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MEDICINAL PLANTS FOR TREATMENT OF DIABETES MELLITUS

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ABSTRACT

Many plants have been used for the treatment of diabetes mellitus in Indian system of medicine and in other ancient systems of the world. Out of these only a few have been evaluated as per modern system of medicine. From many such plants only extracts have been prepared and their usefulness evaluated in experimental diabetes in animals. In some plants like *Allium cepa, Allium sativum, Ficus bengalensis, Gymnema sylvestre, Pterocarpus marsupium* etc. active hypoglycemic principles have been isolated and their mechanism of action studied. Most of them seem to act directly on pancreas (pancreatic effect) and stimulate insulin level in blood. Some have extra pancreatic effect also by acting directly on tissues like liver, muscle etc. and alter favourably the activities of the regulatory enzymes of glycolysis, gluconeogenesis and other pathways. Since the plant products have less side effects, they have the potential as good hypoglycemic drugs. They may also provide clues for the development of new and better oral drugs for diabetes.

KEY WORDS: Medicinal plants, Hypoglycemic agents, Diabetes mellitus

Plants have been the major source of drugs in Indian system of medicine and other ancient systems in the world. Earliest description of curative properties of medicinal plants is found in Rigveda (2500 - 1800 BC). Charaka Samhita and Sushruta Samhita give extensive description on various medicinal herbs (1). Information on medicinal plants in India has been systematically organized (1-4). The World Health Organization expert committee on diabetes has listed as one of its recommendations that traditional methods of treatment of diabetes should be further investigated (5).

Out of the two types of diabetes, the incidence of non insulin dependent diabetes mellitus (NIDDM) is much higher than the insulin dependent diabetes mellitus (IDDM). Sulphonyl ureas and few biaguanides are valuable treatment for hyperglycemia in NIDDM, but they are unable to lower glucose concentration to within normal range and reinstate a normal pattern of glucose homeostasis permanently. Use of these therapies is restricted by their pharmacokinetic properties, secondary failure rates and accompanying side effects (6).

Even insulin therapy does not reinstate a permanent normal pattern of glucose homeostasis, and carries an increased risk of atherogenesis and hypoglycemia. Medicinal plants have the advantage of having no or only few side effects. Some of them are being used in traditional systems of medicine from hundreds of years in many countries of the world. Till today metformin is the only ethical drug approved for the treatment of NIDDM patients which is derived from a medicinal plant *Galega officinalis* historically used for treatment of diabetes in medieval Europe (7). There are many antidiabetic plants which might provide useful sources for the development of drugs which can be used in the treatment of diabetes mellitus. The literature on medicinal plants with hypoglycaemic activity is vast. Since it is difficult to include all such plants in this small review, a few commonly used plants have been covered here.

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PLANTS WITH WELL OR PARTIALLY CHARACTERIZED ANTIDIABETIC PROPERTIES

Raw onion bulb (*Allium cepa*) and cloves of garlic (*Allium sativum*) have long been used as dietary supplement for traditional treatment of diabetes. Former is used as stimulant, diuretic and expectorant (3). Concentrated extract of onion bulbs exerted a week hypoglycemic action in healthy and alloxan diabetic animals (8). Recently S-methyl cysteine sulphoxide (SMCS), a sulphur containing amino acid isolated from onion was shown to have antidiabetic and antihyperlipidemic effect when given at a dose of 200 mg/kg body weight (bw)/day for a period of 45 days to alloxan diabetic rats. Effects were comparable to those of glibenclamide and insulin (9a). Garlic contains many sulphur containing compounds mainly in the form of cysteine derivatives viz. S-alkyl cysteine sulphoxides which decompose into a variety of thiosulfinates and polysulfides by the action of enzyme allinase on extraction. Decomposed products are volatile and are present in the oil of garlic. They possess antidiabetic, hypocholesterolemic, fibrinolytic and various other biological actions (9a). An ether soluble substance 'allicin' was isolated from garlic. An increase in the serum insulin release, an improvement in GTT and increased liver glycogen were shown to be allied actions of allicin (9b). Recently hypoglycemic effects of garlic and onion were compared with that of tolbutamide in rabbits. Both have shown significant fall in hyperglycemic peak (10) in mild diabetic rabbits.

