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Medicinal plants and diabetes mellitus: A review

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Abstract

Diabetes mellitus is a metabolic disorder widespread in developing and well-developed countries. It is the sixth leading cause of death in upper middle-income countries in 2015. Many of the synthetic medicine such as sulfonylureas, biguanides, alpha-glucosidase inhibitor and thiazolidinediones are the diabetic agents currently available to control the hyperglycemic condition. Due to the limitations of the drugs, it is required to find a natural alternative for the control of Diabetes Mellitus. Safe and effective antidiabetic agents can be extracted/separated from the traditional medicinal plants. 80% of the population around the Globe depends on traditional medicine. About 350 plants were traditionally used to treat diabetes mellitus. Medicinal plants were assessed for their antidiabetic activity, but these plants were not scientifically evaluated for the presence of an antidiabetic agent. Identification of anti-hyperglycemic agent without any side effects is the need of the hour. WHO has reported tremendous increase of 433million adults with Diabetes Mellitus in 2014, the prevalence of diabetes mellitus in India increased to 7.8% in India. The review focuses on the commonly available and traditionally used medicinal plants of North TamilNadu, India and their role in the control of diabetes mellitus.

Keywords: Diabetes mellitus, Medicinal plants, antidiabetic, hypoglycemic agent

Introduction

Diabetes Mellitus (DM) is a metabolic disorder. It was first described clinically by the Greek physician Aretaeus Cappadocia in 1500 BC "as a condition where Flesh and Bones run together and are siphoned into the urine". Diabetes mellitus is characterized by hyperglycemic condition along with impaired metabolic functions. Two major types of DM exist; the first type is characterized by insufficient production of insulin and in the other type the target cells do not respond to insulin. The chronic hyperglycemic condition leads to long term damage and failure of target organs. The first WHO global report on diabetes demonstrates that the number of adult living with diabetes has almost quadrupled since 1980 and to 422 million adults in 2014; type 2 diabetes and associated factors such as overweight and obesity were the reason for the dramatic increase.

Prevalence of diabetes in India accounts for 7.8% of the adult population ^[1] Over the past, three decades, the rise in the occurrence of diabetes was dramatic and grows very rapidly in low and middle income countries. The prevalence of diabetes in Tamil Nadu accounts to 13.7% in urban and 7.8% in rural areas in the year 2011 ^[2]. The synthetic drugs used lead to side effects as well as persistence of hyperglycemic conditions for a longer period of time resulting in serious complications and damages to the heart, blood vessels eyes, kidney and nerves, moreover, increases the risk of heart diseases and stroke ^[3]. Progressive reduction in β -cell function made it difficult to maintain glycemic control among many diabetic patients^[4]. Polytherapy with many hypoglycemic agents to attain better glucose control is a common practice ^[5].

Many plants have been found to be useful in managing diabetes mellitus. Plants are the major source of drug and are available in the market as extracts directly or indirectly from the plant sources ^[6]. For the purpose of preventive and curative reasons plants were used as medicine in various parts of the world. Medicinal herbs were used to treat diabetes in large proportion all over the Globe because of the easy availability and affordability ^[7]. Plant medicines show a potential hypoglycemic activity in diabetes-induced animals. Further, the metabolites from the plant were formulated and were administered to control diabetes mellitus. Novel compounds with antihyperglycemic potential have to be isolated from the plant sources. Studies reveal the role of crude extracts of plants with potential antidiabetic activity in alloxan and streptozotocin-induced diabetic animals. It is required to isolate, purify and characterize the specific compounds with the efficacy to control by reducing blood glucose level and by means of regenerating the damaged β cells of the pancreatic islets for the normal secretion of insulin. The objective of the review is to collect and elucidate the antidiabetic properties of the medicinal plants used by the traditional healers to manage diabetes mellitus.

