type 2 diabetic patients on conventional oral anti-hyperglycemic agents. GS4 at 400 mg·d⁻¹ was administered for 18–20 months as a supplement to the conventional oral drugs. During GS4 supplementation, the patients showed a significant reduction in blood glucose, glycosylated hemoglobin, and glycosylated plasma proteins, and conventional drug dosage could be decreased [27].

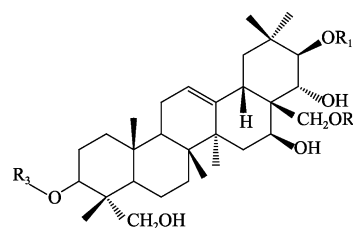


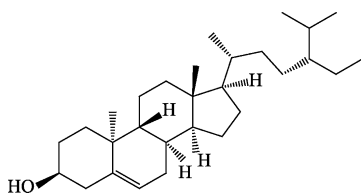
Fig. 2 Structure of gymnemic acid

Table 1 Substituents on gymnemic acid derivatives

	R ₁	R ₂	R ₃
Gymnemic acid I	Tigloyl	Acetyl	Gluconic
Gymnemic acid II	2-Methylbutyloyl	Acetyl	Gluconic
Gymnemic acid III	2-Methylbutyloyl	H	Gluconic
Gymnemic acid IV	Tigloyl	H	Gluconic

Lippia nodiflora

Lippia nodiflora (L.) Michx. (Verbenaceae) is a creeping perennial herb widely used in traditional medicine. γ -Sitosterol (Fig. 3) isolated from *L. nodiflora* was screened for its antidiabetic properties in streptozotocin (STZ)-induced diabetic rats. Insulin secretion in response to glucose was evaluated in isolated rat islets. Oral administration of γ -sitosterol (20 mg·kg⁻¹ body weight) once daily for 21 days in STZ-induced diabetic rats resulted in a significant decrease in blood glucose and glycosylated hemoglobin with a significant increase in plasma insulin level, body weight, and food intake [28].

Fig. 3 Structure of γ -sitosterol*Merremia emarginata*

Merremia emarginata (Burm. f.) Hallier f. (Convolvulaceae) is a procumbent plant spreading up to 1 m, and has yellow colored flowers. The plant is widely distributed in India, Sri Lanka, the Philippines, Malaysia, and tropical Africa, and mainly grows in the rainy and winter seasons. A study showed that *M. emarginata* produced a marked decrease in blood glucose at 100, 200, and 400 mg·kg⁻¹ in streptozotocin-induced diabetic male Wistar rats. The antidiabetic effect of *M. emarginata* may be due to increased release of insulin from the existing β -cells of the pancreas. Further, it was associated with an increase in plasma insulin level, suggesting insulinogenic activity of the plant extract [29].

Murraya koenigii

Murraya koenigii (L.) Spreng. (Rutaceae) commonly known as “Curry Patta” (Hindi) is widely used as a spice and condiment in India, and in other tropical countries. Mahanimbine [30] (Fig. 4) is a carbazole alkaloid, and is present in the leaves, stem bark, and roots of *M. koenigii*. Diabetes was induced in adult male Wistar rats by intra-peritoneal injection of streptozotocin (45 mg·kg⁻¹). Mahanimbine (50 and 100 mg·kg⁻¹) was administered as a single dose per week to the diabetic rats for 30 days. In the diabetic rats, the elevated fasting blood sugar, triglycerides, low density lipoprotein, and very low density lipoprotein levels were reduced, and the high density lipoprotein level was increased by mahanimbine at doses of 50 and 100 mg·kg⁻¹ (i.p.) [31].

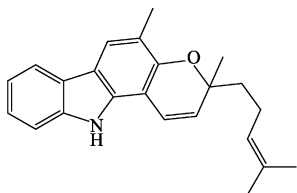


Fig. 4 Structure of mahanimbine

Moringa oleifera

Moringa oleifera Lam. (Syn. *Moringa pterygosperma* Gaerth.) (Moringaceae) is commonly known as drumstick tree, and is indigenous to Northwest India. Doses of 100, 200, and 300 mg·kg⁻¹ of an aqueous extract were administered orally by gavage for evaluating their hypoglycemic and antidiabetic effects on streptozotocin-induced sub, mild, and severely diabetic rats. The aqueous extract of leaves had some direct effect by increasing the tissue utilization of glucose, by inhib-

iting hepatic gluconeogenesis, or absorption of glucose into the muscles and adipose tissues [32].

