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A Review on Herbal Drugs Used for the Treatment of Diabetes

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***Abstract*: Medicinal herbs as potential source of therapeutic aids have attained a significant role in health system all over the world for both humans and animals. Ayurveda other Indian literature mention the use of plants in treatment of various human diseases. India has about 45,000 plant species and among them, several thousands have been claimed to possess medicinal properties. Research conducted in last few decades on plants mentioned in ancient literature or used traditionally for diabetes has shown anti-diabetic property. The present review explain such plants and their products (active, natural principles and crude extracts) that have been mentioned/used in the Indian traditional system of medicine and have shown experimental or clinical anti-diabetic activity. Indian plants which are most effective and the most commonly studied in relation to diabetes and their complications are: *Aloe vera and Aloe barbadensis, Allium sativum, Azadirachta indica, Momordica charantia, Mangifera indica, Eugenia jambolana, Trigonella foenum-graecum, Coccinia indica, Tinospora cordifolia* are evaluated. All plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity.**

***Keywords*: Ayurveda, Diabetes, Indian, Medicinal herbs, Hypoglycemic activity.**

1. Introduction

In the last few years there have been an exponential growth in the field of herbal medicine and these drugs are gaining popularity in both developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from the medicinal plants, minerals and organic matter. A number of medicinal plants, traditionally used for 1000 years named as "RASAYANA" are present in herbal preparations of Indian traditional health care systems. In Indian systems of medicine most practitioners formulate and dispense their own recipes. The World Health Organization (WHO) has listed 21,000 plants, which are used for the medicinal purpose around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as the Botanical garden of the world. The current review focuses on herbal drug preparations and plants used in the treatment of diabetes mellitus; a major crippling disease in the world leading to huge economic loses.

2. Diabetes and significance

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur in developing countries. Studies conducted in India in last decade have highlighted that not only is the prevalence of diabetes high but also that it is that it is rapidly increasing in the urban population. It is estimated that there are approximately 33 million adults with diabetes in India. And it will likely to increase to 57.2 million by the year 2025.

Diabetes mellitus is a complex metabolic disorder resulting either insulin insufficiency or insulin dysfunction. It is of 2 types –

- Type I diabetes –Type I diabetes is insulin dependent is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin.
- Type II diabetes- Type II diabetes is insulin independent are unable to respond to insulin and can be treated with dietary changes, exercise and medication. It is the most common form of diabetes constituting 90% of the diabetic population.

3. Symptoms

Symptoms for both diabetic conditions may include:

- High levels of sugar in the blood.
- Unusual thirst.
- Frequent urination.
- Extreme hunger and loss of weight.
- Blurred vision.
- Nausea and vomiting.
- Extreme weakness and tiredness.
- Irritability, mood changes etc.

As diabetes is a multi-factorial disease leading to several complications, and therefore demands a multi therapeutic approach. Patients of diabetes either do not make enough insulin or their cells do not respond to insulin. In case of total

lack of insulin, patients are given insulin injections. Where as in case of those where cells do not respond to insulin many different drugs are developed taking into consideration possible disturbances in carbohydrate-metabolism.

For example, to manage post-prandial hyper-glycemia at digestive level, glucosidase inhibitors such as, acarbose miglitol and voglibose are used. These inhibit degradation of carbohydrates there by reducing the glucose absorption by the cells. To enhance the glucose uptake by peripheral cells biguanide such as metformine is used.

Although several therapies are in use for treatment, there are certain limitations due to high cost and side effects such as development of hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity etc. Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable anti-diabetic and antioxidant therapy.

Medicinal plants are being looked up once again for the treatment of diabetes. Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformine is an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis* to treat diabetes. *Galega officinalis* is rich in guanidine, the hypoglycemic component. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920's but were discontinued after insulin became widely available. However, experience with guanidine and biaguanides prompted the development of metformine.

To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these received scientific and medical evaluation to assess their efficacy. The hypoglycemic effects of some herbal extracts have been confirmed in human and animal models of type II diabetes. The World Health Organization expert committee on diabetes has recommended that medicinal herbs be further investigated.