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Andrographis paniculata

Andrographis paniculata (Family Acanthaceae) a bitter shrub, commonly known as nila vembu in tamil is a traditional medicinal plant used for centuries in the treatment of infectious diseases [8], Anti-inflammatory and immunosuppression properties [9], Hepatoprotective [10], Antihypertensive [11], antivenom [12], anticancer, antipyretic activity [13]. By restoring glucose uptake and oxidation in the liver, the extracts, of *A. paniculata* exhibits its antihyperglycemic potential [14]. Enhancement of renal function by reducing the level of Creatinine and Urea in diabetic rats treated with ethanol leaf extract of *A. Paniculata* was observed [15]. The presence of andrographolide and polyphenols in the ethanol leaf extract were responsible for the protective activity of the plant [16]. Andrographolide increases the glucose utilization and thereby reduces plasma glucose in diabetic rats [17]. Antihyperglycemic activity of the plant extract by the presence of polyphenols, flavonoids, and diterpenoids was reported [18]. Hypoglycemic activity of ethanol extract was attributed by the increased glucose metabolism in streptozotocin induced diabetic rats [19]. *Andrographis paniculata*, extracts were active in restoring the metabolic profile of obese diabetes rats [20].

Annona squamosa

Annona squamosa of Annonaceae family is a tropical branched tree and is commonly known as custard apple in English, Sitaaphazlam in Tamil. This plant is used as an insecticide agent [21], Post-coital antifertility activity [22], anthelmintic [23], wound healing [24], jaundice [25], cancer [26]. *Annona squamosa* contains flavonoids, phenolic compounds and glycosides and tannins [27]. Antidiabetic potential of the plant is due to the presence of flavonoids [28]. Treatment with extracts showed the marked decrease in the total serum cholesterol level and fasting blood sugar level was observed in alloxan induced diabetic rats [29]. Dose dependent antihyperglycemic activity was observed with ethanolic and methanolic extracts [30]. Enhanced insulin secretion from destructed pancreatic β cells was observed in aqueous extract of *A. squamosa* treated rats. Treatment of *A. Squamosa* hexane extract lowers glucose and triglycerides level and PTPIB inhibition by the bioactive principle in the extract may be one of the possible mechanisms bringing these effects [31]. Aqueous extract of *A. squamosa* is effective against blood glucose level in both streptozotocin and alloxan-induced diabetic rabbits and rats, the preliminary mechanism is that the aqueous extract acts directly on pancreatic cells for the secretion of insulin while increasing the uptake of glucose through specific receptors in muscle and intestine. Aqueous extract of *A. squamosa* either has the insulin like effect on skeletal muscles or direct stimulatory effects on the enzyme involved in the glucose metabolism [32].

Azadirachta indica

Azadirachta indica belonging to the family Meliaceae is a tree, commonly known as neem tree in India, growing in tropical and subtropical regions. It can grow up to a height of about 20-30 m. The canopy of leaves makes it a useful shade tree. All parts of the plant are used to treat disorders such as, intestinal helminthiasis and respiratory disorders [33] viral diseases [34], antifertility [35], anticancer [36], antibacterial [37], anti-inflammatory and antipyretic [38]. The glucose induced hyperglycemic condition has been prevented by the administration of aqueous extract of *A. indica* [39]. Hypoglycemic activity of the neem has been well established

[40]. A dose independent decrease in the blood glucose was observed in alloxan induced diabetes mice [41]. Lipid profile and blood glucose levels were reduced to the normal range in an ethanol extract treated streptozotocin-induced diabetic rats [42]. *Azadirachta indica* exhibits antidiabetic activity in various animals. Administration of neem extract reduces serum glucose, urea, total cholesterol, creatinine, and triglyceride levels in alloxan induced diabetic rats [43].

Cassia fistula

Cassia fistula commonly known as golden rain tree, sarakkonrai in Tamil is a flowering plant belonging to the family Fabaceae. It is traditionally used by local healers and in most of the herbal preparation for diabetes [44], antioxidant [45], laxative [46], antitumor, intestinal disorders [47], anti-inflammatory [48], antipyretic [49]. Urea and creatinine level were significantly reduced by *C. fistula* ethanol extract treated group of alloxan-induced diabetic rats [50]. The alkaloids that exist in the ethanolic extracts and water soluble fractions exhibit antidiabetic activity [51]. The leaves of *C. fistula*, ethylacetate extract, possess significant hypoglycemic activity in alloxan-induced diabetic rats [52]. *C. fistula* possesses antidiabetic potential and the blood sugar; cholesterol levels were similar to the control group [53]. Dose related inhibition of amylase activity was observed in ethanolic root extract treated diabetic rats [54]. Phenolic constituents present in the alcoholic fruit extract of *C. fistula* were reported for antidiabetic activity [55]. Increased level of GSH was observed in extract treated group [56].