Pongamia pinnata

Pongamia pinnata (L.) Pierre (Fabaceae) is a medium-sized, glabrous, semi-evergreen tree, growing up to 18 m or higher, with a short bole, spreading crown with grayish green or brown bark. Leaves are imparipinnate, alternate, and leaflets are 5–7 in number, ovate in shape and opposite in arrangement. *P. pinnata* occurs all over India on the banks of rivers and streams, and is planted as an avenue tree in gardens [33]. A significant decrease in the level of blood glucose and glucose-6-phosphatase activity and a significant increase in the plasma insulin level and hexokinase activity were noted at the end of the experimental period in diabetic rats treated with an aqueous extract of *P. pinnata* flowers (300 mg·kg⁻¹, orally). An aqueous extract of *P. pinnata* flowers also significantly reduced the thiobarbituric acid-reactive substances (TBARS) level, and enhanced the antioxidant status in induced diabetic rats after 45 days of treatment [34].

Scoparia dulcis

Scoparia dulcis L. (Plantaginaceae), commonly known as sweet broomweed, is a perennial herb widely distributed in tropical and subtropical regions. The effects of an aqueous extract of *S. dulcis* (200 mg·kg⁻¹) on the polyol pathway and lipid peroxidation were examined in the livers of streptozotocin adult diabetic male albino Wistar rats [35]. The aqueous extract also resulted in decreased free radical formation in the tissues (liver and kidney) studied. The decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides (HPX) and an increase in the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), and glutathione-S-transferase (GST) showed the antioxidant properties of the *S. dulcis* plant extract, in addition to its antidiabetic effect [36].

Spondias pinnata

Spondias pinnata (L. f.) Kurz (Anacardiaceae) is a glabrous tree up to 10.5 m high with a straight trunk and smooth ash-colored bark having a pleasant aromatic smell. It is found in the plains of Orissa, West Bengal, and Bihar. Chloroform, methanol, and water extracts of the bark of *S. pinnata* were evaluated for hypoglycemic activity in adult Wistar albino rats at dose levels of 300 mg·kg⁻¹ p.o. each using normoglycemic, glucose loaded, and alloxan-induced hyperglycemic rats. It lowers blood glucose levels in both normal and diabetic rats. Among the tested extracts, the methanol extract was found to produce promising results that were comparable to the reference standard glibenclamide (2.5 mg·kg⁻¹). Preliminary phytochemical examination of the methanol extract revealed the presence of flavonoids, tannins, saponins, and terpenoids [37].

Streblus asper

Streblus asper Lour. (Moraceae) is a medicinal plant commonly found in most areas of southern Asia. The methanolic extract of *S. asper* in STZ-induced diabetic rats, at doses

of 200 and 400 mg·kg⁻¹ b.w. produced a reduction in blood glucose levels when compared with the STZ control group. Serum biochemical parameters and antioxidant levels were significantly restored toward normal levels in the *S. asper*-treated rats as compared with the STZ control [38].

Terminalia chebula

The dried ripe fruit of *Terminalia chebula* Retz. (Combretaceae) is used extensively in Ayurveda, and is widely distributed throughout India, Myanmar, and Sri Lanka. Oral administration of an ethanolic extract of the fruit (200 mg·kg⁻¹) significantly reduced the level of blood glucose and glycosylated hemoglobin in diabetic rats [39]. The result indicates a prolonged action in the reduction of blood glucose by *T. chebula*, which is probably mediated through enhanced secretion of insulin from the β -cells of Langerhans or through and extra pancreatic mechanism [40].

Zygophyllum album

Zygophyllum album L. (Zygophyllaceae) leaves are widely used to treat hyperglycemia in Tunisian traditional medicine. Diabetes was induced in Swiss albino mice by the administration of STZ (45 mg·kg⁻¹ b.w.). An aqueous extract of *Z. album* (100 and 300 mg·kg⁻¹ b.w.) was administered by oral gavage once a day for a period of 15 days. The effect of the extract on blood glucose, lipids, and cholesterol levels in plasma, and also on enzymatic and non-enzymatic antioxidants of defense systems, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) enzyme activities, and vitamin C, vitamin E, and glutathione reductase (GSH) levels in the liver and pancreas were studied. The results suggested that the *Z. album* extract exerted anti-diabetic and antihypercholesterolemic activities through its antioxidant properties [41].

