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Review Article

Herbal Medicines Used in Diabetes Mellitus

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Diabetes mellitus is one of the world's major diseases. It currently affects an estimated 143 million people worldwide and the number is growing rapidly. In the India, about 1- 5% population suffer from diabetes or related complication. Plant-based medicinal products have been known since ancient times, and several medicinal plants and their products (active natural principles and crude extracts) have been used to control diabetes in the traditional medicinal systems of many cultures worldwide. Several medicinal plants have found potential use as hypoglycemic in the Indian system of medicines. Several oral hypoglycaemic agents are the primary forms of treatment for diabetes. However, prominent side-effects of such drugs are the main reason for an increasing number of people seeking alternative therapies that may have less severe or no side effects. In this review, we present the profile of plants commonly used in India in the treatment of diabetes, reported in literature. A total of 45,000 plant species have records of a popular use in the treatment of this syndrome in India. The profile presented includes information about scientific name, family, species, methodology used, the degree of hypoglycaemic activity and the active agents. Indian plants which are most effective and the most commonly studied in relation to diabetes and their complications are: *Allium cepa, Allium sativum, Aloe vera, Beta vulgaris, Catharanthus roseus, Azadirachta indica, Gymnema sylvestre, Ipomoea batatas, Momordica cymbalaria,Momordica charantia, Ocimum sanctum, Pterocarpus marsupium, Swertia chirayita, Tinospora cordifolia, and Trigonella foenum graecum.* All plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity with different mechanism of action.

Keywords: Diabetes mellitus, Hypoglycemic, Anti-hyperglycemic, Oral hypoglycaemic agents, Complications

INTRODUCTION

Diabetes mellitus is a common and very prevalent disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin[1].

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Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations. The herbal drugs with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine [2]. The plants provide a potential

source of hypoglycemic drugs because many plants and plant derived compounds have been used in the treatment of diabetes. Many Indian plants have been investigated for their beneficial use in different types of diabetes and reports occur in numerous scientific journals. Ayurveda and other traditional medicinal system for the treatment of diabetes describe a number of plants used as herbal drugs. Hence, they play an important role as alternative medicine due to less side effects and low cost. The active principles present in medicinal plants have been reported to possess pancreatic beta cells re-generating, insulin releasing and fighting the problem of insulin resistance [3]. Hyperglycemia is involved in the etiology of development of diabetic complications. Hypoglycemic herbs increase insulin secretion, enhance glucose uptake by adipose or muscle tissues and inhibit glucose absorption from intestine and glucose production from liver [4]. Insulin and oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in the management but there is quest for the development of more effective anti-diabetic agents.

Mechanism involve in treatment of diabetes

The present treatment of diabetes is focused on controlling and lowering blood glucose to a normal level. The mechanisms of the Medicines to lower blood glucose are:

- To stimulate cell of pancreatic islet to release insulin;
- To resist the hormones which rise blood glucose;
- To increase the number or rise the appetency and sensitivity of insulin receptor site to insulin;
- To decrease the leading-out of glycogen;
- To enhance the use of glucose in the tissue and organ;
- To clear away free radicals, resist lipid per oxidation and correct the metabolic disorder of lipid and protein;
- To improve microcirculation in the body.

Anti-diabetic medicinal plants undoubtedly have significant effect on the lowering of blood sugar but their mechanism of action is yet to be elucidated. The first evidence that the natural products have insulin potentiating activity was reported in 1929 by Glazer and Halpern. There are several mechanisms through which these herbs act to control the glucose level. They are more or less similar actions to the synthetic drugs. The mechanism of action of herbal anti-diabetics could be grouped as:

- Stimulation of insulin secretion

(*Teucrium polium, Allium sativum, Allium cepa, Panax ginseng*)

- Inhibition in renal glucose reabsorption (*Fraxinus excelsior*)
- Stimulation of glycogenesis and hepatic glycolysis (*Momordica charantia*)
- Protective effect on the destruction of the beta-cells (*Thea sinensis*)
- Improvement of digestion and reduction of blood sugar and urea (*Aegle marmelos*)
- Prevents pathological conversion of starch to glucose (*Eugenia jambolina, Pterocarpus marsupium*)
- Increasing the use of glucose by tissues and effect on adrenergic receptors (*Panax ginseng, Allium sativum, Allium cepa*)
- Potentiates the action of exogenously injected insulin
- Cortisol lowering activities (*Boerhaavia diffusa, Ocimum sanctum*)