Cassia auriculata

Cassia auriculata of family Caesalpiniaceae is commonly known as "Tanner's cassia" and in Tamil it is known as "Avaram". It is distributed in dry and semi-dry parts of India and Asia. All parts of the plant have various activities such as antipyretic activity [57]. It acts against disorders such as conjunctivitis and ophthalmia [58], liver injury [59], ulcer [60] and anti-inflammatory activity [61]. Lipid peroxide mediated tissue damage in alloxan-induced diabetic rats was protected by the water soluble fraction of ethanol extract of *C. auriculata* flowers [62]. A mixture of roots, leaves, flowers, barks and unique fruits of *C. auriculata* shrub is used in Avarai panchaga chooranam which controls the blood sugar level [63]. *C. auriculata* treated animals shows increased serum insulin levels in streptozotocin treated diabetic animals when compared to diabetic control, the β cells regeneration substantiate with increased level of insulin [64]. Administration of *C. auriculata* leaves and flowers extract stimulates the insulin secretion by regenerating β cells in alloxan-induced diabetic rats [65]. *C. auriculata* leaf extract controls the elevated blood glucose by inhibiting the activity of α -amylase and α -glucosidase by which it implies the postprandial hypoglycemic control in diabetes [66].

Catharanthus roseus

Catharanthus roseus belonging to family Apocynaceae commonly called as periwinkle and nithyakalyani in Tamil is an ornamental shrub that grows upto a height of 30-100 cm and it is widely distributed around the world. The plant is used to treat the disorders such as ulcer [67], lymphoblastic leukemia [68], and possess antibacterial [69], antimicrobial, antioxidant, anticancer [70], antiviral activities [71], antifertility [72], antifungal [73], and antipyretic [74]. The activity of glucokinase, malate dehydrogenase, succinate dehydrogenase were increased gradually in the streptozotocin induced

diabetic rats treated with *C. roseus* extracts [75]. The hepatic enzyme such as hexokinase was significantly increased and glucose 6-phosphatase, fructose 1, 6-bisphosphate activity came to normal level in *C. roseus* treated animals [76]. The increase in serum insulin level and restoration of β cells were evident in aqueous extract treated rats [77]. Treatment of diabetic animals with extracts resulted in significant decrease in serum LDL level; the reduced level of LDL may possibly occur due to the presence of flavonoids in the ethanol extract of *C. roseus* [78]. *C. roseus* was found to be more effective in reducing fasting blood glucose level, and increased GLUT-2 mRNA and GLUT-4 mRNA concentrations [79]. The increased level of protein was decreased by the treatment of *C. roseus* in alloxan-induced diabetic rats [80].

Centella asiatica

Centella asiatica belonging to family Apiaceae commonly called as centella, and vallarai in tamil is a slender, tender, faintly aromatic herb, which has numerous creeping stoloniferous stems grows up to 2m long. The plant is indigenous to South-East Asia, India, Sri Lanka, part of China and Western South Sea Islands. All parts of the plant is used to treat various diseases such as psoriasis [81], ulcer [82], wound healing [83], antioxidant [84]. The aqueous, ethanol and methanol extract of *C. asiatica* have been proved to possess antidiabetic activity in various animals [85, 86]. The decrease in the blood glucose, cholesterol and triglycerides were observed in *C. asiatica* treated alloxan-induced diabetic rats [87]. The possible mechanism of antihyperglycemic activity of *C. asiatica* is to reduce carbohydrate breakdown, and glucose fiber binding, which in turn reduces the glucose absorption through the gastrointestinal tract [88].

