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AN EXHAUSTIVE REVIEW ON HERBS USED IN THE MANAGEMENT OF DIABETES MELLITUS TYPE 2

Salman M[1]*, Saleem S[1], Kimothi V[1], Joshi V[1], Singh S[1]

[1]Department of Pharmacology, Siddhartha College of Pharmacy, Uttrakhand Technical University, Dehradun, Uttarakhand, India-248001

ABSTRACT

Diabetes mellitus is one of the most common metabolic disorders associated with disturbed hormonal secretion. Diabetes is characterized by high blood glucose levels over a prolonged period of time. High sugar levels are due to abnormal metabolism of carbohydrates and lipids which is caused by absolute or relative insulin deficiency. Herbal medicines have been the highly esteemed source of medicine throughout the human history. Herbs are becoming more popular today because of their least side effects, holistic beliefs, easy availability and low cost. Individual herbal products and formulations are gaining popularity because of their quality manufacturing using modern analytical techniques and standardized raw materials. Herbal drugs are widely used for the treatment of diabetes worldwide in various dosage forms. India has a long list of native herbal drugs with scientifically proven blood sugar lowering properties. The seeds of *Nigella sativa*, *Olea europaea*, fruits of *Aegle marmelos, Momordica charantia*, *Coccinia indica, Nigella sativa,Gymnema sylvestre* leaves,whole plant o*f Pterocarpus marsupium, Syzygium cumini* fruits*, Swertia punicea, Urtica dioica,* gum of *Ferula assa-foetida* and seeds of *Trigonella foenum graecum* were discussed along with their reported mechanisms of action. In this review paper an attempt has been made to give an overview of certain Indian plants which have shown their anti-diabetic activity in various pre-clinical studies.

Keywords: Diabetes mellitus, Hypoglycaemic effect, Insulin, Glucose, Herbal medicines, Standardized**.**

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Correspondence:
Mau Salman
Department of Pharmacology, Siddhartha College of Pharmacy,
Uttrakhand Technical University, Dehradun, Uttarakhand, India-248001
Phone: +91-9012361766
Email: mohd.salman1020@gmail.com

INTRODUCTION

Diabetes is a common disorder caused by a lack of insulin or insulin resistance leading to impaired glucose metabolism. Glucose is the key component used by the body's cells to make energy. In order for glucose to move from the blood into most cells insulin is required with exceptions of the brain and exercising muscles. [1] [2] Insulin is a hormone produced by the beta cells of the pancreas and is secreted into the blood in response to the increase in blood glucose level. In Diabetic condition human body does not produce or properly utilizes insulin which is responsible for conversion of sugar, starches, and other food into glycogen an energy form to be stored in the liver. Diabetes mellitus is characterized by constant high levels of blood glucose (sugar). Human body has to maintain the blood glucose level at a very narrow range, which is done with insulin and glucagon. The function of glucagon is to release the stored glucose in the liver (glycogen) from its cells into the blood, for the production of energy. There are three types of diabetes.

Type 1 diabetes

It is Insulin dependent diabetes mellitus where the body stops producing insulin or produces too little insulin to regulate blood glucose level. Type I diabetes comprises about 10% of total cases of diabetes in the United States. It is typically recognized in childhood or adolescence. It is used to be known as juvenile-onset diabetes or insulin dependent diabetes mellitus (IDDM).

Type II diabetes

Type II diabetes mellitus is a Non–insulin dependent (NIDDM). It is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute. The body tries to overcome this resistance by secreting more and more insulin. At least 90% of patients with diabetes have type II diabetes. [3] [4]

Gestational diabetes

Gestational diabetes is a form of diabetes that start during the second half of pregnancy and produced by the hormones of pregnancy or by a shortage of insulin. Women who have gestational diabetes are more likely than other women to develop type II diabetes later in life.

Women with gestational diabetes are more likely to have large babies. However, such kind of diabetes resolves as the nannies delivers.