Wide range of plant constituents could have different site of action within the body and herbs exert similar mechanism of action like synthetic oral hypoglycemic drugs. Many of these herbs may have a direct or an indirect impact on blood glucose levels, thus interfering with the clinical management of diabetic patients. The above mentioned plants have been considered for possible hypoglycemic actions and some preliminary investigations have been carried out by the researchers. Scientific studies available on a good number of medicinal plants indicate that promising phytochemicals can be developed for diabetes too. However, there are numerous other plants which are mentioned in the indigenous systems of health care but still await scientific inquiry. There are many grey areas, which need substantial amount of work in the case of herbal antidiabetics. For a given dose of herbal medicine, its physiological effect will be governed by the effective tissue concentration of the remedy, which in turn is determined by pharmacokinetic parameters, absorption, distribution, metabolism and excretion of its various components. Only knowledge of herbal pharmacokinetics can provide valuable information to practitioners in prescribing herbs safely and effectively. Much more work should be done in this direction to make the herbs useful [5].

Indian medicinal plants with hypoglycemic activity

India has an officially recorded list of 45,000 plant species and a various estimation of 7500 species of medicinal importance [6]. India has a rich history of using various potent herbs and herbal components for treating diabetes. Many Indian plants have been investigated for

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Table 1:List of plants have Anti-diabetic activity

Common name	Botanical Name	Part Used	Family	Uses
Methi	*Trigonella foenum-gracecum*	Seeds	Fabaceae	Antidiabetic
Fern	*Nephoelepsis tuberose*	bulb	Oleandraceae	Antidiabetic
Keukand	*Costus specious*	rhizome	Costaceae	Antidiabetic
Indian wheat	*Plantago ovate*	husk	Plantaginaceae	Antidiabetic
Garlic	*Allium sativum*	bulb	Alliaceae	Antidiabetic
Indian Sarsaparilla	*Hemidesmus indicus*	root	Asclepiadaceae	Antidiabetic
Onion	*Allium cepa*	bulb	Liliaceae	Antidiabetic
Pinyn	*Acontium carmichaeii*	Root	Ranunculaceae	Antidiabetic
Chilli pepper	*Capsicum annum*	Fruit	Solanaceae	Antidiabetic
Goat's rue	*Galega officinalis*	Seed	Fabaceae	Antidiabetic
Lingzhi mushroom	*Gandoderma lucidium*	Fruit	Ganodermataceae	Antidiabetic
Sea pea	*Lathyrus japonica*	Seed	Fabaceae	Antidiabetic
Rice	*Oriza sativum*	Root	Poaceae	Antidiabetic
Guduchi	*Tinospora cardifolia*	Plant	Menispermaceae	Antidiabetic
Bitter gourd	*Momordica charantia*	fruit	Cucurbitaceae	Antidiabetic
Indian Kino Tree	*Pterocarpus marsupium*	bark	Fabaceae	Antidiabetic
Ginger	*Zingiber officinale*	rhizome	Zingiberaceae	Antidiabetic
Gowar plant	*Cyamospsis tetragonolobus*	Fruit	Fabaceae	Antidiabetic
Phalsa	*Grewia asiatica*	Fruit	Malvaceae	Antidiabetic
Indian Gum Arabic	*Acacia Arabica*	seeds	Leguminosae	Antidiabetic
Holy Fruit Tree	*Aegle marmelos*	Root bark	Rutaceae	Antidiabetic
Aloe	*Aloe vera*	Leaf pulp extract	Aloaceae	Antidiabetic
Davana	*Artemisia pallens*	aerial parts	Compositae	Antidiabetic
Sugar apple	*Annona squamosa*	leaf extract	Annonaceae	Antidiabetic
King of Bitter	*Andrographis paniculata*	plant extract	Acanthaceae	Antidiabetic
Neem	*Azadirachta indica*	plant extract	Meliaceae	Antidiabetic
Life Plant	*Biophytum sensitivum*	plant leaf extract	Oxalidaceae	Antidiabetic
Tar vine	*Boerhavia diffusa*	aqueous leaf extract	Nyctaginaceae	Antidiabetic
Tanner's Cassia	*Cassia auriculata*	flower extract	Leguminosae	Antidiabetic
Ivy gourd	*Coccinia indica*	Leaf extract	Cucurbitaceae	Antidiabetic
Carilla Fruit	*Casearia esculenta*	Root extract	Flacourtiaceae	Antidiabetic
Madagascarperi winkle	*Catharanthus roseus*	leaf extract	Apocynaceae	Antidiabetic
Green tea	*Camellia sinensis*	leaf extract	Theaceae	Antidiabetic

their beneficial use in different types of diabetes and reported in numerous scientific journals. This article highlight on the chemo profiles from Indian biosphere for treating diabetes with major thrust on the dosage and possible mode of action of the herbal hypoglycemic so far reported. Various Indian medicinal plants of different families having potent hypoglycemic activity are described in Table 1

Medicinal Plants With Antidiabetic And Related Beneficial Properties

Various Indian medicinal plants of different families having potent hypoglycemic activity are described in the following section.