Hyperlipidemia and Significance

Mortality from cardiovascular diseases is the second leading cause of death worldwide [42]. Along with hyperglycemia and abnormalities in serum lipids, diabetes is associated with micro- and macro-vascular complications, which are the major causes of morbidity and death in diabetic subjects [43]. Patients suffering from cardiovascular diseases usually have an increase in blood cholesterol and low-density lipoprotein (LDL), as well as an increased activity of lipid peroxidation: these are the hallmarks of hypercholesterolemia [44–45].

Due to dramatic changes in living and food styles in the last century, the intake of a large variety of high-lipid snacks and an excessive intake of high-lipid foods could result, subsequently, in hyperlipidemia [46]. Hyperlipidaemia is mainly characterized by increased levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), along with a decrease in high-density lipoprotein cholesterol (HDL-C). This condition is an indicator of both coronary artery disease and atherosclerosis, and is the main cause of cardiovascular disease worldwide [47]. Clinically,

hyperlipidemia is considered to be one of the major risk factors for cardiovascular diseases, including atherosclerosis, myocardial infarction, heart attacks, stroke, and cerebrovascular diseases [48–49]. Treatment of hyperlipidemia involves dietary control, exercise, and pharmaceutical therapy. However, lipid-lowering drugs, such as the statins and fibrates, typically have adverse effects or contraindications. As a result, there continues to be a high demand for new oral anti-hyperlipidemic drugs, without any side effects. Plants play a major role in the introduction of new therapeutic agents because they have fewer toxic side effects than synthetic drugs. Additionally, plants have received attention for being sources of biologically active substances, including antioxidants, hypoglycemics and hypolipidemics [50].

Mechanism of action of antihyperlipidemic agents

There are different classes of antihyperlipidemic drugs available in the market which exert their effect in different ways. Statins exert their major effect by reducing LDL levels in the body through a mevalonic acid-like moiety that competitively inhibits HMG-CoA reductase. By reducing the conversion of HMG-CoA to mevalonate, statins inhibit an early and rate-limiting step in cholesterol biosynthesis, and produces an antihyperlipidemic action [51].

Fibric acid derivatives or fibrates activate PPAR α receptors, increase the activity of lipoprotein lipase, decrease hepatic very low-density lipoprotein production, and enhance the clearance of LDL-C by the liver. They markedly lower serum triglycerides, and modestly increase HDL cholesterol. Bile acid binding resins interfere with cholesterol absorption. Niacin reduces LDL cholesterol and triglycerides, and increases HDL cholesterol [52].

Various medicinal plants produce antihyperlipidemic action by decreasing the levels of serum total cholesterol, free fatty acids, phospholipids, non-HDL cholesterol, very low density lipoprotein (VLDL), triglycerides, and HMG-CoA reductase, and increasing the high-density lipoprotein (HDL) cholesterol levels [53–55].

Plant Drugs Used in the Treatment of Hyperlipidemia

Amaranthus caudatus

Amaranthus caudatus L. is a plant belonging to the family Amaranthaceae. *Amaranthus* plants are spread throughout the world, growing under a wide range of climatic conditions, and they are able to produce grains and leafy edible vegetables [56]. The antihypercholesterolemic and antiatherogenic effects of hydroalcoholic extracts of *A. caudatus* were examined in experimental rabbits maintained on a high cholesterol diet. In a regression period, the dietary use of *A. caudatus* (150 mg·kg⁻¹ body weight daily) for 30 days significantly decreased total cholesterol, LDL cholesterol, malondialdehyde, and C-reactive protein, while apolipoprotein A and HDL-cholesterol were significantly increased. Blood samples (from marginal ear vein) after 12 h of fasting were collected

on days 0, 45, and 75 for analysis. The atherosclerotic area was significantly decreased in the group with the dietary use of *A. caudatus* [57].