Signs and symptoms: There are the following signs and symptoms of diabetes:

Increased fatigue: Due to inefficiency of the cell to metabolize glucose, reserve fat of body is metabolized to gain energy. When fat is broken down in the body, it uses more energy as compared to glucose; hence body goes in negative calorie effect, which results in fatigue.

Polydipsia: As the concentration of glucose increases in the blood, brain receives signal for diluting it and, in its counteraction the person feels thirsty.

Polyuria: Increase in urine production is due to excess glucose present in body. Body gets rid of the extra sugar in the blood by excreting it through urine. This leads to dehydration because along with the sugar, a large amount of water is excreted out of the body.

Polyphagia: The hormone insulin is also responsible for stimulating hunger. In order to cope up with high sugar levels in blood, body produces insulin which leads to increased hunger.

Weight fluctuation: Factors like loss of water (polyuria), glucosuria metabolism of body fat and protein may lead to weight loss. Few cases may show weight gain due to increased appetite.

Blurry vision: Hyperosmolar hyperglycaemia non-ketotic syndrome is the condition when body fluid is pulled out of tissues including lenses of the eye, which affects its ability to focus, resulting blurry vision.

Irritability: It is a sign of high blood sugar because of the inefficient glucose supply to the brain and other body organs, which make the person, feel tired and uneasy.

Pathophysiology

Mechanism of insulin release in normal pancreatic β-cells

Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is primarily triggered by food, chiefly food containing absorbable glucose. The chief trigger for insulin release is the rise in blood glucose levels after eating. Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells).

Hereby deficiency of insulin or the insensitivity of its receptors plays a major key role in all forms of diabetes mellitus. Most of the carbohydrates in food are converted within a few hours to the monosaccharide glucose, the principal carbohydrate found in blood and used by the body as fuel. Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels results both in the reduced release of insulin from the β-cells and in the reverse conversion of glycogen to glucose when glucose levels fall.

Herbs used in management of Diabetes Mellitus

Nigella sativa L.

Nigella sativa L. (NS) is an herbaceous plant belonging to the Ranunculaceae family which grows spontaneously and wildly in several southern Mediterranean and Middle Eastern countries. [5] The seeds of NS, also known as black seed or black cumin, are often used as a spice but are also used extensively in the traditional medicine system of many of these countries including Morocco, to treat diabetes and several other disorders.

Mechanism of action

Balance concept for any variable in the body is based on equalization of its input to its output. Glucose plasma input could be through intestinal absorption, endogenous production (glycogenlysis and gluconeogenesis), while output from plasma is contributed by tissues glucose utilization (glycolysis, pentose phosphate pathway, tricarboxylic acid cycle and glycogen synthesis. [6] Several hormones, insulin being the most important one, play an important role in glucose homeostasis.

The normal function of insulin releasing cells (β cells in pancreas), as well as other cellular mechanisms are distorted by oxidative stress which would contribute in induction of diabetes mellitus and associated complications.[7] Several studies have reported a powerful antioxidant effect of seeds of *Nigella sativa* and its constituents, which is supposed to assist in its hypoglycaemic effect. [8] These findings showed that *Nigella sativa*'s exerts its hypoglycaemic effect through multiple mechanisms like reduction of oxidative stress, elevation of insulin levels, attenuation of insulin resistance and hepatic gluconeogenesis and direct insulin-like effects at the cellular and molecular levels in various organs. [9]

Olive oil

Olive oil is a liquid fat obtained from the fruits of *Olea europaea* (Oleaceae). An olive-oil-rich diet is not only a good alternative for lowering bad cholesterol levels but can also posses' beneficial effects on diabetes. [11]

Mechanism of action

A diet rich in olive oil is not only a good supplement in the treatment of diabetes but it may also help to prevent or delay the onset of the disease. It causes decrease in glycaemic load particularly when replacing carbohydrates with monounsaturated fatty acids (MUFA) and the consecutive attenuation in insulin secretion as well as increased insulin sensitivity may explain the beneficial effects of MUFA on glycaemic control.[12] Olive oil is a component of the Mediterranean diet, containing variable amounts of triacylglycerols and small quantities of free fatty acids, glycerol,

pigments, aroma compounds, sterols, tocopherols, phenols, unidentified resinous components and others. [13] The pharmacological properties of olive oil, the olive fruit and its leaves have been recognized as important components of medicine and a healthy diet because of their phenolic content. [14]

