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Anti-diabetic phyto resources: A review

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Abstract
Diabetes is an important human ailment affecting many from various walks of life in different countries. The limitations of currently-available oral antidiabetic medication either in terms of efficacy/safety coupled with the emergence of the disease into a worldwide epidemic have encouraged concerted effort to discover newer phytomedicines that can be used to manage diabetes more efficiently. Many plants around us have been reported to possess antidiabetic property. During the last few years, bioactive drugs have been isolated from plants showing anti-diabetic potential. Many studies have been carried out to prove the benefits of medicinal plants with hypoglycemic effects for managing diabetes. Here a list of medicinal plants with proven antidiabetic and related beneficial effects is reviewed and compiled.

Keywords: Diabetes, Hypoglycemic agents, Herbs, Phytomedicines

1. Introduction
Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. In India it is proving to be a major health problem, especially in the urban areas. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Over the past 30 year, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people. It is estimated that in 2010 about 300 million people were estimated to have diabetes globally and this number expected to increase to near about 450 million by 2030 [1]. The therapeutic measurements include use of insulin and other agents like amylin analogues, sulphonyl ureas, biguanides, alpha glycosidase inhibitors like acarbose, miglitol and voglibiose for the treatment of hyperglycemia. These drugs also have certain adverse effects like causing hypoglycemia at higher doses, liver problems, lactic acidosis and diarrhoea. Oral agents and delivery measures only partially correct the multiple disturbances. The use of herbs in the management of *Diabetes mellitus* has been prevalent in Indian society from a long time. From the ethno botanical information, about 800 plants possessing antidiabetic potential have been found. The popularity of herbal usage can be attributed to its fewer side effects compared to the synthetic hypoglycemic agents and also their safety, effectiveness, and availability. Further, herbal action may delay the development of diabetic complications and correct the metabolic abnormalities. During the last few years, bioactive drugs have been isolated from plants showing anti-diabetic potential. Many studies have been carried out to prove the benefits of medicinal plants with hypoglycemic effects for managing the *Diabetes mellitus*. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost. Therefore, investigation on such agents from traditional medicinal plants has become more important.

2. Phytoconstituents with hypoglycemic potentials
Researchers have proved that the anti-diabetic activity of medicinal plants is due to the presence of phenolic compounds, flavonoids, terpenoids, coumarins and other ingredients which show hypoglycemic activity. However lots of investigations are needed for the evaluation of mechanism of action of medicinal plants with antidiabetic activity. Compound with different structure but with the same therapeutic activity isolated from different plant species act as active moieties for the treatment of various diseases. Some of these active principles originate from edible plants and their inclusion in the diet would undoubtedly be of some value because of their hypoglycemic potential. Several phytomolecules including flavonoids, alkaloids, glycosides, saponins, glycolipids, dietary fibres, polysaccharides, peptidoglycans, carbohydrates, amino acids and others obtained from various plant sources have been reported as potent hypoglycemic agent.

2.1 Alkaloids
Various alkaloids have been isolated from numerous Indian medicinal plants and investigated for their possible hypoglycemic activity in different animal models. Berberine is known to have potent hypoglycemic activity. It is obtained from *Tinospora cordifolia* [2]. Alkaloids like catharanthine, vindoline and vindolinine obtained from *Catharanthus roseus* also lower blood sugar level [3].

2.2 Dietary fibers
The role of dietary fibers in diabetes has been studied by several workers. Long term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose levels and reduces the number of hypoglycemic events in type I diabetic patients [4].Consumption of dietary fiber improves insulinbinding and decrease the rate of glucose absorption significantly.

2.3 Flavonoids
Flavonoids represent another beneficial group of naturally occurring compounds with hypoglycemic potentials. These are widely distributed in plant kingdom and exhibit distinctive pharmacological properties. The flavonoids can be widely classified into different categories like flavanols, flavones, catechins, flavanones *etc*. Some flavonoids have hypoglycemic properties because they improve altered glucose and oxidative metabolisms of diabetic states. Quercetin is an important flavonoid known to possess a vast array of pharmacological activities. Quercetin suppressed the glucose level, reduce plasma cholesterol and triglycerides significantly and increased their hepatic glucokinase activity probably by enhancing the insulin release from pancreatic islets of the diabetic rats [5].