Major default in amalgamation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their safety and efficacy. Therefore, there is a need for conducting clinical research in herbal drugs, developing simple bioassays for biological standardization, and developing various animal models for toxicity and safety evaluation. It is also important to establish the active constituent/s from these plant extracts.

4. Plants with antidiabetic potential

There are many herbal remedies suggested for diabetes and diabetic complications. Medicinal plant forms the important ingredients of these formulations. Some of the herbal remedies for diabetes treatment are as follows:

Aloe vera and Aloe barbadensis:

Common name: aloe, musabbar, kumari.

Family: Liliaceae

Fig. 1. Aloe vera

Aloe is cultivated or grows wildly as hedgerows in the drier part of India. It is a popular house plant. Aloe vera plant contains at least 75 active compounds such as vitamins, enzymes, minerals, polysaccharides, amino acids etc., it also contains trace elements such as chromium, magnesium, manganese and zinc known to be important for glucose metabolism by improving the effectiveness of insulin. Aloe vera is the leaf pulp or the mucilage, aloe latex, commonly referred to as "aloe juice"- it contains active constituents and trace elements used for the treatment of diabetes in both normal and normal and diabetic rats.

5. Experiment on animals

Single as well as chronic administration of aloe juice (5mg/kg IP) shows significant hypoglycemic effect. The hypoglycemic effect of single dose of aloe juice was extended over a period of 24hrs with maximum hypoglycemia observed at 8hrs while chronic administration (excaudate twice daily and the aloe juice once a day for 4 days) shows maximum reduction in plasma glucose level at the 5th day. Hypoglycemic effect of aloe and its juice is mediated through stimulation of synthesis and/or release of insulin from beta-cells of Langerhans.

Azadirachta indica:

Common name: neem, Indian lilac.

Family: Meliaceae

Fig. 2. Azadirachta indica

Azadirachta is a medium to large size tree native to the Indian subcontinent i.e., India, Nepal, Pakistan, Bangladesh, Srilanka, and Maldives and is also widely cultivated. It is grown in

typically grown in tropical and semi-tropical regions. It has a complex of various constituents including nimbin, nimbidin, nimbolide, limonoids, and also loaded with flavonoids, triterpenoid, anti-viral compounds, and glycosides which may help manage blood sugar levels and there no surge in glucose.

Experiment on animals: Azadirachta indica has showed hypoglycemic and anti-hyperglycemic effect in normal, glucose fed and streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemi diaphragm. 70% alcoholic neem root bark extract shows statistically significant results in 800mg/kg dose. The extract blocks the action of epinephrine on glucose metabolism, thus increasing the peripheral glucose utilization. It significantly reduces the glucose levels at 15th day in diabetic rats.

Allium sativum:
Common name: garlic
Family: Amaryllidaceae

Fig. 3. Allium sativum

Allium sativum is a perennial herb cultivated throughout India and is commonly used as a food ingredient. Garlic contains volatile oil which gives garlic its medicinal properties. It has 33 sulphur compounds, important ones are: aliin, allicin, ajoene, allylpropl, diallyl, trisulfide, sallylcysteine, vinyldithiines, S-allylmercaptocystein, etc., and it also contains 17 amino acids and glycosides, arginine etc., it is also rich in minerals. Selenium, allinase, peroxidases and myrosinase enzymes are important constituents of garlic. Allicin, a sulphur-containing compound is responsible for its pungent odor and it has been shown to have significant hypoglycemic activity. This effect is due to increased hepatic metabolism, increased insulin from pancreatic beta cells and/or insulin sparing effect.

Experiment on animals: Oral administration of 0.25gm/kg of ethanol, petroleum ether, ethyl ether extract of Allium sativum causes 18.9, 17.9, 26.2% reduction in blood sugar in alloxan-diabetic rabbits (150mg/kg IV). Oral administration of 0.25gm/kg allicin (isolated from A. sativum) produce hypoglycemia comparable to tolbutamide in mildly diabetic rabbits (glucose levels ranging from 180 to 300 mg %). Aqueous homogenate of garlic (10ml/kg/day) administered orally to sucrose fed rabbits (10gm/kg/day in water for 2 months) significantly increased hepatic glycogen and free amino acid contents, decreased fasting blood sugar, triglyceride levels in serum, liver and aorta and protein levels in serum and liver.