Aegle marmelos

Aegle marmelos L. (Rutaceae), commonly known as bael, golden apple, stone apple or wood apple, is a species of tree native to the Indian subcontinent and Southeast Asia. [15] *Aegle marmelos* L. is a moderate sized, slender tree, 5.0 -8.5 m in height found wild throughout the Indian deciduous forests, up to an altitude of 1300 meter in the western Himalayas and also in Andaman Island. [16]

Mechanism of action

It was reported that *Aegle marmelos* fruits extract was capable enough to reduce oxidative stress by scavenging DPPH free radicles, lipid peroxidation and enhancing levels of antioxidant enzymes which causes lowering of elevated blood glucose level. [17]

Coccinia indica

The *Coccinia indica* (Bimba, Kundru) fruits belonging to Cucurbitaceae family are a common vegetable consumed in north India. It is traditionally known to reduce the high glucose levels. [19]

Mechanism of action

The blood sugar lowering effects of ethanol extracts of whole plant and root of Coccinia indica (Bimba) were tested in different experimental models. While the plant-extract reduced the blood sugar levels of fasted, glucose loaded and streptozotocin-induced diabetic albino mice to different degrees, root extract reduced the blood sugar only of glucose-loaded animals. [20]

Gymnema Sylvestre

Gymnema sylvestre (Asclepiadaceae) also known as ‘gudmar’ or ‘sugar destroyer’ is a woody, climbing traditional medicinal herb which has many therapeutic applications in Ayurvedic system of medicine. It is used for lowering serum cholesterol, triglycerides and blood glucose level (hypoglycemic or antihyperglycemic).G. sylvestre (Asclepiadaceae) a vulnerable species is a slow growing, perennial, medicinal woody climber found in central and peninsular India. Its leaves, called “Gudmar” in India are well known for their sweet taste suppressing activity and are used for the treatment of diabetes mellitus. [21]

Mechanism of action

Hypoglycaemic activity or anti-hyperglycaemic activity *Gymnema sylvestre* has long been used as a treatment for diabetes. [22][23][24].When Gymnema leaf extract is administered to a diabetic patient; there is stimulation of the pancreas by virtue of which there is anincrease in insulin release. [25] These compounds have also been found to increase faecal excretion of cholesterol. [26] The effects of an alcoholic extract of *G. sylvestre* (GS4) on insulin secretion from islets of Langerhans and several pancreatic β-cell. [27] GS4 stimulated insulin release from β-cells and from islets in the absence of any other stimulus, and GS4-stimulated insulin secretion was inhibited in the presence of 1mM EGTA.

Momordica charantia

Experimental and clinical studies revealed anti-diabetic and adapt genic properties of the aqueous extract of *Momordica charantia*. The aqueous extract of the fruits was more effective in diabetes than the powder of the dried fruit. [28]

Mechanism of action

M. charantia and its various extracts and components are believed to exert their hypoglycemic effects via different physiological, pharmacological and biochemical modes.[29][30][31] The possible modes of the hypoglycemic actions of *M. charantia* and its various extracts and compounds are its hypoglycaemic effect, [32] stimulation of peripheral and skeletal muscle glucose utilisation,[33][34] inhibition of intestinal glucose uptake,[35] inhibition of adipocyte differentiation, suppression of key gluconeogenic enzymes stimulation of key enzyme of HMP pathway, [36] and preservation of islet β cells.It inhibits glucose 6-phosphatase in addition to fructose-1, 6- bis-sepsfatase in the liver and stimulates glucose 6-phosphate dehydrogenase

Pterocarpus marsupium

Pterocarpus marsupium Roxb. (Leguminosae) is a plant drug belonging to the group called *Rasayana* in ayurvedic system of medicine.[37] In Ayurveda, aqueous extract of heart-wood of *P. marsupium* is used in treatment of diabetes. *Pterocarpus marsupium* is one such plant that has been used for over thousands of years as a treatment of different diseases. It is used in 'Ayurveda' as 'Rasayana' for the management of various metabolic disorders It has a long history of numerous traditional and ethnobotanical applications in diverse cultures. Many tribes considered it as a cure for all ailments.