***Andrographis paniculata* Burm. (Acanthaceae)**

It is a herbaceous plant native to India, Sri Lanka and widely cultivated in southern Asia. Oral administration of andrographis significantly increases the activity of SOD and Catalase. Also decreases blood glucose levels due to its antioxidant properties [7]. The ethanolic extract of *A. paniculata* possesses antidiabetic property and may be attributed at least in part to increase glucose metabolism. Its hypotriglyceridemic effect is also beneficial in the diabetic state [8].

***Annona squamosa* L (Annonaceae)**

It is a small well-branched tree or shrub, grows at lower altitudes. Administration of 15 mg/kg/day of isolated juercetin-3-O-glucoside from *Annona squamosa* leaves for 10 consecutive days to the hyperglycemic animals reverse these effects and simultaneously inhibits the activity of hepatic GIucose-6-phosphatase. It further decreases the hepatic and renal lipid peroxidation with a concomitant increase in the activities of antioxidative enzymes, such as Catalase and Superoxide dismutase as well as glutathione content, indicating its safe and antiperoxidative effects [9].

***Catharanthus roseus* (L)G.Don.(Apocynaceae)**

Oral administration at dose-dependent of 0.5, 0.75 and 1.0 ml/kg body weight reduced the blood glucose of both normal and diabetic rabbits comparable with that of the standard drug, glibenclamide. The results indicate a prolonged action in reduction of blood glucose by *C. roseus* and the mode of action of the active compound(s) is probably mediated through enhance secretion of insulin from the betacells of Langerhans or through extra pancreatic mechanism[10].

***Acacia arabica* (Lam) Wild. (Mimosaceae)**

It is found all over India. The plant extract acts as an antidiabetic agent by acting as secretagouge to release insulin. It induces

hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of *A. arabica* when administered (2, 3 and 4 g/kg body weight) to normal rabbits, induces hypoglycemic effect by initiating release of insulin from pancreatic beta cells [11].

***Allium cepa* L. (onion): (Liliaceae)**

Allium cepa is known only in cultivation but related wild species occur in Central Asia. Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. *A.cepa* also known to have antioxidant and hypolipidemic activity. Administration of a sulfur containing amino acid, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues. It normalizes the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase [12, 13]. When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels [14].

***Allium sativum* L. (garlic): (Liliaceae)**

It is a perennial herb cultivated throughout India. Oral administration of the garlic extract significantly decreases serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT levels, while increases serum insulin in diabetic rats but not in normal rats when compared with antidiabetic drug glibenclamide. The antidiabetic effect of the extract was more effective than glibenclamide. It is concluded that the plant must be considered as excellent candidate for future studies on diabetes mellitus [15].

***Aloe barbadensis* Mill.(Liliaceae)**

The species has been widely cultivated throughout the world. Treatment of chronic but no single dose of exudates of *Aloe barbadensis* leaves shows hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also show hypoglycemic effect in diabetic rats. This action is through stimulation of synthesis and/or release of insulin from pancreatic beta cells [16].

***Aloe vera* (L) Burm.(Asphodelaceae)**

It grows in arid climates and is widely distributed in Africa, India and other arid areas. *Aloe vera* gel at 200 mg/kg possesses significant antidiabetic, cardioprotective activity, reduces the increased TBARS, maintains the Superoxide dismutase and Catalase activity up to the normal level and increases reduced glutathione by four times in diabetic rats. [17] The leaf pulp extract showed hypoglycemic activity on

IDDM and NIDDM rats, the effectiveness being enhanced for type II diabetes in comparison with glibenclamide [18].

***Azadirachta-indica* A. Juss. (Meliaceae)**

Commonly known as Neem. It is a tree native to India, Burma, Bangladesh, Sri Lanka, Malaysia and Pakistan, growing in tropical and semi-tropical regions. A low (0.5g tid) and high (2g tid) doses of powdered part, aqueous extract and alcoholic extract of *A. indica* shows significant hypoglycemic activity in high dose and can be successfully combined with oral hypoglycemic agents in type-2 diabetic patients whose diabetes is not controlled by these agents [19].

