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REVIEW

ANTIDIABETIC POTENTIAL OF MEDICINAL PLANTS

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Abstract: It is the fact that diabetes can't be cured and it has never been reported that someone had recovered totally from diabetes. The rapidly increasing incidence of diabetes mellitus is becoming a serious threat to mankind health in all parts of the world. Moreover, during the past few years some of the new bioactive drugs isolated from plants showed antidiabetic activity with more efficacy than oral hypoglycemic agents used in clinical therapy. The traditional medicine performed a good clinical practice and is showing a bright future in the therapy of diabetes mellitus. The present paper reviews natural medicines with their mechanism of action and their pharmacological test results. Many studies have confirmed the benefits of medicinal plants with hypoglycemic effects in the management of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. WHO has pointed out this prevention of diabetes and its complications is not only a major challenge for the future, but essential if health for all is to attain. Therefore, in recent years, considerable attention has been directed towards identification of plants with antidiabetic ability that may be used for human consumption. Further, it emphasizes strongly in this regard the optional and rational uses of traditional and natural indigenous medicines.

Keywords: diabetes mellitus, medicinal plants and WHO

Diabetes mellitus is a group of metabolic disorders with one common manifestation – hyperglycemia (1, 2). Chronic hyperglycemia causes damage to eyes, kidneys, nerves, heart and blood vessels (3). It is caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. It results either from inadequate secretion of hormone insulin, an inadequate response of target cells to insulin, or a combination of these factors. This disease requires medical diagnosis, treatment and changes in life style. It is projected to become one of the world's main disablers and killers within the next 25 years. The management of diabetes is a global problem until now and successful treatment is not yet discovered. There are many synthetic medicines developed for patients, but it is the fact that it has never been reported that someone had recovered totally from diabetes (4). The modern oral hypoglycemic agents produce undesirable and side effects. Thus, alternative therapy is required, a need of hour is to shift towards the different indigenous plant and herbal formulations (5). The traditional medicines demonstrated a bright future in therapy of diabetes and to understand the importance of traditional herbs, the aim of the review is to collect the available data on plants with antidiabetic activity reported in the pharmaceutical journals.

NATURAL MEDICINES USED FOR DIABETES THERAPY

Recently, some medicinal plants have been reported to be useful in diabetes worldwide and have been used empirically as antidiabetic and antihyperlipidemic remedies. Despite the presence of known antidiabetic medicine in the pharmaceutical market, diabetes and the related complications continued to be a major medical problem. Antihyperglycemic effects of these plants are attributed to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances

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which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, cartenoids, etc., that are frequently implicated as having antidiabetic effect. Species will be described in alphabetical order and information about each species will include in sequence: general botanical and taxonomic data, distribution in the world, experimental study and mechanism of action.

***Anacardium occidentale* Linn. (Anacardiaceae),** herb originated from Brazil, it is used as folk medicine in African countries, mainly in Cameroon, for the treatment of diabetes mellitus. Hypoglycemic and protective role of *A. occidentale* was reported (6, 7). The antihyperglycemic and renal protective activities of leaves of this herb were reported in streptozotocin induced diabetic rats. It reduces diabetes-induced functional and histological alterations in the kidneys. It was shown that histopathological study of *A. occidentale* significantly reduced accumulation of mucopolysaccharides in the kidneys of diabetic animal (8).

***Annona squamosa* Linn. (Annonaceae),** commonly called custard apple in English and sharifa in Hindi. It is cultivated throughout India. The pharmacological active ingredients are present in seeds, leaves and aerial parts of the plant (9). The research reveals that the plant possesses both hypoglycemic and antidiabetic activity. It acts by enhancing insulin level from the pancreatic islets, increases utilization of glucose in muscle and inhibits the glucose output from liver. Its margin of safety is high. The extract obtained from leaves of this plant is useful in maintaining healthy blood sugar and cholesterol levels (10).

***Annona muricata* Linn. (Annonaceae),** commonly called soursop. It is small evergreen tree growing 5 to 6 meters in height. Young branches are rusty-hairy, the malodorous leaves, and the plant is evergreen. *Annona muricata* is indigenous to most of the warmest tropical areas in South and North America, including the Amazon. The researchers revealed the immunohistochemical and biochemical effects of aqueous extract of leaves on pancreatic β cells of STZ (streptozotocin) treated diabetic rats. *A. muricata* Linn. leaf extract played important role in reduction of oxidative stress on pancreatic β cells of streptozotocin treated diabetic rats. The treatment increased the area of insulin immunoreactive β-cells and partially prevents degeneration of β-cells (11).