Cichorium intybus

Cichorium intybus was commonly known as chicory and Kasini keera in Tamil. It belongs to the family Asteraceae, is a root vegetable and perennial plant having blue or white flowers. Chicoric acid present in this plant stimulates the immune system and prevents inflammatory and bacterial diseases [89], antioxidant [90], anticancer [91], antiulcerogenic [92]. Administration of chicory roots reduces the level of plasma glucose, cholesterol, HDL cholesterol in STZ induced diabetic rats [93]. Reduce glucose uptake from the perfused jejunum of rats [94]. Methanolic extract of *C. intybus* is beneficial in reducing blood glucose as well as the level of glucose and ketone in the urine of STZ induced diabetic rats [95]. Decrease in blood glucose level, as well as normal levels of lipid profile, were observed in chicory leaves treated diabetic rats [96].

Coccinia indica

Coccinia indica belongs to Cucurbitaceae family and is commonly known as Kundru, Kovai in Tamil. It is a perennial twin with tuberous roots, stem smooth with white flowers. This plant is grown all over India, different parts of this plant were traditionally used to treat various ailments such as antihepatotoxic [97], hypolipidemic [98], Gastrointestinal disturbance [99], Diabetes bronchitis and skin disease [100]. Triterpenes present in the extract acts like insulin [101]. Animals treated with ethanolic extract of *C. indica* showed significant hypoglycemic, hypolipidemic and antioxidant effects [102]. The triterpenes were responsible for antidiabetic activity and altered metabolic activity by restoration properties of β cells against alloxan-induced damages [103]. Antidiabetic activity of *C. indica* can be initiated by insulin

effect on plasma by increasing pancreatic secretion of insulin for existing β cells [104]. Decreased blood glucose level was due to the inhibition of glucose uptake in the intestine and insulinotropic activity of the extract [105]. Administration of *C. indica* extracts for a period of 21 days controls the elevated serum lipids secondary to diabetic state [106]. Alcoholic extract of *C. indica* possess antidiabetic activity in streptozotocin-induced diabetic rats [107]. Fresh *C. indica* reduces the hyperglycemic condition and diabetic nephropathy in streptozotocin induced diabetic rats [108]. Concentrate and time dependent hypoglycemic activities were observed in *C. indica* treated group of animals compared to standard drugs [109].

Eugenia jambolana

Eugenia jambolana, belongs to the family Myrtaceae is an evergreen tree indigenous to India and it is cultivated for its delicious fruit, commonly called as Jamun and Naaval Pazhamin Tamil. The plant is used in the treatment of various diseases and disorders such as Constipation [110] and Piles [111]. The seeds of the *E. jambolana* promote the release of insulin [112]. A significant decrease in plasma glucose level in the patients with type 2 diabetes mellitus [113]. The restoration of lipid profile was noticed after *E. jambolana* seed kernel treatment [114]. Plasma insulin and C-peptide levels were increased in diabetic rats treated with bark extract reveals the hypoglycemic potential of *E. jambolana* [115]. Mycominose a compound isolated from the seed of *E. jambolana* which significantly reduces the blood glucose level as that of glibenclamide standard [116]. The metabolites of the flower extract of *E. jambolana* possess antidiabetic activity [117]. Reversal of blood urea, blood creatinine, and urine microalbumin were observed in seed extract of *Eugenia jambolana* treated Wistar rats [118]. The seed extracts induces the regeneration of β cells in Streptozotocin-induced diabetic rats [119].

Gymnema sylvestre

Gymnema sylvestre is a perennial woody climber belonging to family Asclepiadaceae. It is a slow growing herb common in hills of evergreen forests found ideally in tropical, subtropical and humid climate and, it is commonly known as "miracle fruit" and Cirukurinca in tamil language. The plant is used to treat various disorders, such as snake bite [120], cardiovascular diseases [121]. The aqueous, methanol and hydroalcoholic extract of *G. sylvestre* have antidiabetic activity in various animals [122]. Secretary granules of β cells of pancreatic islets revealed normal level in *G. sylvestre* leaf and callus treated group of rats [123]. Hypoglycemic activity of leaf extract of *G. sylvestre* was reported in rabbits [124]. Alcoholic extracts of *Gymnema sylvestre* act on pancreatic β cells to increase the level of insulin [125]. Reversal of damaged β cells of islets was recorded in *G. sylvestre* treated rats [126]. *G. sylvestre* increases the enzyme activity which is responsible for the uptake and utilization of glucose, which impairs the ability to discriminate sweet taste [127]. The methanolic leaf extract of *G. sylvestre* achieved good antihyperglycemic activity in streptozotocin induced diabetic rats [128].