From *Anemarrhena asfoetida* four compounds were isolated Anemarans A, B, C and D glycans. Anemarans C reduced blood glucose level in alloxan induced hyperglycemic mice (11).

Azadirachta indica (Neem) is a large evergreen tree found all over India, used in leprosy, piles and urinary disease. Oil from nuts and leaves acts as local stimulant, insecticide and antiseptic (3). A bitter principle nimbidin isolated from seeds of the tree was effective at a dose of 200 mg/kg in reducing blood glucose in alloxan diabetic rabbits and was 50% as potent as tolbutamide (12). Aqueous extract of tender leaves was reported to be effective in reducing blood glucose and this effect was due to blocking the action of epinephrine on glycogenolysis and peripheral utilization of glucose (13).

Leaves of *Bouganvillea spectabilis* have been reported to possess hypoglycemic effect. Pinitol isolated from leaves (0.01 gm/kg, bw) produced significant hypoglycemic effect in normal and diabetic mice (2). *Coccinia indica* (Hindi Kanduri) grows in wild state abundantly in Bengal and in other parts of India. The plant has the reputation in Bengal of having a remarkable effect in reducing the amount of sugar in urine of patients suffering from diabetes mellitus (3). Ethanolic extract of the leaves showed hypoglycemic effect in rats and in human subjects. It has insulin secretagogue effect and inhibited enzymes of gluconeogenesis (14). The hypoglycemic activity was stated to be due to the presence of water soluble and dialyzable alkaloidal principle (15). *Eugenia jambolana or Syzygium jambolana* (Eng. Jambul, Hindi Jamun, Telugu Neredu) is a tree grown throughout the plains. Bark, leaves, seeds and fruits of this plant are astringent. Juice of the fruit is stomachic, astringent, diuretic and antidiabetic (3). Oral administration of powdered seeds to normal rats and to NIDDM patients for 15 days caused marked lowering of blood glucose level (16). Both the fruit pulp and seeds were found to be effective in diabetic rats. They also increased cathepsin B activity and had insulin secretogogue effect (17). In our laboratory Sharma et. al. isolated few highly active hypoglycemic compounds from pulp and seed (Patent applied).

Pods of *Cyamopsis tetragonolobus* (Indian cluster bean, Hindi Guar phali; Telugu - Goruchikkudu) contain an antidiabetic principle (18). Seeds of this plant are the source of galactomanan gum (guar) that is used as bulking agent for food and cosmetics (19). The viscosity effect of guar is exploited as a dietary adjunct to delay the rate of glucose absorption and thereby reduce postprandial hyperglycemia (20).

Ficus bengalensis (English: Banyan tree; Hindi: Bargar, Telugu: Marrichettu) is a large tree with aerial roots. It grows wild in lower Himalayas and is found all over country. Leaves are good for ulcers. Milky juice is externally applied for pains and bruises and in rheumatism. The aerial roots are aphrodisiac, useful in gonorrhea, syphilis, dysentery

and inflammation of liver. Seeds and fruits are cooling and tonic (3). Bark of this plant has antidiabetic properties. The hypoglycemic effect of extract of bark was demonstrated in alloxan diabetic rabbits, rats and in humans (21-27). A potent hypoglycemic water insoluble principle was isolated (Patent applied) from the bark in our lab by Babu et. al. (25a, 25b). A water soluble hypoglycemic principle was also isolated from the bark (patent applied) in our lab by Shukla et. al. (26a, 26b) which was effective at a low dose of 10 mg/kg, bw/day. Both the banyan bark principles were effective in mild as well severe alloxan induced diabetes in rabbits, and improved lipid profile. Mechanism of action of water soluble and insoluble hypoglycemic compounds was investigated by Shukla et. al. and Babu et. al.