Momordica charantia:
Common name: Bitter gourd, Karela, Bitter melon.
Family: Cucurbitaceae.

Fig. 4. Momordica charantia

Bitter gourd is a popular plant amongst the indigenous populations of Asia, South America, India, Caribbean and East Africa. Bitter gourd fruits are rich in minerals including potassium, calcium, zinc, magnesium, phosphorus and iron and are a good source of dietary fiber. It also contains phenols flavonoids, isoflavones, terpenes, anthraquinones fixed oils and free acids reducing sugars alkaloids and glucosinolates etc., which of all confer a bitter taste. The fruit pulp has soluble pectin but no free pectic acid. The leaves are nutritious sources of calcium, magnesium, potassium, phosphorus and iron; both the edible fruit and the leaves are great sources of the B vitamins.

Experiment on animals: Extracts of fruit pulp, seeds, leaves and whole plant was shown to have hypoglycemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of bitter melon shows hypoglycemic effect when administered subcutaneously to langurs and humans. Ethanolic extracts of bitter melon showed an anti-hyperglycemic and also hypoglycemic effect in normal and streptozotocin diabetic rats. This may be because of inhibition of glucose-6-phosphate besides fructose-1, 6-biphosphatase in the liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities.

Mangifera indica:
Common name: Mango
Family: Anacardiaceae

Fig. 5. Mangifera indica

Mango is the important herb in the Ayurvedic and indigenous medical systems for over 4000 years. Mango is the most

popular of all tropical fruits. It is native tropical Asia and has been cultivated in the Indian subcontinent and is now found naturalized in most tropical countries. The parts of used for the treatment are roots, leaves, fruits, seeds and flowers etc,. Mainly mango leaves are very useful in managing diabetes. As the leaves contain tannins called anthocyanidins that may help in treating early diabetes. Chemical constituents of mango are - flavonoids, triterpenoids, polyphenolics, and Mangiferin (xanthone glycoside) major bio-active constituent, isomangiferin, and gallic acid derivatives.

Experiment on animals: A 50% ethanolic extract of the leaves of mango produced a significant hypoglycemic effect at a dose of 250mg/kg, both in normal and streptozotocin-induced diabetic animals. However, anti-diabetic activity was seen when the extract and the glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The results indicate that aqueous extract of mango possess hypoglycemic activity. This may be due to an intestinal reduction of the absorption of glucose.

Eugenia jambolana:
Common names: malabar plum, java pulm, black pulm, jamun
Family: Myrtaceae.

Fig. 6. Eugenia jambolana

Jamun is a berry fruit, which grows abundantly in tropical regions of South Asia and South America, and is used in traditional medicines such as Ayurveda. Jamun contains polyphenolics anthocyanin derivatives, glucoside, ellagic acid, isoquercetin, kaemferol and myrecetin. The seeds are claimed to contain alkaloid, and glycoside jambolin and jambosine. The seeds have been reported to be rich in flavonoids and also found to have high total phenolics which are used to treat hyperglycemia.

Experiment on animals: In India decoction of kernels of jamun is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Aqueous and alcoholic extract as well as lyophilized powder shows reduction in blood glucose level. They differ with different levels of diabetes. In mild diabetes (plasma sugar >180mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar > 280mg/dl) and severe diabetes (plasma sugar >400mg/dl) it is reduced to 55.62% and 17.72% respectively. The extract of jamun pulp showed the hypoglycemic activity in streptozotocin induced diabetic mice within 30 minutes of administration while seed extract of the same fruit requires 24hrs. These extracts also inhibited insulinase activity from liver and kidney.

Trigonella foenum-graecum:
Common name: Fenugreek.
Family: Fabaceae.

Fig. 7. Trigonella foenum-graecum

Fenugreek is an annual plant. It is cultivated worldwide as a semiarid crop. Fenugreek is widely grown in South Asia, North Africa and parts of Mediterrian. The seeds and leaves are common dishes. Leaves of fenugreek are used as green, leafy vegetable and are a good source of calcium, iron, β-carotene and several vitamins. Seeds is a good source of protein (20-30%) high in tryptophan and lysine, free amino acids (4-hydroxyisoleucine, arginine, lysine, histidine); (25.8%), fat (6.53%), ash content (3.26%), crude fiber (6.28%) and moisture (11.76%). It also contains lecithin, choline, minerals, saponins and phenolic acid used for the treatment of diabetes.