Cassia auriculata

Cassia auriculata L. (Fabaceae), common name: Tanner's Cassia, is a common plant in Asia, and has been widely used in Ayurvedic medicine as "Avarai Panchaga Choornam". It is a main constituent of Kalpa herbal tea. It has shown diverse biological activities and pharmacological functions, including reduction of blood glucose and serum lipids [58]. The flower extract of *C. auriculata* has been used traditionally in India for medicinal purposes. Hyperlipidemia was induced in rats by a single intravenous (iv) injection of Triton WR 1339 (300 mg·kg⁻¹ b.w.), and it produced sustained, elevated levels of serum cholesterol and triglycerides. An ethanolic extract of *C. auriculata* flowers (Et-CAF) (150, 300, 450 mg·kg⁻¹ b.w./day) was administered to normal and hyperlipidemic rats for 14 days. Lipid peroxidation decreased, whereas the activities of superoxide dismutase, glutathione peroxidase, and catalase increased in the Et-CAF-treated rats. Pronounced activity was observed at a dose of 450 mg·kg⁻¹ b.w. of Et-CAF for two weeks, and it was comparable to the standard drug lovastatin. In addition, Et-CAF is better in lowering the lipids and improving the antioxidant effects without any side effects at the dosage and duration studied [59].

Eclipta prostrata

Eclipta prostrata (L.) L. (Asteraceae) is a common plant growing in moist soils throughout India up to an altitude of 6000 ft. The total alcoholic extract of the plant, when tested for antihyperlipidemic potential, exhibited dose-dependent activity in Wistar male albino rats when compared to standard drugs. Administration of exogenous cholesterol resulted in a significant increase of various parameters of the lipid profile in rats. Treatment with standard drugs (clofibrate/guggul), as well as the total alcoholic extract of the plant (150 and 200 mg·kg⁻¹), appreciably decreased the gain in body weight. The lipid-lowering activity was dose-dependent for the total alcoholic extract and was significant for the 150 mg·kg⁻¹ dose. The extract of *E. prostrata* might have acted at the liver level in metabolizing and hastening the process of excretion of excess lipids, thereby producing a hypolipidemic condition, as the liver is the key organ in the synthesis and metabolism of lipids [60].

Helicteres isora

Helicteres isora L. (Malvaceae) is a shrub or small tree available in forests throughout Central and Western India. The hypolipidemic effect of an aqueous extract of the bark of *H. isora* was investigated in streptozotocin (STZ)-induced diabetic rats. Administration of the bark extract of *H. isora* (100 and 200 mg·kg⁻¹ b.w.) for 21 days resulted in significant reduction in serum and tissue cholesterol, phospholipids, free fatty acids, and triglycerides in STZ-diabetic rats. In addition, a significant ($P < 0.05$) decrease in high-density lipoprotein (HDL), and a significant increase ($P < 0.05$) in low-density

lipoprotein (LDL) and very low-density lipoprotein (VLDL) were also observed in the STZ-diabetic rats, which were normalized after 21 days of bark extract treatment. The bark extract at a dose of 200 mg·kg⁻¹ b.w. showed a more significant hypolipidemic effect than the dose of 100 mg·kg⁻¹ body weight [43].

Lagenaria siceraria

Lagenaria siceraria (Molina) Standl. (Cucurbitaceae) commonly known as bottle gourd, is official in the Ayurvedic Pharmacopoeia of India. The dried fruit juice extract was fractionated using the solvents according to polarity in ascending order, i.e. chloroform:acetic acid, methanol, pyridine, and water. Antihyperlipidemic activity was investigated on isolated compounds. The study exhibited that elevated levels of blood cholesterol, triglycerides, LDL, were significantly reduced, and HDL was significantly increased by the administration of fractions of *L. siceraria* fruit juice [61]. Another study included a preliminary phytochemical screening of the extracts. Oral administration at doses of 200 and 400 mg·kg⁻¹ body weight in rats, dose-dependently inhibited the total cholesterol, triglycerides, and LDL levels, and significantly increased the HDL level. Preliminary phytochemical screening revealed the presence of flavonoids, sterols, cucurbitacin saponins, polyphenolics, proteins, and carbohydrates. The results obtained suggest marked antihyperlipidemic and hypolipidemic activity of the extracts [62].

Melothria maderaspatana

Melothria maderaspatana (L.) Cogn. (Cucurbitaceae) is a monoecious plant having scandent or prostrate stems, very hispid, leaves are variable in size, densely covered with white hairs. The antihyperlipidemic effect of a crude ethanolic extract of *M. maderaspatana* leaf (CEEM) (200 mg·kg⁻¹ b. w.) was investigated on deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Hypertension was induced by subcutaneous injection of a DOCA-salt solution, twice a week, and the rats received a 1% sodium chloride solution as drinking water throughout the experimental period. CEEM or nifedipine was administered orally, once a day for 6 weeks. In DOCA-salt hypertensive rats, the level of plasma and tissues of total cholesterol (TC), triglycerides (TG), free fatty acids (FFA) and phospholipids (PL) significantly increased, and administration of CEEM significantly reduced these parameters towards normality. Further, the levels of low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) significantly increased, while the high density lipoprotein cholesterol (HDL-C) decreased in the hypertensive rats. Administration of CEEM brought these parameters to normality, which suggested their antihyperlipidemic action. These findings provided evidence that CEEM was protecting the liver, kidney, and heart against DOCA-salt administration, and the protective effect could be attributed to its antihyperlipidemic activities [63].

