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ANTIDIABETIC TREATMENT WITH HERBAL DRUGS

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ABSTRACT

Diabetes is an important human ailment afflicting many from various walks of life in differentcountries. In India it is proving to be a major health problem, especially in the urban areas. Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. These include, *Allium sativum*, *Eugenia jambolana*, *Momordica charantia Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *Tinospora cordifolia*, *Trigonella foenum graecum* and *Withania somnifera*. However, the selection of herbs might depend on several factors, which include the stage of progression of diabetes, types of co morbidities that the patients are having, availability, affordability as well as the safety profile of the herbs. India is the largest producer of medicinal herbs and is called as botanical garden of the world. The current review focuses on herbal drug preparations and plants used inthe treatment of diabetes mellitus, a major crippling disease in the world leading to huge economic losses.

KEYWORDS: Diabetes, herbal medicines, medicinal plants, treatment, anti-diabetes.

INTRODUCTION

Diabetes mellitus is a syndrome that is characterized by hyperglycemia, change in the metabolism of lipids, carbohydrates, and proteins, and in the long term, with eye, kidney, cardiovascular, and neurological complications. This disease is also associated with symptoms such as polyuria, fatigue, weight loss, delayed wound healing, blurred vision, increases in urine glucose levels, etc. Destruction of beta-cells of the islets of Langerhans in the pancreas and consequently development of insulin-dependent diabetes is one of the impairments of the regulation of the immune system. Several environmental and genetic factors affect the immune system, leading to the attack of lymphocytes, especially lymphocytes, and pancreatitis. This inflammatory response may cause insulitis and diabetes. There are currently more than 150 million people with diabetes across the globe, which seems to reach 300 million by 2025. In the absence of proper treatment, cardiac, vascular, neurological, and renal damage and neuropathy may occur. Treatment includes diet, exercise, and medication. Currently, the main and effective treatment for diabetes is the use of insulin and hypoglycemic drugs, but these compounds also have many adverse side effects. Medicinal plants have a long history of usage and today, they are being extensively used for various diseases. There are several reasons for increasing the use of medicinal plants. Many plants from different parts of the world have been investigated for antidiabetic effects. A number of medicinal plants, traditionally used for over1000 years named 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 medicinal purposes around the world. Among these 2500 species are in India, out of which 150species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as 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 losses.

Clinical Overview Of Diabetes Mellitus

Type I Diabetes Mellitus (T1DM) and Type II Diabetes Mellitus (T2DM). In T1DM, β-cells of the pancreas are damaged, leading to a decreased insulin supply to the circulation. Patients will be fully dependent on exogenous insulin administration for existence.

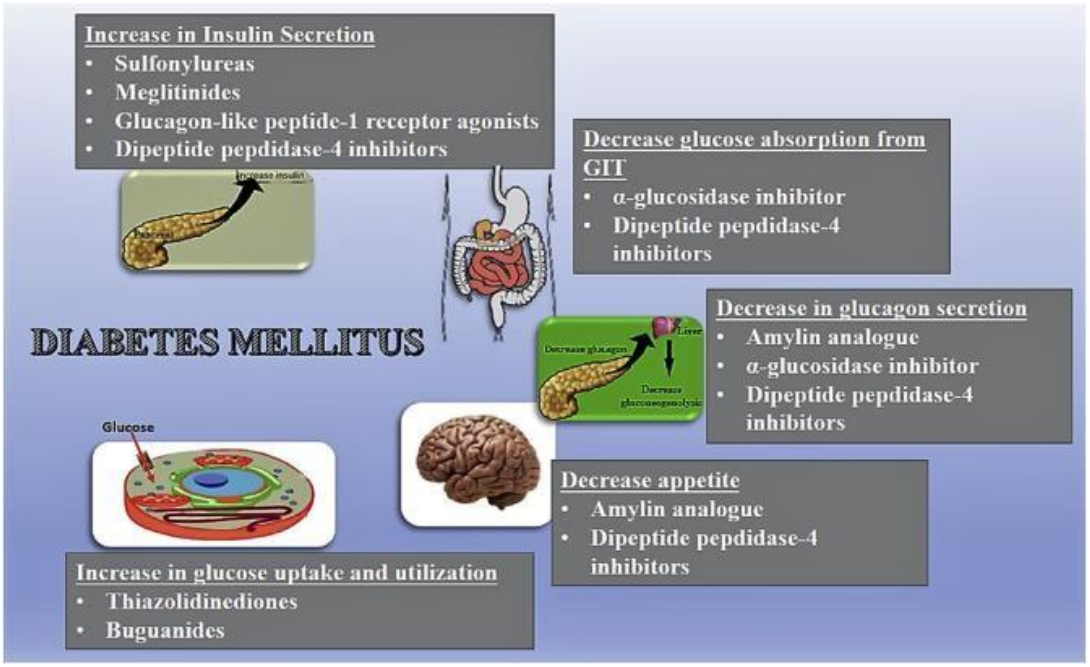

Fig. 1: Mechanism of actions of different anti-diabetic agents in the treatment of high glucose level in the circulation.