Gymnema sylvestre is a climbing plant growing in tropical forests of central and southern part of India. The leaves have a peculiar property of neutralizing temporarily the taste sensation for sugar and hence the name gurmar is given to it (29). The effect of alcoholic extract of these leaves was investigated in normal and anterior pituitary treated hyperglycemic rats at a dose of 100 mg/kg. The effect was comparable to that of tolbutamide (50 mg/kg) (30). An active principle GS4 was isolated from alcoholic extract of the leaves. Administration of GS4 for 4-6 weeks to streptozotocin diabetic rats led to glucose homeostasis. Increase in number of beta cells in pancreas was demonstrated after GS4 therapy (31). It was also reported that extract of GS leaves suppressed elevation of blood glucose level by inhibiting glucose uptake in the intestine (32).

Fruits of *Momordica charantia* (English: bitter gourds, Hindi: karela, Telugu: Kakara) are widely used to treat diabetes mellitus in India. They are considered to have prophylactic properties and inspite of their bitter taste, often included in diet in India. Fruits or dry powder of fruits reduced blood glucose level and improved glucose tolerance (33). It's juice was effective in streptozotocin induced diabetic rats (34). Alcoholic extract showed significant reduction in fasting blood glucose and improvement in glucose tolerance in alloxan diabetic rabbits (35). Pugazhenthy and Murthy isolated 3 hypoglycemic compounds from fruits, kakara Ia, IIIa and IIIb (36,37) which had both pancreatic as well as extrapancreatic mechanism of action. A polypeptide similar to bovine insulin has been isolated from the fruit of momordica charantia. It was clinically tried and shown to produce 45% fall in blood sugar of diabetic patients (38).

Pterocarpus marsupium (Roxb) is popularly known as Vijaysar in Hindi and Indian malabar in English. It is a moderate to large deciduous tree, 30 meters high commonly found in hilly regions. The gum (kino) obtained from the tree is used in diarrhea, pyrosis and toothache. Bruised leaves are used externally for boils, sores, and various skin diseases. The water kept in tumblers made out of the wood of this plant is said to be beneficial for chest pain and diabetes in several parts of North India (4). Aqueous extract of the wood of this plant is used in treatment of diabetes mellitus (39). An active principle (-)epicatechin was isolated from the ethanolic extract of the bark. The active principle when administered at a dose of 30mg/kg, bw. twice daily for 4-5 days lowered blood glucose level of diabetic rats to near normal. Regeneration of β cell has been proposed in diabetic rats treated with (-) epicatechin. It was found to increase cAMP content of islets, increase insulin release and conversion of proinsulin to insulin (40,41). However the hypoglycemic activity of (-)epicatechin was contradicted. Although it can enhance insulin release from healthy rat islets *in vitro*, the antidiabetic and regenerating effect have not been substantiated in recent studies (42). Recently two phenolics are isolated from heart wood of this plant - marsupin and pterostilbene which significantly lowered blood glucose in hyperglycemic rats and effect was comparable to metformin (43).

Trigonella foenum graecum (English: Fenugreek, Hindi: Methi, Telugu: Menthulu) is an annual herb, widely used for culiniary and medicinal purposes for centuries in many parts of the world. The seeds and leaves are extensively used as tonic, carminative, antipyretic, anthelmintic, appetiser, astringent to bowel, useful in dropsy, chronic cough, internal and external swellings and hair decay (44). Chemical analysis of the seeds reveals that they

are composed of moisture 13%, protein 26%, fat 46%, fiber 7%, carbohydrate 4%, ash and vitamins 4% (45). Seeds of fenugreek are known to have antidiabetic effect (46-48). An alkaloid trigonelline present in seeds, counterected the hyperglycemic effect of cortisone in nondiabetic rabbits when administered concomitantly. Other hypoglycaemic compounds were nicotinic acid, coumarin and scopoletine (45). On the basis of the study conducted on streptozotocin diabetic rats it was suggested that the blood glucose modulating effects were mainly due to delayed gastric emptying coupled with direct interference with intestinal absorption of glucose and cholesterol (49). An active principle was isolated from the seeds by Moorthy et. al. (Patent applied) (50), which was found to have considerable hypoglycaemic activity in mild as well as severe alloxan induced diabetes in rabbits. It's mechanism of action was also studied (unpublished data). Hypoglycemic activity is located in high density part of seed rich in fiber and a galactomannan (51a). Furostanol saponins called trigoneosides Ia, Ib, IIa, IIb, IIIa, IIIb, glycoside D and trigoenoside A with hypoglycemic activity were isolated from fenugreek (51b).