Pachyptera hymenaea

Pachyptera hymenaea (DC.) A.H.Gentry belonging to the

family Bignoniaceae, and commonly known as garlic vine, is a woody climber with tendrils on the leaves. Hypolipidemic and antihyperlipidemic effects from an aqueous extract *P. hymenaea* were studied. The extract was administered to normal and diet-induced hypercholesterolemic rats for 28 days, and serum lipid profiles were estimated. An oral dose, at 200 mg·kg⁻¹·d⁻¹, resulted in significant declines in plasma LDL-cholesterol, triglycerides (TG), and total cholesterol (TC) by 44.0%, 27.9%, and 28.1% respectively, compared to normal rats. The extract at 400 mg·kg⁻¹·d⁻¹, given to hypercholesterolemic rats, resulted in significant declines in plasma TC, LDL-cholesterol, and TG, by 66.1%, 60.0% and 57.6%, respectively, compared to a hypercholesterolemic control. GC–MS study of the volatile oil revealed the presence of two main organosulfur compounds, diallyldisulfide (65.9%, *V/V*) and diallyltrisulfide (29.6%, *V/V*). Evidently, the extract possesses pronounced hypolipidemic and antihyperlipidemic effects which are comparable to those of atorvastatin. These effects are due to the presence of organosulfur compounds, flavonoids, and polyphenols present in the extract [64].

Solanum nigrum

Solanum nigrum L. (Solanaceae), commonly known as black nightshade, grows as a weed, and is found in the dry parts of India and other parts of the world. The possible protective effect of *S. nigrum* fruit extract (SNFet) was investigated for its antioxidant and antihyperlipidemic activity against ethanol-induced toxicity in rats. The experimental animals were intoxicated with 20% ethanol (7.9 g·kg⁻¹·d⁻¹) for 30 days through gastric intubation. SNFet was administered at a dose of 250 mg·kg⁻¹ body weight, along with a daily dose of ethanol for 30 days. From the results, it was observed that the ethanol-induced rats showed a significant elevation in the levels of thiobarbituric acid reactive substances (TBARS), which lowered the antioxidant defense systems, such as reduced glutathione (GSH) and vitamins C and E, when compared to the controls. In the lipid profiles, the levels of total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL), very low density lipoproteins (VLDL), free fatty acids (FFA), and phospholipids were significantly elevated in the ethanol induced group, whereas, the high density lipoproteins (HDL) were found to be reduced in the plasma, and the phospholipid levels were significantly decreased in the tissues. These activities were also compared to the standard drug silymarin (25 mg·kg⁻¹ body weight). Thus the findings of the present study indicated a significant antioxidant and antihyperlipidemic activity of *S. nigrum* fruits, which offered protection against ethanol-induced toxicity [65].

Tamarindus indica

The tamarind (*Tamarindus indica* L.) is a tree belonging to the Fabaceae family. It is indigenous to tropical Africa, and has become naturalized in North and South America from Florida to Brazil, and is also cultivated in subtropical China, India, Pakistan, Indochina, Philippines, Java, and Spain. The effects of the crude extract from the pulp fruit of *T. indica* were evaluated on lipid serum levels and early atherosclerotic

lesions in hypercholesterolemic hamsters *in vivo*. Animals were fed on either chow or atherogenic diet during 10 weeks and concomitantly received either water or *T. indica* extract for drinking. Treatment of hypercholesterolemic hamsters with the *T. indica* pulp fruit extract (5%) led to a decrease in the levels of serum total cholesterol (50%), non-HDL cholesterol (73%), and triglycerides (60%), and to an increase of high-density lipoprotein (HDL) cholesterol levels (61%). *In vivo*, the extract improved the efficiency of the antioxidant defense system, as assessed by the superoxide dismutase, catalase, and glutathione peroxidase activities. Together, these results indicate the potential of tamarind extracts in diminishing the risk of atherosclerosis development in humans [66].

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