Mechanism of action

Comparative studies of (-) epicatechin and insulin confirm the similarity between these two compounds. They both exert protective effects on human erythrocyte osmotic fragility, stimulate oxygen uptake in fat cells and tissue slices of various organs, increase the glycogen content in rat diaphragms while simultaneously increasing the glucose uptake, and inhibit theophylline induced lipolysis in isolated fat pads.Despite their similar properties, both insulin and (-) epicatechin act by a different mechanism of action due to separate binding sites. Correlations between (-)-epicatechin stimulated cAMP content in the islets of Langerhans and insulin release as well as the conversion of proinsulin to insulin and cathepsin activity have

been observed. These effects were studied in mature and immature rats. It was found that exposure of the islets in vitro to (-)-epicatechin increased the cAMP content of the islets even with non-stimulatory concentrations of glucose.

The increase in cAMP activity is attributed to epicatechin and glucose that raise intracellular Ca concentration in the islets.(-)-Epicatechin has also been shown to have an effect on the conversion of proinsulin to insulin. Several researchers have attributed the conversion to cathepsin B (an enzyme that digests proteins) although it is not known how this compound is involved. Ahmad and coworkers confirmed their findings. They observed a corresponding increase in the cathepsin B activity in islets with the conversion of proinsulin to insulin even at suboptimal glucose concentrations. [38]

Swertia punicea

Swertia plants are most widely used traditional medicines in the treatment of diabetes. It belongs to the family Gentianaceae. Some plant extracts and xanthonoids, the major class of compounds among the chemical constituents of this genus, have been reported to show significantly anti-diabetic activities. [39]

Mechanism of action

The mechanism of action of the *Swertia Punicea* is glucose reducing effect by improving insulin resistance, which increases the absorption and secretion of insulin.[40] The varied ethnobotanical uses of *S. chirayita* have led to the initiation of various pharmacological investigations. Previous research demonstrates that the *S. chirayita* extracts exhibit a wide range of biological activities, such as antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, and others like anti-diabetic and antioxidant activities.[41]

Ferula assa-foetida

Ferula asafoetida is herbaceous plant of the Umbelliferae family. It is a oleo gum resin obtained from the rhizome and root of plant. Plants have been a constant source of drugs and recently, much emphasis has been placed on finding novel therapeutic agents from medicinal plants. Today many people prefer to use medicinal plants rather than chemical drugs. It is popular household remedies and its components are used for many prescriptions in traditional healing.[42] Asafoetida is used as a flavouring agent and forms a constituent of many spice mixtures. It is used to flavour, curries, meatballs, dal and pickles.

Mechanism of action

Presence of antioxidant compounds in *Ferula asafoetida* gum can acts by reducing the amount of intracellular free radicals and stimulation of the synthesis and secretion of insulin or hyperplasia of the remaining beta cells pancreas. Anthoczone gum may reduce blood glucose by stimulating the synthesis and secretion of insulin and hyperplasia of the remaining β- pancreatic β-cells.[43]

Syzygium cumini

Syzygium cumini, commonly known as *Jamun* belonging to family Myrtaceae, is one of them. It is a large evergreen tree up to 30 m in height and a girth of 3.6 m. *Syzygium cumini* has been valued in Ayurveda and Unani system of medication for possessing variety of therapeutic properties. It is mainly cultivated in the Eastern Africa, Madagascar, South America. [44] The ripe part of this fruits is used to make health drinks, squashes, jellies and wine and used to treat different health problems, and most effective for diabetes mellitus. Traditionally the fruits, leaves, seeds, and bark are all used in Ayurvedic medicine.