PLANTS WITH UNCHARACTERIZED ANTIDIABETIC PRINCIPLES:

In some plants hypoglycemic effect was demonstrated with extracts only but the active principles were not isolated or studied.

Ethanolic extract of seeds of *Zizyphus zujuba* (Hindi: baer; Telugu: regipallu) and *Tichosanthus diocea*, were reported to exhibit hypoglycaemic activity (52,53). Ethanolic extract of stem bark of *Michelia champaca* (Hindi Champa) showed hypoglycemic effect in rats (54). Ethanolic extract of root of *Hedychium spicatum* was found effective in rats (55). Extract of root of *Panax bipinntifidum* and *Hamiltonia scaveolens* were found to be effective in diabetic mice and rabbits respectively (56, 57). Aqueous extract of leaves of *Murraya koenigii* showed hypoglycemic action in normal and alloxan diabetic dogs (58). Whole plant of *Aloe vera* (Hindi Ghikanvar), and *Phyllanthus amarus* have antidiabetic effect (59). Whole dried plant of latter was effective at a dose of 5 gm/day (60). Whole plant of *Indigophora tinctoria* (Hindi: Nil) excluding root was found to be effective (61). Leaves and stems of *Salacia prenoids* were found to reduce blood sugar (62).

Several traditionally recommended vegetables, like leaves of *Bassica oleracea* (cabbage) and *Letuca satina* (Lettuce), tuber of *Solanum tuberosum* (Potato) and roots of *Brasica rapa* (turnip) have been claimed to yield non fibrous hypoglycemic extracts. Aqueous extract from the pods of *Phaseolus vulgaris* (harriot bean) showed hypoglycemic activity in alloxan induced diabetic rats and rabbits (63,64).

Toxicity studies

Toxicity studies have not been conducted for most of these plants. As many of these plants were used for many centuries and some times as regular constituents of the diet, it is assumed that they do not have many side effects. Chronic consumption of large amounts of traditional remedies must always be taken with caution. Large quantities of extract of *Momordica charantia* (bitter gourd) induced testicular lesion in dogs (65). Alkaloids from *Catharanthus roseus* caused cytotoxic and neurological effects, and increased risk of infection (3). *Gymnema sylvestre* (gurmar) can reduce or abolish the taste sensation of sweetness or bitterness (29).

Conclusion

Plants have been used in treatment of diabetes mellitus all over the world for centuries. Wide variety of plant derived active principles representing numerous classes of chemical compounds have shown potential for the use in treatment of diabetes. Among the classes of chemical compounds isolated from plants with documented biological activity are alkaloids, glycosides, galactomannan, gum, peptidoglycan, glycopeptide, amino acids and inorganic ions. To date metformin is the only ethical drug approved for treatment of non insulin dependent diabetes mellitus derived from a medicinal plant *Galega officinalis* historically used to treat diabetes. There is every possibility of developing a few useful drugs from medicinal plants with a long history of human use.

Table 1. Names of medicinal plants, their parts and active ingredients studied for hypoglycemic activity.