2.4 Polysaccharides
Various Indian hypoglycemic plants like *Aloe vera*, *Ocimum sanctum*, *Alpinia galangal* are found to contain polysaccharides. The results indicated that the polysaccharidesincreased the levels of serum insulin, reduce the blood glucoselevels and improve tolerance of glucose [6].

2.5 Saponins
Triterpenoid and steroidal glycosides, referred to collectively as saponins, are bioactive compounds present naturally in many plants and known to possess potent hypoglycemic activity[7]. Charantin, a steroidal saponin, obtained from *Momordica charantia* is known to have an insulin-like activity, responsible for its hypoglycemic effect [8]. β-Sitosterol, a steroid obtained from *Azadirachta indica*, may be responsible for its hypoglycemic property [9].Andrographolide, another diterpenoid lactone, obtained from *Andrographis paniculata* was found to possess significant hypoglycemic activity [10]. Gymnemic acid, obtained from leaves of *Gymnema sylvestre* exhibits potent hypoglycemic activity in experimental animals models of diabetes [11].

3. Mechanism of Action of Herbal Antidiabetics
Mechanism of action of herbal antidiabetics depends on presence of active chemical component in plant material. Different mechanism of action of herbal medicines are Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes, stimulation of insulin secretion, reduction in insulin resistance, providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells, increasing the size and number of cells in the islets of Langerhans and regenerating and/or repairing pancreatic beta cells [12]. However, only a few have been subjected to detailed scientific investigation.

4. Medicinal plants with antidiabetic activity
In India indigenous remedies have been used in the treatment of diabetes since the time of Charaka and Sushrutha. Plants have always been an explempary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. The use of herbal medicines for the treatment of *Diabetes mellitus* has gained importance throughout the world. The World Health Organization also recommended and encouraged this practice especially in countries where access to the conventional treatment of diabetes is not adequate. There is an increased demand to use natural products with antidiabetic activity due to the side effects associated with the use of insulin and oral hypoglycemic agents. Here a list of herbs with proven hypoglycemic effect reviewed is given.

4.1. *Aegle marmelos* (Family: Rutaceae)
A moderate sized tree found throughout the deciduous forests of India. Different extracts obtained from the leaves, bark and fruit of this plant have been investigated for possible hypoglycemic activity in various experimental animal models of diabetes like streptozotocin and alloxan induced diabetes along with possible mechanism of action. It increases utilization of glucose; either by direct stimulation of glucose uptake or via the mediation of enhanced insulin secretion and also decreases the elevated glucose and glycosylated haemoglobin levels. The leaves have antihyperglycemic activity in glucose induced hyperglycemic rat at an oral dose equivalent to 250 mg/kg [13]. Antihyperglycemic activity of aqueous fruit extract (250 mg/kg, twice daily for 1 month) in streptozotocin induced female albino Wistar diabetic rats also have been reported [14].

4.2. *Aerva lanata* (Family: Amaranthaceae)
It is a branched herb widely used in Indian folk medicine for the treatment of *Diabetes mellitus*. The effect of an alcoholic extract of *Aerva lanata* on blood glucose and other biochemical parameters in alloxan-induced diabetic rats was studied and it was observed that the extract reduced the increase of blood sugar in alloxanized rats by 42% at 375 mg/kg and 48% at 500 mg/kg body weight [15].The methanolic and aqueous extract also reduced blood sugar level of streptozotocin induced rats significantly upon chronic administration (400mg/kg) for 2 weeks [16].