Experiment on animals: Oral administration of 2 and 8 g/kg of plant extract produce dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats. Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats.

Coccinia indica:
Common names: Bimba, Kanduri
Family: Cucurbitaceae.

Fig. 8. Coccinia indica

It is a cultivated crop and it is used for culinary and medical

purposes. It grows abundantly all over India, tropical Africa, Australia, and throughout the oriental countries. The plant has also been extensively in Ayurvedic and Unani practice in Indian subcontinent. It contains triterpenoid; saponins, flavonoids glycoside, β-carotene and amino acids such as Aspartic acid, Glutamic acid, Asparagine, Histidine etc., Saponins and flavonoids are responsible for the anti-diabetic activity.

Experiment on animals: Dried extracts of kanduri (500mg/kg bodyweight) were administered to diabetic patients for 6 weeks. These extracts restored the activities of enzyme lipoprotein lipase (LPL) that was reduced and glucose-6-phosphatase and Lactate dehydrogenase, which were raised in untreated diabetes. Oral administration of kanduri leaves shows significant hypoglycemia in alloxanized diabetic dogs and increase glucose tolerance in normal and diabetic dogs.

Tinospora cordifolia:
Common names: heart-leaved moonseed, gaduchi, giloya
Family: Menispermaceae

Fig. 9. Tinospora cordifolia

Gaduchi is an herbaceous vine indigenous to the tropical areas of Bangladesh, India, Myanmar and Srilanka. It is a large, deciduous, climbing shrub, with greenish yellow typical flowers, found at higher altitude. A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, and glycosides that have been isolated from the different parts of plant body, including root, stem and whole plant. Alkaloids, tannins, cardiac glycosides, flavonoids and steroids are responsible for the anti-diabetic activity of gaduchi.

Experiment on animals: Oral administration of extract of gaduchi roots for 6 weeks resulted in significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight. Oral administration of gaduchi root extract to alloxan rats caused a significant reduction in blood glucose. Daily administration of either alcoholic or aqueous extract of gaduchi decreases the blood glucose level and increases glucose tolerance in rodents.

Hazelnuts:
Common name: Cobnut, filbert nut
Family: Corylus avellana

Fig. 10. Hazelnuts

Cobnuts are native to Europe, western Asia, Greece, Turkey and Cyprus. The wood was traditionally grown as coppice; poles cut being used for wattle-and-daub building and agricultural fencing. Hazelnuts are rich in protein, phosphorus, potassium, magnesium, monosaturated fat such as oleic acid; polysaturated fat mainly as linoleic acid; saturated fat such as palmitic acid and stearic acid vitamin E, manganese and iron. As it contain more manganese potassium and phosphorus is used to manage diabetes.

Experiment on animals: Animals were randomly assigned to five groups of equal number and weight. Group 1 kept as normal control group; Group 2 kept as diabetic control group; Group 3,4,5 kept as diabetic groups and feeding supplemented diet with 10% and 15% of cobnuts significantly lower food intake compared to the positive control group. Body weight gain significantly increased in treated diabetic group compared with positive control group. Feeding supplemented diet with cobnuts at the 3 different levels caused significantly lower in concentrations of blood glucose, total lipids, triglycerides, total cholesterol etc., are significantly lower in levels of insulin, thyroid stimulating, follicle stimulating and luteinizing hormones compared to that of untreated diabetic rats.

6. Conclusion

The prevalence of diabetes mellitus continues to rise worldwide and treatment with oral hypoglycemic drugs ends with numerous side effects and huge monitory expenditure. There is increasing demand by patients to use the natural products with anti-diabetic activity. This paper has presented various anti-diabetic plants that have been pharmacologically tested and shown to be of some value in treatment of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. However, more investigations must be carried out to evaluate the mechanism of action of medicinal plants with anti-diabetic effect.

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