Contrarily, T2DM has been observed in majority of diabetic patients (85%) and results in peripheral insulin resistance, thereby results in decreased insulin sensitivity to the skeletalmuscles, adipose tissues and liver.

Fig. 2: Condition to develop diabetic mellitus disease and herbal approaches in the improvement of insulin secretion or improvement in insulin resistivity of the body cells.

Indian Medicinal Plants with Antidiabetic and Related Beneficial Effects

There are many herbal remedies suggested for diabetes and diabetic complications. Medicinal plants form the main ingredients of these formulations. A list of Indian medicinal plants with antidiabetic and related beneficial effects is given in Table.

Plant Name	Ayurvedic/common name/ herbal formulation	Antidiabetic and other beneficial effects in traditional medicine
Annona squamosa	Sugar apple	Hypoglycemic and antihyperglycemic activities of ethanolic leaf-extract,Increased plasma insulin level
Artemisiapallens	Davana	Hypoglycemic, increases peripheral glucose utilization or inhibits glucose reabsorption
Areca catechu	Supari	Hypoglycemic
Beta vulgaris	Chukkander	Increases glucose tolerance in OGTT
Boerhaviadiffusa	Punarnava	Increase in hexokinase activity,decrease inglucose-6-phosphatase and fructose bis- phosphatase activity, increase plasma insulin level, antioxidant
Bombax ceiba	Semul	Hypoglycemic
Butea monosperma	Palasa	Antihyperglycemic
Camellia sinensis	Tea	Anti-hyperglycemic activity, antioxidant
Capparisdecidua	Karir or Pinju	Hypoglycemic, antioxidant,hypolipidaemic
Caesalpiniabonducella	Sagarghota, Fevernut	Hypoglycemic, insulin secretagogue,hypolipidemic
Cocciniaindica	Bimb or Kanturi	Hypoglycemic
Emblica officinalis	Amla, Dhatriphala, a constituent of herbal formulation, "Triphala"	Decreases lipid peroxidation, antioxidant, hypoglycemic
Eugeniauniflora	Pitanga	Hypoglycemic, inhibits lipase activity
Enicostemalittorale	Krimihrita	Increase hexokinase activity, Decrease glucose 6-phosphatase and fructose 1,6 bisphosphatase activity. Dose dependent hypoglycemic activity
Ficus bengalenesis	Bur	Hypoglycemic, antioxidant
Gymnemasylvestre	Gudmar or Merasingi	Anti-hyperglycemic effect, hypolipidemic
Hemidesmusindicus	Anantamul	Anti snake venom activity, anti-inflammatory
Hibiscus rosa-sinesis	Gudhal or Jasson	Initiates insulin release from pancreaticbeta cells
Ipomoeabatatas	Sakkargand	Reduces insulin resistance
Momordicacymbalaria	Kadavanchi	Hypoglycemic, hypolipidemic
Murrayakoenigii	Curry patta	Hypoglycemic, increases glycogenesis anddecreases gluconeogenesis and glycogenolysis
Musa sapientum	Banana	Antihyperglycemic, antioxidant
Phaseolusvulgaris	Hulga, white kidney bean	Hypoglycemic, hypolipidemic, inhibitalpha amylase activity, antioxidant. Altered level of insulin receptor and GLUT-4 mRNA in skeletal muscle
Punica granatum	Anar	Antioxidant, anti-hyperglycemic effect
Salacia reticulata	Vairi	inhibitotory activity against sucrase, α-glucosidase inhibitor
Scopariadulcis	*Sweet broomweed*	Insulin-secretagogue activity, antihyperlipidemic, hypoglycemic, antioxidant
Swertia chirayita	Chirata	Stimulates insulin release from islets
Syzygium alternifolium	Shahajire	Hypoglycemic and antihyperglycemic
Terminaliabelerica	Behada, a constituent of"Triphala"	Antibacterial, hypoglycemic
Terminaliachebula	Hirda	Antibacterial, hypoglycemic
Tinosporacrispa		Anti-hyperglycemic, stimulates insulinrelease from islets
Vinca rosea	Sadabahar	Anti-hyperglycemic
Withania somnifera	Ashvagandha, winter cherry	Hypoglycemic, diuretic andhypocholesterolemic

- **Acacia arabica: (Babhul)**

It is found all over India mainly in the wild habitat. 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 *Acacia arabica* when administered (2,3 and 4 g/kg body weight) to normal rabbits induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells.