Mechanism of action

The cAMP content increases langerhans, which is associated with increased insulin production. This plays a vital role in converting perinsulin to insulin with increased activity of catepsin. It increases the activity of insulin and inhibits the activity of Na / K ATPase from the patient's erythrocytes.[45]

Urtica Dioica

Anti-diabetic drugs from natural plants are still attractive because of their low side effects, easy availability, roughly low cost, and also high effectiveness. *Urtica dioica* L., is a perennial herbaceous plant belonging to the Urticaceae family, [46] is one of the medical herbs that has been traditionally consumed for a long time as medicinal plants in Iran and many parts of the world. Several studies showed the beneficial effects of *U.dioica* against different diseases such as rheumatoid arthritis and diabetes. [47]

U. dioica has been extensively studied and has been promising in the treatment of prostate enlargement,[48] urinary tract infections and inflammation, nephrolithiasis, allergies, poor circulation, spleen enlargement, diabetes and other endocrine disorders.

Mechanism of action

The aqueous *Urtica dioica* extract plays an important role by improving the morphology and or function of beta cells. Preventing damage to beta-cell cells, repair damaged β-cells, rebuilding new cells, and stimulating insulin secretion in functional cells is one of the mechanisms of action of the extract of this plant. [49]

Trigonella foenum graecum

Trigonella foenum graecum L. (fenugreek) belongs to family Fabaceae is a self-pollinating plant that grows annually throughout regions of North and South America, Africa, Australia, Asia and Europe and is used as a daily ingredient in Africa, Asia, and the Mediterranean. [50] It is used as an ingredient in curry dishes, bread, and condiments, and tastes similar to maple syrup. Fenugreek can be consumed as a powder, dried seed, fried, or raw. Fenugreek seeds and leaves consist of vitamins, minerals, fibers, saponins, alkaloids, flavonoids, carbohydrates, proteins and lipids, iron, and calcium. [51] Fenugreek seeds also have a high volume of

antioxidants. These phytochemical and chemical compounds serve as protective agents for diabetes mellitus and hypoglycaemia, liver, and kidney disorders. Various studies have shown the positive effect of fenugreek seed extract in curbing symptoms of diabetes mellitus, including glucose absorption and insulin resistance.

Mechanism of action

The therapeutic effect of fenugreek seed on diabetes is at least partly due to the direct stimuli of an amino acid called hydroxysolecuine-4 on insulin secretion from beta cells. After the cellular damage, the activity of Ca ATPase and Na/K ATPase pumps decreases by due to the consumption of fenugreek seeds by reducing the free radicals eliminating these disorders. The seeds of the fenugreek were investigated for anti-diabetic potential. The inhibitory potential of ethyl acetate and water extract of *T. foenum-graecum* on enzymes α-amylase and α-glucosidase was investigated. Fenugreek demonstrated α-amylase and α-glucosidase inhibitory potential which may serve as a lead for isolation and identification of compounds responsible for it. In a study of the effects of the hydro-alcoholic extract of *T. foenum-graecum* seeds in a mouse model of diabetes induced by a standardised high-fat diet (HFD), *T. foenum-graecum* extracts opposed the development of diabetes compared with untreated HFD mice, *T. foenum-graecum* -treated HFD mice showed lower mean plasma glucose, plasma insulin and triglycerides, and less insulin resistance as estimated by the homeostasis model assessment. [52]

CONCLUSION

This review discussed selective herbal plants and showed that they have anti-diabetic activity. Diabetes mellitus is a most common endocrine disorder, affecting more than 300million people world-wide. For this, therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Hereby, treating diabetes mellitus with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, an attempt has been made to compile the reported hypoglycaemic plants from India and abroad and may be useful to the health professionals, scientists and scholars working the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of diabetes in man and animals. It assists the researchers to understand mechanism of action, structure and potential anti-diabetic activities of scientific evaluated plants.

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CONFLICT OF INTEREST

The author do not have any conflict of interest.

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