Momordica charantia

Momordica charantia is a tropical subtropical vine belonging to the family Cucurbitaceae, commonly called as Bitter gourd and Pagakkai in tamil, is traditionally used as an antidiabetic agent. *M. charantia* possess medicinal properties such as antioxidant [129], antimalarial [130], antifertility [131] and antihelmintic property [132]. A significant decrease in blood

glucose and increased serum insulin were observed when powdered fruit of plant administrated to diabetic rats [133]. It appears to act by repairing damage β cells, rise in insulin secretion and promotes glucose uptake by enhancing the sensitivity to insulin [134]. The metabolic profile of the diabetic

rats was close to the normal range in *M. charantia* fruit extract treated diabetic rats [135]. Serum glucose level was reduced in the aqueous extract of *M. charantia* fruit treated diabetic rats [136].

Table 1: Antidiabetic and other beneficial effects of medicinal plants

S. No	Plant name	Family	Parts used	Extract	Activity	References
1	<i>Andrographis paniculata</i>	Acanthaceae	Leaves	Ethanol	Antidiabetic and Antioxidant	[15]
2	<i>Annona squamosa</i>	Annonaceae	Leaves	Aqueous	Hypoglycemic and Antidiabetic	[32]
3	<i>Azardica indica</i>	Meliaceae	Root and Bark	Ethanol	Antidiabetic	[168]
4	<i>Cassia fistula</i>	Fabaceae	Leaves	Ethanol	Hypoglycemic and Antidiabetic	[56]
5	<i>Cassia auriculata</i>	Cesalpiniaceae	Flower	Methanol Ethanol	Antioxidant and Antidiabetic. Antihyperglycemic	[66] [62]
6	<i>Catharanthus roseus</i>	Apocynaceae	Leaves	Dichloromethane	Antidiabetic and Antioxidant	[169]
7	<i>Centella asiatica</i>	Apiaceae	Whole plant	Ethanol	Antidiabetic	[85]
8	<i>Cichorium intybus</i>	Asteraceae	Root	Methanol and Ethanol	Antidiabetic	[170]
9	<i>Coccinia indica</i>	Cucurbitaceae	Fruits	Aqueous Ethanol Chloroform	Hypoglycemic	[171]
10	<i>Eugenia jambolana</i>	Myrtaceae	Seed	Ethanol, Ethyl acetate and Methanol	Antihyperlipidemic Antidiabetic	[114] [116]
11	<i>Gymnema sylvestre</i>	Asclepiadaceae	Callus and Leaves	Ethanol Aqueous	Antihyperglycemic Antidiabetic and Hypolipidemic	[68] [172]
12	<i>Momordica charantia</i>	Cucurbitaceae	Fruit	Ethanol	Antidiabetic	[135]
13	<i>Pergularia daemia</i>	Asclepiadaceae	Callus and Leaves	Ethanol	Antihyperlipidemic	[145]
14	<i>Phyllanthus niruri</i>	Euphorbiaceae	Leaves	Aqueous	Antioxidant and Antihyperglycemic	[156]
15	<i>Trigonella foenum graecum</i>	Menispermaceae	Seed	Ethanol	Antihyperglycemic	[173]

Pergularia daemia

Pergularia daemia belonging to family Asclepiadaceae is commonly known as Uttamani, and Vellipparuthi in Tamil. The plant is perennial slender, hispid, fetid smelling climber. It grows throughout the hotter parts of India. All parts of the plant are used for the treatment of various diseases and disorders such as rheumatic swelling [137], infantile diarrhoea [138], snakebite [139], antifertility [140], gastric ulcer [141], anaemia and piles [142], tooth ache [143], purgative [144]. The aqueous, methanol and ethanol extract of *Pergularia daemia* is found to possess antidiabetic activity in various animals. The biochemical parameter assessed has shown hypoglycemic activity in streptozotocin induced rats [145]. Glycosylated hemoglobin levels were significantly reduced after the administration of methanol and aqueous extract of *P. daemia* in alloxan induced diabetic rats [146]. The decreasing level of plasma triglycerides and cholesterol levels following the treatment with *P. daemia* extract may be due to their stimulating effect or insulin secretion, a decrease in serum protein content and a concomitant increase in protein levels of diabetic rats [147]. The methanol extract inhibits both the enzymes namely α -amylase and α -glucosidase very effectively, which showed a potent antidiabetic activity than the other extracts and the standard [148]. Decreased blood glucose levels were observed in *P. daemia* treated alloxan-induced diabetic mice [149].