- **Aegle marmelos: (Bengal Quince, Bel or Bilva)**

Administration of aqueous extract of leaves improves digestion and reduces blood sugar and urea, serum cholesterol in alloxanized rats as compared to control. Along with exhibiting hypoglycemic activity, this extract also prevented peak rise in blood sugar at 1h in oral glucosetolerance test.

- **Allium cepa: (onion)**

Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. *Allium cepa* is also known to have antioxidant and hypolipidaemic activity. Administration of a sulfur containing amino acid from *Allium cepa*, 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 and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase . When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post- prandial glucose levels.

- **Allium sativum: (garlic)**

This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity. This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect. Aqueous homogenate of garlic (10 ml/kg/day) administered orally to sucrose fed rabbits (10 g/kg/day in water for two months) significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum in comparison to sucrose controls.

S-allyl cystein sulfoxide (SACS), the precursor of allicin and garlic oil, is a sulfur containing amino acid, which controlled lipid peroxidation better than glibenclamide and insulin. It also improved diabetic conditions. SACS also stimulated *in vitro* insulin secretion from beta cells isolated from normal rats. Apart from this, *Allium sativum* exhibits antimicrobial, anticancer and cardioprotective activities.

- **Aloe vera and Aloe barbadensis**

Aloe, a popular houseplant, has a long history as a multipurpose folk remedy. The plant can beseparated into two basic products: gel and latex. Aloe vera gel is the leaf pulp or mucilage, aloe latex, commonly referred to as "aloe juice," is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats. Treatment of chronic but not single dose of exudates of *Aloe barbadensis* leaves showed hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also showed hypoglycemic effect in diabetic rats. This action of *Aloe vera* and its bitter principle is through stimulation of synthesis and/or release of insulin from pancreatic beta cells. This plant also has an anti- inflammatory activity in a dose dependent manner and improves wound healing in diabetic mice.

- **Azadirachta indica: (Neem)**

Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition inisolated rat hemidiaphragm. Apart from having anti-diabetic activity, this plant also has anti- bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects.

- **Caesalpinia bonducella**

Caesalpinia bonducella is widely distributed throughout the coastal region of India and used ethnically by the tribal people of India for controlling blood sugar. Both the aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic type II diabetic models. These extracts also increased glycogenesis thereby increasing liver glycogen con. Two fractions BM 169 and BM 170 B could increase secretion of insulin from isolated islets. The aqueous and 50% ethanolic extracts of *Caesalpinia bonducella* seeds showed antihyperglycemic and hypolipidemic activities in streptozotocin (STZ)-diabetic rats. The antihyperglycemic action of the seed extracts may be due to the blocking of glucose absorption. The drug has the potential to act as antidiabetic as well as antihyperlipidemic 33.

- **Capparis decidua**

This is found throughout India, especially in dry areas. Hypoglycemic effect was seen in alloxanized rats when the rats were fed with 30% extracts of *Capparis decidua* (*C. decidua*) fruit powder for 3 weeks. This extract also reduced alloxan induced lipid peroxidation significantly in erythrocytes, kidney and heart. *C. decidua* was also found to alter superoxide dismutase and catalase enzyme levels to reduce oxidative stress. *C. decidua* additionally showed hypolipidaemic activity.

- **Coccinia indica**

Dried extracts of *Coccinia indica* (*C. indica*) (500 mg/kg body weight) 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 diabetics. Oral administration of 500 mg/kg of *C. indica* leaves showed significant hypoglycemia in alloxanized diabetic dogs and increased glucose tolerance in normal and diabetic dogs.

- **Eugenia jambolana: (Indian gooseberry, jamun)**

In India decoction of kernels of *Eugenia jambolana* is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Antihyperglycemic effect of aqueous and alcoholic extract as well as lyophilized powder shows reduction in blood glucose level. This varies with different level of diabetes. In mild diabetes (plasma sugar >180 mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/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 min of administration while the seed of the same fruit required 24 h. The oral administration of the extract resulted in increase in serum insulin levels in diabetic rats. Insulin secretion was found to be stimulated on incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals. These extracts also inhibited insulinase activity from liver and kidney.