4.3. *Allium sativum* L. (Family: Liliaceae)
Garlic (*Allium sativum*), a member of the Liliaceae family, is a common food for flavour and spice and it is one of the herbs most commonly used in modern folkloric medicineto reduce various risk factors associated with cardiovascular diseases. Garlic is stated to possess many therapeutic benefits. Garlic's strong odour is largely due to sulphur-containing compounds (S-allyl cysteine sulphoxide), which are believed to account for most of its medicinal properties.Garlic has been found to be effective in lowering blood glucose level in STZ-induced diabetic rats as a response of administration of 500mg/kg of aquous extract [17].However, garlic treatment did not reduce glucose level of diabetic animals to normal levels. But the study strongly suggests that garlic may be very useful in the alleviation of diabetic complications.

4.4. *Aloe barbadensis (*Family: Aloaceae)

Aloes have long been used all over the world for their various medicinal properties. The extract of aloe gum is effective in enhancing glucose tolerance in normal as well as diabetic rats [18].Several other works have revealed the hypoglycemic activity of this plant along with possible mode of action.Oral administration of *Aloe* gel significantly reduced the fasting blood glucose, hepatic transaminases, plasma and tissue cholesterol, triglycerides, free fatty acids and phospholipids. It significantly increases plasma insulin levels [19]. The hypoglycemic activity of leaf pulp extracts (200 and 300 mg/kg) in streptozotocin-induced diabetic rat was also reported [19]. Leaf pulp juice of 10–20 ml is used to control diabetes in humans.

4.5. *Andrographis paniculata* (Family: Acanthaceae)

It is an erect annual herb commonly known as Kalmegh or 'King of Bitters', found throughout India and cultivated in many states of India. A number of studies have shown that *Andrographis paniculata* extract and the active metabolite andrographolide can exert potent antihyperglycemic activity. A water-soluble polysaccharide (APP) was isolated from *Andrographis paniculata* and the synergestic effect of APP in combination with andrographolide on renal complication in streptozotocin (STZ) induced diabetic mice was investigated. APP and/or andrographolide were administered to diabetic mice continuously for two weeks. APP plus andrographolide decreased the levels of blood glucose in diabetic rats, as well as the relative kidney weight. In summary, APP plus andrographolide can improve the metabolic abnormalities of diabetic mice and prevent or delay the progression of diabetic renal complications, which may be useful as a therapeutic agent for inhibiting the progression of diabetic nephropathy [9].

4.6. *Azadirachta indica* (Family: Meliaceae)

Azadirachta indica commonly referred as the neem tree is a broad-leaved evergreen tree found throughout India and is widely recognized as a potent insecticide. Hypoglycemic activity of hydro alcoholic *Azadirachta indica* extract in normal rats and hypoglycemic activity in glucose fed and streptozotocin induced diabetic rats has been reported [8] [20]. Hypoglycemic activities of leaf extract in normal and streptozotocin-induced diabetic rat has been reported by Chattopadhyay [3]. Crude ethanolic extract of neem inhibited action of epinephrine on glucose metabolism, resulting in increased utilization of peripheral glucose in alloxan diabetic albino rats [21].

4.7. *Coccinia indica* (Family: Cucurbitaceae)

A creeper grows wildly in many parts of the Indian subcontinent and is well known as a hypoglycemic herb. Hypoglycemic activity of Pectin, isolated from the fruit of *Coccinia indica* was studied in normal rats at a dose of 200 mg/100 g/day upon oral administration and it showed significant reduction in blood glucose and an increase in the liver glycogen level [22]. Aqueous - methanolic (40:60) extract of leaf of *Coccinia indica* significantly reduced the blood glucose level [23].

4.8. *Costus speciosus* (Family: Zingiberaceae)

It is a rhizomatous herbaceous plant. It has a very wide distribution in India and widely used in several indigenous system of medicine for the treatment of various ailments. The rhizomes are used as an alternative source for diosgenin, tigogenin and saponins. Aqueous and methanolic extract of *Costus speciosus* have shown significant decrease in fasting blood glucose level in diabetic rats. As a response of administration of 200 mg/kg of both the extract there was drastic and significant reduction in blood glucose level starting from 30 min and is maintained till 240 min and is highly significant [24].