S. No.	Plant (Botanical name)	Family	Active part/ Active compound	Activity demonstrated	References
1.	*Allium cepa* Eng - Onion; Hindi - Piyaz, Telugu -Neerulli	Liliaceae	Bulb, allyl propyl disulphide, S-methyl sulphoxide	Diabetic rats	8, 10
2.	*Allium sativum* Eng - Garlic; Hindi - Lasan, Telugu - Vellulli	Liliaceae	Cloves, allicin	Diabetic rabbits	9, 10
3.	*Aloe vera* Indian Aloe Ghikanvar	Liliaceae	Whole plant	Diabetic mice, NIDDM patients	59
4.	*Anemarrhena* asphodeloides	Liliaceae	Rhizome, anemarans A, B, C & D	Diabetic mice KK-AY mice	11
5.	*Azadirachta indica* Eng - Margosa, neem Hindi - Neem Telugu - Vepa	Meliaceae	Leaves, seeds, nimbidin	Dogs, diabetic rabbits	12,13
6.	*Bouganvillea spectabilis*		Leaves, pinitol	Diabetic mice	2
7.	*Coccinia indica* Hindi - Kanduri Telugu - Dondatiga	Cucurbitaceae	Whole plant, alkaloid	Diabetic rabbits & patients	14, 15
8.	*Cymopsis tetragonolobus* Indian cluster beans	Leguminaceae	Seeds	NIDDM patients	18-20
9.	*Eugenia jambolana* Eng - Black plum, Hindi - Jamun; Telugu - Neredupallu	Myrtaceae	Fruit pulp seed	Diabetic rats,	16, 17
10.	*Ficus bengalensis* Eng - Banyan tree Hindi - Bargad Telugu - Marrichettu	Urticaceae	Bark, leucocyanidin, pellargonidin, a water soluble principle and water insoluble principle	Diabetic rats, rabbits and NIDDM patients	22-26
11.	*Gymnema sylvestre*	Asclepidaceae	Leaves, GS4	Diabetic rats	30, 31
12.	*Hamiltonia suaveolens*	Rubiaceae	Root, alcoholic extract	Rabbit	57
13.	*Hedychium spicatum*	Zingiberaceae	Root, alcoholic extract	Rats	55
14.	*Indigophora tinctoria* Hindi - Nil	Papillionaceae	Whole plant including roots	Rats	61

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Table 1. Contd..

S. No.	Plant (Botanical name)	Family	Active part/ Active compound	Activity demonstrated	References
15.	*Michelia champaca* Yellow champa Champa	Magnoliaceae	Stem bark, ethanolic extract	Rats	54
16.	*Momordica charantia* Eng - Bitter gourd; Hindi - Karela Telugu - kakara	Cucurbitaceae	Fruits, charantin, kakara Ia, IIIa, IIIb	Diabetic rats, rabbits, diabetic patients	34-38
17.	*Murraya koenigi* Eng -Curry leaf; Hindi - Meetha neem Telugu - Karivepa	Rutaceae	Leaves	Normal and diabetic dog	58
18.	*Musa paradisiaca* Eng - Banana; Hindi - Kela; Telugu - Aratichettu	Musaceae	Flowers	Rabbits	64
19.	*Panax bipinnatifidum*		Root	Diabetic mice	56
20.	*Phyllanthus amarus*	Euphorbiaceae	Whole plant	Diabetic patients	60
21.	*Potrerium ancisroide* Derf	Tormentic acid			66
22.	*Pterocarpus marsupium Roxb.* Vijayasar	Papilionaceae	Wood, (-) epicatechin marsupin, pterostilbene	Rat	39-43
23.	*Saccharum officinarum* Eng - Sugarcane; Hindi - Ganna; Telugu - Cheruku	Poaceae	Stem, Saccharans A, B, C, D, E & F	Diabetic mice	67
24.	*Salacia prenoids* Saptrangi	Hippocrotaceae	Leaves and stem	62	
25.	*Trichosanthus dioica*	Cucurbitaceae	Seeds	Rabbits	53
26.	*Trigonella foenum graecum* Eng - Fenugreek Hindi - Methi Telugu - Menthulu	Papilionaceae	Seeds, trigonelline	Rabbits	45-50
27.	*Zizyphus zujuba* Hindi - Baer Telugu - Kasi regi	Rhamnaceae	Seeds	Rabbits, rats	52

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