***Boerhaavia diffusa* Linn. (Nyctaginaceae)**, distributed widely all over in India, is a small perennial creeping herb, commonly known as "Red hogweed". The root and the whole plant are used as an Ayurvedic medicine in India and Unani medicine for the treatment of diabetes, stress, dyspepsia, abdominal pain, inflammation, jaundice, enlargement of spleen, congestive heart failure and bacterial infections (12-14). Aqueous leaf extract of the plant has been studied for its antidiabetic effect in alloxan-induced diabetic rats (15, 16). The antidiabetic activity of the chloroform extract of the plant leaves on chronic treatment of streptozotocin-induced NIDDM (non insulin dependent diabetes mellitus) model diabetic rats was evaluated and the herb possesses antidiabetic activity. The herb mainly acts by reducing blood glucose level and increasing insulin sensitivity (17).

***Bougainvillea spectabilis* Linn. (Nyctaginaceae),** is a very familiar ornamental plant commonly grown in Indian gardens. *Bougainvillea* is a genus of flowering plants native to South America from Brazil west to Peru and south to southern Argentina. The traditional plant has the antidiabetic potential. The blood glucose lowering potential of *Bougainvillea spectabilis* Willd leaf extract in streptozotocin-induced type I diabetic albino rats was reported. The ethanolic extract of the leaves has antihyperglycemic activity probably due to increased uptake of glucose by enhanced glycogenesis in the liver and also due to increase in insulin sensitivity (18).

***Bridelia ndellensis* Beille. (Euphorbiaceae),** a medicinal plant used in Cameroon against diabetes. The water and methanol extract of leaf of allied species B. ferruginea has been proved as an active hypoglycemic agent in alloxan induced diabetic rats (19). The study of the glucose lowering of the ethanol extract and fractions of B. ndellensis stem bark in STZ (streptozotocin) type I and II diabetes rats at different prandial states was performed and significant lowering in blood glucose level was observed. The extract act by stimulation of islets cells and requires functional β-cells for its action (20).

***Canavalia ensiformis* DC. (Leguminosae),** known as horse bean, native of Central America and West Indices has been widely cultivated in humid tropics of Africa and Asia. The seeds have been reported to possess antihypercholesterolemic (21) and hypoglycemic activities (22). The effect of aqueous

extract of *C. ensiformis* seeds on hyperlipidemia and hyperketonemia in alloxan-induced diabetic rats proved it as active antidiabetic herb. The oral administration of aqueous extract of *C.ensiformis* seeds reduce urinary and blood glucose levels, and also elevated levels of triacylglycerol, ketone bodies and cholesterol associated with diabetes mellitus (23).

Casearia esculenta **Roxb. (Flacourtiaceae),** is a plant with medicinal properties known as wild cowrie fruit in English. The plant is in the form of shrub distributed in South India. *C. esculenta* has been a remedy which is popular for diabetes mellitus (24-26). It has been reported that plant contains hypoglycemic effect (27). *C. esculenta* root extract contain hypoglycemic factors, which reduced blood sugar level in experimental animals. *C. esculenta* root extract has influence on protein metabolism and marker enzymes in streptozotocin-induced diabetic rats. The study revealed that *C. esculenta* root extract has the antihyperglycemic effect and it may elevate liver and renal damage associated with streptozotocin-induced diabetes in rats (28).

Cassia kleinii **Wight & Arn. (Caesalpiniaceae),** is the medical remedy for the folk diabetic practitioners in South India. The traditional systems like Ayurveda and Siddha systems don't use this plant. The alcoholic extracts of leaves seem to show promising results for the development of phytomedicines by exhibiting the antihyperglycemic activity on glucose feed hyperglycemic and alloxan-induced diabetic rats. The leaf extract of *Cassia kleinii* may not act by potentiation of insulin but it could be used in insulin independent diabetes because drug exhibited antihyperglycemic effect but not hypoglycemic effect in fasted rats. The action of drug may be mimicking some or all of the action of insulin on the metabolism of glucose (29).