- **Mangifera indica*: (Mango)***

The leaves of this plant are used as an antidiabetic agent in Nigerian folk medicine, although when aqueous extract given orally did not alter blood glucose level in either normoglycemic or streptozotocin induced diabetic rats. However, antidiabetic activity was seen when the extract and 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 *Mangifera indica* possess hypoglycemic activity. This may be due to an intestinal reduction of the absorption of glucose.

- **Momordica charantia: (bitter gourd)**

Momordica charantia is commonly used as an antidiabetic and antihyperglycemic agent in India as well as other Asian countries. Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of *M. charantia* showed significant hypoglycemic effect when administered subcutaneously to langurs and humans. Ethanolic extracts of *M. charantia* (200 mg/kg) showed an antihyperglycemic and also hypoglycemic effect in normal and STZ diabetic rats. This may be because of inhibition of glucose-6-phosphatase besides fructose-1, 6- biphosphatase in the liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities.

- **Ocimum sanctum: (holy basil)**

It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties. The aqueous extract of leaves of *Ocimum sanctum* showed the significant reduction in blood sugar level in both normal and alloxan induced diabetic rats. Significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride and total lipid indicated the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats. Oral administration of plant extract (200 mg/kg) for 30 days led to decrease in the plasma glucose level by approximately 9.06 and 26.4% on 15 and 30 days of the experiment respectively. Renal glycogen content increased 10 fold while skeletal muscle and hepatic glycogen levels decreased by 68 and 75% respectively in diabetic rats as compared to control. This plant also showed antiasthemitic, antistress, antibacterial, antifungal, antiviral, antitumor, gastric antiulcer activity, antioxidant, antimutagenic and immunostimulant activities.

- **Phyllanthus amarus: (bhuiawala)**

It is a herb of height up to 60 cm, from family Euphorbiaceae. It is commonly known as Bhuiamala. It is scattered throughout the hotter parts of India, mainly Deccan, Konkan and south Indian states. Traditionally it is used in diabetes therapeutics. Methanolic extract of *Phyllanthus amarus* was found to have potent antioxidant activity. This extract also reduced the blood sugar in alloxanized diabetic rats. The plant also shows antiinflammatory, antimutagenic, anticarcinogenic, antidiarrhoeal activity.

- **Pterocarpus marsupium**

It is a deciduous moderate to large tree found in India mainly in hilly region. Pterostilbene, a constituent derived from wood of this plant caused hypoglycemia in dogs showed that the hypoglycemic activity of this extract is because of presence of tannates in the extract. Flavonoid fraction from *Pterocarpus marsupium* has been shown to cause pancreatic beta cell regranulation. Marsupin, pterosupin and liquiritigenin obtained from this plant showed antihyperlipidemic activity. (−) 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 dose-dependent manner.

- **Trigonella foenum graecum: (fenugreek)**

It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in both rats and humans. Oral administration of 2 and 8 g/kg of plant extract produced 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. It also reduced hepatic and renal glucose-6-phosphatase and fructose −1,6-biphosphatase activity. This plant also shows antioxidant activity.

- **Tinospora cordifolia: (Guduchi)**

It is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of *Tinospora cordifolia* (*T. cordifolia*) roots for 6 weeks resulted in a 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. *T. cordifolia* is widely used in Indian ayurvedic medicine for treating diabetes mellitus. Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant anti-hyperglycemic effect

in different animal models, its effect was equivalent to only one unit/kg of insulin. It is reported that the daily administration of either alcoholic or aqueous extract of *T. cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents.

CONCLUSIONS

Plants are natural antioxidants and effective herbal medicines, in part due to their anti-diabetic compounds, such as flavonoids, tannins, phenolic, and alkaloids that improve the performance of pancreatic tissues by increasing the insulin secretion or decreasing the intestinal absorption of glucose. More researches are needed in order to separate the active components of plants and molecular interactions of their compounds for analysis of their curative properties. As a conclusion, treating pre-diabetes or diabetic patients with herbals might be an alternative choice of oral hypoglycaemic effects since it is not only showing benefit in lowering the blood glucose but also helps in improving the lipid profile, antioxidant role, control of hypertension, etc.

Although thorough toxicological studies need to be carried out before the extracts are incorporated as an adjunctive agent in the management of diabetes.

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