***Biophytum sensitivum* (L) DC. (Oxalidaceae)**

The annual perennial herbaceous plant is a traditional medicine in Nepal. Initial dose-response studies shows a dose of 200 mg/kg body weight is optimum for hypoglycemia. In 16-h fasted non-diabetic rabbits, a single administration brings about a 16.1% fall in fasting plasma glucose at the end of 1 and 2 h, and the hypoglycemic effect persists at the end of 6 h (13.8% fall). Serum insulin levels shows a significant rise in the treated animals, which suggests a pancreatic mode of action (i.e. insulinotropic effect), suggesting that the hypoglycemic response of *B. sensitivum* may be mediated through stimulating the synthesis/release of insulin from the beta cells of Langerhans [20].

***Cassia auriculata* L.(Caesalpinaceae)**

It occurs in the dry regions of India and Sri Lanka. Oral administration of CLEt- to mildly diabetic (MD) and severely diabetic (SD) rats at a dose of 400 mg/kg once a day for 15 days shows significant reduction in fasting blood glucose, also enhances the activity of hepatic hexokinase, phosphofructokinase, suppresses glucose-6-phosphatase and fructose-l,6-bisphosphatase in both MD and SD rats. Histopathological examination of pancreatic sections reveals increased number of islets and beta-cells in CLEt-treated MD as well as SD rats [21].

***Catharanthus roseus* (L)G.Don. (Apocynaceae)**

Oral administration at dose-dependent of 0.5, 0.75 and 1.0 ml/kg body weight reduced the blood glucose of both normal and diabetic rabbits comparable with that of the standard drug, glibenclamide. The results indicate a prolonged action in reduction of blood glucose by *C. roseus* and the mode of action of the active compound(s) is probably mediated through enhance secretion of insulin from the betacells of Langerhans or through extra pancreatic mechanism [22].

***Cyamopsis tetragonoloba* (L) Taubert. (Papilionaceae)**

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The species are distributed across Africa, Asia and the Pacific. The aqueous extract of beans at 250 mg/kg body wt. significantly lowers blood glucose levels in alloxan-induced diabetic rats within 3 h of administration. Continuation for 10 days produces statistically significant reduction in the blood glucose levels while shows marginal activity is in normal and glucose-loaded rats [23].

***Emblica officinalis* Gaertn. (Euphorbiaceae)**

Different solvent extracts of *E. officinalis* acts as α-amylase and α-glucosidase inhibitor. Significant antiglycation activity also confirms the therapeutic potential of these extracts against diabetes. Methanol extracts significantly inhibits the oxidation of LDL under in vitro conditions [24].

***Pterocarpus marsupium* Roxb. (Papilionaceae)**

It is widely used in 'Ayurveda' as 'Rasayana' for management of various metabolic disorders. An aqueous extract of *P. marsupium* wood, at an oral dose of 250 mg/kg, shows statistically significant hypoglycemic activity [25]. Marsupin, pterosupin and Iiquiritigenin obtained from this plant show antihyperlipidemic activity [26]. (-)Epicatechin, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin in vitro. Like insulin, (-)epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dosedependent manner [27].

***Trigonella foenum* graecum L. (Papilionaceae)**

Used both as an herb (the leaves) and as a spice (the seed) and cultivated worldwide as a semi-arid crop. Oral administration of 2 and 8 g/kg of plant extract produces dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats [28]. Administration of fenugreek seeds improves glucose metabolism and normalizes creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduces hepatic and renal glucose-6-phosphalase and fructose -1, 6-biphosphatase activity [29].

CONCLUSION

Diabetes is a disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Herbal treatments for diabetes have been used in patients with insulin-dependent and non-insulin-dependent diabetes, diabetic retinopathy, diabetic peripheral neuropathy, etc. Scientific validation of several Indian plant species has proved the efficacy of the botanicals in reducing the sugar level. From the reports on their

potential effectiveness against diabetes, it is assumed that the botanicals have a major role to play in the management of diabetes, which needs further exploration for necessary development of drugs and nutraceuticals from natural resources. However lack of scientific and experimental evidence about effective constituents, toxicity, pharmacokinetics, effectiveness and efficacy resulted in deficiency of belief in effectiveness, quality and safety of herbal medicines. The need for adequate standards of herbal preparations to ensure quality, safety and efficacy has been highlighted since the use of herbal medicines and phytotherapies. This requires biological testing of plant extracts, isolation of bioactive components, as well as toxicological, pharmacodynamical and, ultimately, clinical studies. For Indian medicinal preparations, which are made from plant extracts, and often considered to be effective due to a mixture of active ingredients rather than a single constituent, standardization is difficult, furthermore, possible to lose active principles. However, the standardization is an absolute requirement. It is a significant work to isolate active components of Indian medicinal plants with confirmed hypoglycemic activity, to explain their pharmacological mechanism, and lastly, develop normalized Chinese medicinal preparations for anti diabetes and it complications.

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