Catharanthus roseus **Linn. (Apocyaceae),** commonly used as an anticancer agent, but the hot water decoction of the leaves and or the whole plant is used for the treatment of diabetes in subtropical and tropical areas of the world (30). The reports indicate blood glucose lowering activity in the alcoholic extract of the leaves of *C. roseus* .The herb have prophylactic activity against the necrotic actions of alloxan monohydrate (31-33). Antidiabetic activity of dichloromethane-methanol extract of the leaves and twigs was evaluated and its effect on enzymes of carbohydrate metabolism was studied. The mechanism may be due to enhanced secretion of insulin. The other researchers revealed that extract may be helpful in the prevention of damage caused by oxygen free radicals and increase in glucose utilization (34).

Coccinia indica **Wight & Arn. (Cucurbitaceae),** widely used in traditional treatment of diabetes mellitus in sub-Saharan Africa and Southeast Asia. Pectin isolated from the fruits of *C. indica* has hypoglycemic activity (35). Alcoholic extract of plant was found to be active in reducing blood glucose level, then this extract was subjected to further fractionation to evaluate its biochemical parameters effecting diabetes and results suggested toluene as an active fraction. The exact action of these principles may be due to their β-cell restorative properties against alloxan induced damage (36).

Cocculus hirsutus **Linn. (Menispermaceae),** roots are bitter, acrid, laxative, demulcent and antiperiodic in fever, tonic and diuretic, also known as patalagarudi. The plant grows all over India, especially in dry regions. It is a straggling shrub, with softly villous young parts and resembles the plant path. Badole et al. have demonstrated the antihyperglycemic activity of aqueous extract of leaves of *Cocculus hirsutus* (L) Diels in alloxan-induced diabetic mice. The antihyperglycemic potential of aqueous extract of *C. hirsutus* may be due to lowering of serum glucose level in diabetic mice and increased glucose tolerance. Additionally, the extract prevents loss of body weight (37).

Coscinium fenestratum **Colebr. (Menispermaceae),** commonly known as tree in Western Ghats (India) and Sri Lanka. The plant has been mainly used for diabetes mellitus in the traditional, Ayurvedic and Siddha systems of medicine. Alcoholic stem extract of this plant regulates metabolism and improves antioxidant status in streptozotocin, nicotinamide-induced diabetic rats. The alcoholic extract regulates glucose homeostasis and decreased gluconeogenesis by *C. fenestratum*. The drug also has protective action on cellular antioxidant defense (38).

Dioscorea dumetorum **Pax. (Dioscoreaceae),** used in treatment of diabetes in traditional medicine, possesses hypoglycemic effect. *D. dumetorum* Pax. is commonly known as bitter yam. It occurs in Africa. An alkaloid present in an extract, dioscoretine, has been reported to possess hypoglycemic effect (39). It has been reported that aqueous extract of *D. dumetorum* tuber control hyperlipidemia, hypercholesterolemia and hyperketonemia. The herb mainly act

as an active hypoglycemic agent and works on the complications of diabetes (40).

***Ficus hispida* Linn. (Moraceae),** also known as Daduri for the treatment of diabetes. This small tree may be found throughout India. Different workers have reported for the hypoglycemic effects of different compounds obtained from *F. bengalensis* (41-43). The hypoglycemic activity of *F. bengalensis* Linn. (bark) in normal and diabetic albino rats concluded that the water-soluble fraction of the alcoholic extract of *Ficus hispida* significantly decreases fasting blood glucose levels in normal and alloxan-induced diabetic rats. The extract has direct peripheral action on β cells but drug interaction can occur between *Ficus hispida* bark extract and insulin if given together (44).

***Hypoxis hemerocallidea* Fisch. Mey. (Hypoxidaceae),** it is tuberous perennial plant which was previously known as *H. rooperi*. It is called wonder plant in South Africa and has been reported to be an effective remedy for the adult onset diabetes mellitus (45). The methanolic extract of *H. hemerocallidea* was reported for its hypoglycemic effect in normoglycemic and in streptozotocin-induced diabetic rats, the herb can be used as hypoglycemic agent and it has property to cure the adult onset diabetes mellitus (46). The action of the herbal plant material is not yet clear.