4.9. *Euphorbia hirta* (Family Euphorbiaceae)

It is a slender- stemmed, annual hairy plant with many branches from the base to top, spreading upto 40 cm in height, reddish or purplish in color. *Euphorbia hirta* has been studied by various workers and a number of active constituents like Afzelin, Quercitrin, and Myricitrin have been isolated. Ethanolic extract of *Euphorbia hirta* leaves have hypoglycemic activity in STZ induced diabetic wistar rats [25]. Ethanolic extract of *Euphorbia hirta*leaves was administered to streptozotocin induced rats. Glibenclamide was used as a standard drug. Blood glucose levels were determined after oral administration of a dose of *Euphorbia hirta* (400 mg/kg b. wt) in diabetic groups. Blood glucose levels were determined on 0, 7th, 14th and 21st day after oral administration and was found to reduce blood sugar in diabetic rats. Reduction in blood sugar could be seen from 7th day after continuous administration of the extract. These results indicated that *Euphorbia hirta* possesses significant hypoglycemic and antihyperlipidemic effect.

4.10. *Gymnema sylvestre* (Family: Asclepediaceae)

Gymnema sylvestre is one of the Asclepiad strains, native to the tropical regions of India and commonly known as the "sugar destroyer" because the leaves effectively block sweet tastes in the mouth when chewed. The plant has been used in the treatment of *Diabetes mellitus* for a long time in India and reported by different workers for its blood glucose lowering activity both *invitro* and *in vivo.* Aqueous leaf extract of *Gymnema sylvestre* significantly reduced the fasting blood glucose in diabetic rats [26]. Treatment with *Gymnema sylvestre* powder significantly reduced the glucose and triglycerides levels [10]. The study revealed the anti-diabetic effect in stomach of albino wistar rats using *Gymnema sylvestre* herbal powder. The different concentration of *Gymnema sylvestre* treated were 5, 10, 15, 20/gms/25 days. Treatment with *Gymnema sylvestre* reduced the stomach weight of animals and reduced levels of insulin, protein, triglycerides, cholesterol and glucose significantly. Thus it could be recommended that *Gymnema sylvestre* could be used in various ailments in limited dosage on the advice of a physician.

4.11. *Mangifera indica* L. (Family: Anacardiaceae)

It is a well-known perennial tree commonly known as Mango, distributed and widely cultivated throughout India. The aqueous leaf-extract (1 g/kg) exert hypoglycemic activity in streptozotocin-induced diabetic rats upon oral administration [27].The glucose lowering effect of mangiferin, a xanthoneglucoside, isolated from the leaves of *Mangifera indica* was also studied and possible mode of action could be through the intestinal reduction of absorption of glucose as well as pancreatic and extra pancreatic mechanisms.

4.12. *Momordica charantia* (Family: Cucurbitaceae)

It's a slender, climbing annual vine commonly known as 'bitter gourd' grows in India and other tropical countries. Several earlier and recent studies have indicated the

hypoglycemic activity of various parts of this plant. Fruit powder and aqueous fruit extract of *Momordica charantia* was investigated for its effect on blood glucose and other biochemical parameters in alloxan-induced diabetic rats and found to exert potent blood glucose lowering effect. Alcoholic extract of fruits of *Momordica charantia* decreases the blood sugar level significantly. Blood glucose once lowered by this treatment remained static even after discontinuation of drug for 15 days [28].

4.13. *Pterocarpus marsupium* (Family: Leguminosae)

It is a small tree attaining a height of 7.5m and traditionally used in the treatment of diabetes, bleeding piles, dysentery and in all skin inflammations. It is a well-known plant commonly known as Vijaysar, found throughout India. In folk medicine the plant is used as hypoglycemic, which was proved by some earlier studies. Different parts of the plant like bark, latex, etc. were investigated and reported to have hypoglycemic activity [21] [29]. Various active components like epicatechin, marsupsin, pterosupin and pterostilbene, isolated from the bark and heartwood of the plant, were also found to possess blood sugar lowering activity

4.14. *Stevia rebaudiana* (Family: Asteraceae)