Phyllanthus niruri

Phyllanthus niruri of family Euphorbiaceae is a small tropical herb which occurs widely as a rainy season weed in various

parts of India. Commonly known as kidney stone crusher and Keelanelli in Tamil, a small erect annual herb growing up to 30-40cm indigenous to tropical regions. The plant possess various activities such as antiviral [150], antimalarial [151], anticancer [152], and antioxidant [153] activities. The methanol, ethanol and aqueous extract of *P. niruri* have great potential as antidiabetic agent due to its ability to lower blood glucose and suppress postprandial risk, in the blood glucose level [154]. The plant extract exhibits antidiabetic activity by increasing serum insulin level in alloxan-treated rats [155]. The administration of *P. niruri* could reduce oxidative stress in the kidney via preventing the decrease in the activity level of indigenous antioxidant enzymes in streptozotocin-induced diabetic rats [156]. The possible mechanism may be the stimulation of β cells and subsequent release of insulin and activation of the insulin receptors by the extract maybe the reason for hypoglycemic activity of *P. niruri* [157]. The extracts of *P. niruri* exhibits hypoglycemic and antihyperglycemic effect in normoglycemic and diabetic rats, respectively and suppressed postprandial hyperglycemia in normoglycemic rats [158].

Trigonella foenum graecum

Trigonella foenum graecum L of family Leguminaceae is commonly known as Fenugreek and Vendhayam in Tamil. It acts as dietary fibers; one of the oldest traditional plants originates in India and Northern Africa, used medicinally as lactation stimulators [159]. High cholesterol inflammation and Gastrointestinal ailments [160], Immunomodulatory and anticarcinogenic [161]. Extract powder and gum of fenugreek

seeds and leaves possess antidiabetic and hypocholesterolemic properties ^[162]. Antidiabetic activity of fenugreek is attained by the presence of Saponins ^[159], Fenugreek administration inhibits the histopathological changes of the pancreas of alloxan-induced diabetes. Seed fiber of *Trigonella foenum graecum* reduces the level of glucose absorption and may also delay gastric emptying there by preventing the rise in blood sugar level following a meal ^[163]. The plant extract lowers blood glucose by increasing glycogenesis, inhibiting gluconeogenesis in the liver or inhibiting the absorption glucose from the intestine. Insulinotropic properties of *T.foenum graecum* seeds of hydroalcoholic extract showed improved glucose homeostatic along with effective glycerides control ^[164]. Quercetin, Diosgenin, Trigonelline, Galactomium and 4-hydroxy isoleucine, the constituents of fenugreek seeds have potential antidiabetic properties ^[165]. Administration of fenugreek seed extract brings the range of biochemical parameters almost normal in diabetic rats ^[166]. Compounds present in the extract are responsible for the regeneration of β cells affecting normal secretion of insulin ^[167].

Conclusion

Diabetes mellitus a metabolic syndrome characterized by defects in insulin action and insulin secretion is increased rapidly in developing countries like India. The disease related complications were increasing rapidly in spite of treatment with standard drugs. Plant medicines were traditionally used and they were less toxic with no side effects. The ability of the plant extracts was due to the capacity to restore the activity of pancreatic β -cells to secrete the insulin or decrease the intestinal absorption of glucose. Plants have been reported to possess secondary metabolites with antidiabetic potential. This review in-sighted the activity of various medicinal plants in managing diabetes mellitus in experimental animals. Hence, it is required to isolate and characterize the plant mediated compound with novel mode of mechanism to control and manage diabetes as the disease possesses many challenges.

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