***Murraya koenigii* Linn. (Rutaceae),** is commonly known as Curry patta and is widely used condiment and spice in India. In normal and alloxan diabetes the aqueous extract of the leaves of *M. koenigii* produced hypoglycemic effect (47). Oral feeding of this plant for 60 days diet to normal rats showed an increase in the concentration of hepatic glycogen due to hypoglycemic activity (48). It has been reported that feeding different doses of *M. koenigii* leaves to diabetic rats play a role in control of mild diabetic rats to moderate, severe and type I diabetes (49). It suppresses blood glucose level and was found to have beneficial effect on carbohydrate metabolism (50).

***Panax ginseng* Linn. (Asian ginseng, Araliaceae),** root has been used clinically in the treatment of type II diabetes throughout Asian countries. Historical records revealed that *P. ginseng* has been used clinically to treat type II diabetes. *In vitro* and *in vivo* animal studies and clinical trials support the claim that the roots of this plant possess antihyperglycemic activity. The ginsenoside play important role in antihyperglycemic action and other constituents has distinct pharmacological effect on energy metabolism (51).

***Syzyguim cumini* Linn. (Formerly *Eugenia jambolana,* Myrtaceae),** with putative antihyperglycemic effects. Many parts of the plant, like fruit, seeds, bark and tea prepared from the leaves, have been used in treatment of diabetes throughout Asian countries. (52, 53). Antihyperglycemic effect has been reported in leaves (54), seeds (55) fruits (56), and bark (57), but researchers failed to identify any blood glucose lowering effect with extracts or tea prepared from leaves of plant in normal rats and in rats with STZ-induced diabetes mellitus, and in normal volunteers. Tea prepared from leaves of *S. cumini* has no hypoglycemic effect but, as its mechanism of action could depend on specific abnormalities with the disease, the effect in diabetes is still possible (58).

***Terminalia chebula* Retz. (Combretaceae),** has been widely used in diabetes in Ayurveda and is widely distributed in India. An herbal formulation containing *T. chebula* named TRIPHALA is traditional medicine for the treatment of diabetes. Antidiabetic and renoprotective effects of the chloroform extract of *T. chebula* Retz seeds in streptozotocin-induced diabetic rats was proved. It has potent renoprotective action (59).

***Terminalia catappa* Linn. (Combretaceae)**, is found throughout the warmer parts of India and called an Indian almond. The antidiabetic potential of petroleum ether, methanol and aqueous extract of *T. catappa* fruits on fasting blood sugar levels and serum biochemical analysis in alloxan-induced diabetic rats was performed. All the three extracts produced a significant antidiabetic activity at dose levels of 1/5 of their lethal doses.

The extract may act by β-cells regeneration. The effect may be due to β-carotine in reducing diabetic complications like glycosylation in alloxan-induced diabetic rats (60).

CONCLUSION

Diabetes mellitus is a syndrome, initially characterized by loss of glucose homeostasis resulting from defects in insulin secretion, insulin action both resulting in impaired metabolism of glucose and other energy-yielding fuels such as lipids and proteins (61). Currently, many countries face large increases in the number of people suffering from

diabetes. The World Health Organization estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. It is estimated that the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years (62).

Experimental diabetes in animals has provided considerable insight into the physiological and biochemical derangement of the diabetic state. Many of these derangements have been characterized in hyperglycemic animals. Significant changes in structure and lipid metabolism occur in diabetes. In these cases the structural changes are clearly oxidative in nature and are associated with development of vascular disease in diabetes. In diabetes, increased lipid peroxidation is also associated with hyperlipidemia. The liver, an insulin dependent tissue that plays a vital role in glucose and lipid homeostasis, is severely affected during diabetes. The liver and kidney participate in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids and triglycerides. During diabetes, a profound alteration in the concentration and composition of lipids occurs. Despite the great strides that have been made in the understanding and management of diabetes, the disease and disease related complications are increasing unabated (63). In spite of the presence of known antidiabetic medicine in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease. Many traditional plant treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic ones. Based on the WHO recommendations, hypoglycemic agents of plant origin used in traditional medicine are important. The attributed antihyperglycemic effects of these plants are due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or a decrease in the intestinal absorption of glucose. Hence, treatment with herbal drugs has an effect on protecting β-cells and smoothing out fluctuation in glucose levels. In general, there is very little biological knowledge on the specific modes of action in the treatment of diabetes, but most of the plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavonoids etc. that are frequently implicated as having antidiabetic effects. The research for alternate remedies (from the plant kingdom) for diabetes mellitus will continue all over the world as the disease poses many challenges not only to the physician but also to the researcher.

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