Stevia, one of the genera of the Asteraceae Family is a genus of more than 200 species. Members of *Stevia* comprise mostly of herbs but also shrubs and trees. It is a non-calorie sweetener (250-300 times sweeter than sucrose at 0.4% solution) in medicinal green teas for treating heart burn and other ailments [30]. The alkaloids Stevioside & Rebaudioside present in leaves is responsible for its antidiabetic action. Bekele [31]. reported that the crude aqueous extract of *Stevia rebaudiana* lowered elevated blood glucose level in alloxan induced diabetic mice. The fasting mean blood glucose level of diabetic mice treated with crude aqueous extract (300 mg/kg and 500 mg/kg body weight), and crude ethanol extract (300 mg/kg and 500 mg/kg body weight) was reduced significantly compared to diabetic control (positive control) mice. The effect was more pronounced in the case of crude aqueous extract compared to crude ethanol extract. The result of the ethanol extract did not show dose-dependence whereas the aqueous extract showed a dose-dependent reduction of blood glucose levels.

4.15. *Syzygium cumini* (Family: Myrtaceae)

Large evergreen tree of Indian subcontinent, commonly known as 'Jamun'. In India, the decoction of kernels of *Eugenia jambolana* is used as a household remedy for diabetes. Hypoglycemic activity of ethanolic whole seeds, kernel and seed coat extracts (100 mg/kg) in streptozotocin-induced diabetic rats has been reported [32]. The seeds and decoction of dry leaves were found to produce hypoglycemic effect.

4.16. *Tinospora cordifolia* (Family: Menispermaceae)

It is a large climbing shrub found throughout India and used in various ailments. Various extracts of the leaves of this plant were investigated for their blood sugar lowering activity in normal and alloxanized rats in graded doses and the findings have proved that the plant has potent hypoglycemic activity. Supplementation of methanol extract of *Tinospora cordifolia* significantly reduced the fasting blood glucose level and glucose -6-phosphatase activity [33]. The oral administration of various extracts (Hexane, Ethyl acetate and Methanol) of *Tinospora cordifolia* stem (TCS) were found to have potent antidiabetic activity that reduces blood sugar level in streptozotocin-(STZ) induced diabetic rats. In this study, the chronic (100 days) Antihyperglycemic effect of the extracts at a dose of 250 mg/kg TCS were investigated. Insulin was used as areference drug at a dose of 3 I.U/kg.

4.17. *Trigonella foenumgraecum* L. (Family: Fabaceae)

Fenugreek is a well-known hypoglycemic agent used in traditional Indian medicines. Various extracts of different parts of this plant; fibres, proteins and saponins isolated from the seeds were investigated and found to possess significant hypoglycemic activity. Fenugreek seeds and the major alkaloid component, Trigonelline, exerted a mild hypoglycemic effect on streptozotocin-induced diabetic rat [34].

Karthik and Ravikumar [35]. reported the antidiabetic activity of Ethanolic extract of *Cynadon dactylon* (450mg) on blood glucose level. Regular intake of *Ipomea digitata* tuber root powder is reported to be beneficial to persons suffering from or prone to diabetic and coronary disease [36].

5. Conclusion

The prevalence of *Diabetes mellitus* continues to rise worldwide and treatment with oral hypoglycemic drugs ends with numerous side effects and huge monetary expenditure. There is increasing demand by patients to use the natural products with antidiabetic activity. Therefore, treating *Diabetes mellitus* with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. Conclusively, it appears that we are approaching a 'new era' in the drug development from higher plants and indeed, from natural sources in general. Now a day it is an urgent need to target the drugs with anti-diabetic potentials as diet to cure the causes and restrict the diabetes at the edge of new millennium where we can move ahead with a health and healthy living. The collective efforts of ethno botanists, phytochemists, pharmacognostists & pharmacologists are needed to document and evaluate the usefulness and safety of the claim. Major hindrance in amalgamation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their efficacy and safety. There is a need for conducting clinical research in herbal drugs, developing simple bioassays for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation. It is also important to establish the active component/s from these plant extracts.

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