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Medicinal plants with anti diabetic potential

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Abstract

Since ancient times, plants have been an exemplary source of medicine. Human mortality has been significantly increased in last few decades due to the increased prevalence of obesity and associated chronic disorders such as type 2 diabetes, non-alcoholic fatty liver disease, coronary heart disease and atherosclerosis. Aside from hereditary and medicine or drugs related side effects, almost nearly 90– 95 % people become obese due to the imbalanced calorie intake and lack of nutritional information. Although different therapeutic approaches reported with pharmacological drugs to reduce diabetes, the higher cost and severe side effects such as increased blood pressure, dry mouth, constipation, headache, oily stools and insomnia made them less popular to the people for long-term use. In order to develop safer alternative medicines for reducing Diabetes a number of natural products have been evaluated from various medicinal plants. Although a wide range of studies was conducted on in vitro and in vivo models targeting different cell signaling pathways, none of these studies was either isolated or examined the anti-diabetic effects of pure bioactive compounds from any one of these plants. In our present review, we differentiated the anti-diabetic effects of various medicinal plant extracts, fractions and their bioactive compounds at in vitro, in vivo and clinical conditions. During our review, we could likewise distinguish the most effective plants with strong anti-diabetic effects at in vitro or in vivo studies with lack of clinical trials when nobody tried to isolate pure bioactive compounds from these plants. Subsequently, the scientific community, government agencies/pharmaceutical industries should work together not only to isolate pure bioactive compounds but also to conduct clinical trials including toxicity to develop better alternative anti-diabetic drugs.

Keywords: Type 2 Diabetes, Hypoglycemic drugs, Holy basil, *Momordica charantia*, Insulin.

Introduction

Diabetes 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 Diabetes mellitus. 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].Type 2 diabetes usually occurs in obese individuals and is associated with hypertension and dyslipidemia. Thus, the treatment aims to reduce insulin resistance and to stimulate insulin secretion. Diabetes is a metabolic disorder wherein human body does not produce or properly use insulin, a hormone that is required to convert sugar, starches, and other food into energy. Diabetes mellitus is characterized by constant high levels of blood glucose (sugar). The human body has to maintain the blood glucose levels at a very narrow range which is done with insulin and

glucagon. The function of glucagon is causing the liver to release glucose from its cells into the blood for the production of energy. Type 1 Diabetes leads to an inability to release insulin results in low rates of glucose uptake into muscles and adipose tissue [2].

There are different approaches to the treatment of diabetes, like insulin treatment in type 1 diabetes: Sulphonylureas (e.g: Glipizide, Tolbutamide, Glicazide), which release insulin from pancreas by blocking the ATP-sensitive potassium channels ;Biguanides (e.g: Metformin), which decrease the insulin resistance; Thiazolidinediones (e.g: Pioglitazone), which increase the insulin sensitivity; alpha-glucosidase inhibitors like acarbose, which decrease glucose absorption from intestine, thereby decreasing postprandial hyperglycemia; mitiglinide like repaglinide and nateglinide, which are insulin secretagogues.

Some of the mineral remedies consist of Bangabhasma (calcinated tin), Jistbhasma (calcinated zinc), Abrhabhasma (mica ash), and Lohabhasma (calcinated iron). Some of the commercial preparations (e.g., Nowojar) containing bhasmas were very effective in NIDDM; in case of IDDM, it helped in reducing the dose of insulin. Some complexes with metformin and tolbutamide with zinc, cadmium, cobalt, and copper have some complexes with the exception of complexes have shown good hypoglycemic effect. Zinc complexes have shown to have good blood-sugar-lowering activity. Shilajit, an organo-mineral preparation found in nature, has been used as a tonic in diabetes mellitus [3].

In the described conventional drugs gives various adverse effects as like- hypoglycemia (it is the commonest problem but may become occasionally severe and rarely fatal), nonspecific side effects tend to gain 1-3 kg weight, Hypersensitivity (it produce rashes, photosensitivity, purpura, etc).

The Herbal medicine is the use of plants to prevent and treat an illness or to achieve good health, as well as the drugs and tinctures that are used. Traditional herbal mineral plays an important part in the treatment of diabetes. If we were able to even identify some [4-6] herbal drugs that can reduce the dose of insulin by increasing resistance sensitivity, reducing insulin resistance, then we would have positively contributed to the treatment of diabetes. Herbal medicines are often used as therapeutic remedies in combination with allopathic drugs. Most of the doctors did not report any complication.

This review article enumerates some medicinal plants possessing antidiabetic activity and elucidating their mechanisms of action such as *Brassica juncea* (*B.juncea*), *Combretum micranthum* (*C. micranthum*), *Elephantopus scaber* (*E. scaber*), *Gymnema sylvestre* (*G.sylvestre*), *Liriope spicata* (*L. spicata*), *Parinari excels* (*P.excelsa*), *Ricinus communis* (*R. communis*), *Sarcopoterium spinosum* (*S. spinosum*), *Smallanthus sonchifolius* (*S.sonchifolius*), *Swertia punicea* (*S.punicea*), *Vernonia anthelmintica* (*V. anthelmintica*) etc. and method ofexperiment on animals and therapeutic efficiency of plant extracts were exploited.

Synthetic drugs and herbal medicine

Oral hypoglycemic drugs are used only in the treatment of type 2 diabetes which is a disorder involving resistance to secreted insulin. Type 1 diabetes involves lack of insulin and requires insulin for treatment. There are now four classes of hypoglycemic drugs: These drugs are approved for use only in patients with type 2 diabetes and are used in patients who have not responded to diet, weight reduction, and exercise. They are not approved for the treatment of women who are pregnant with diabetes. Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes and appear to function by stimulating insulin secretion. The net effect has increased the responsiveness of ß-cells (insulin secreting cells located in the pancreas) to both glucose and non-glucose secretagogues, resulting in more insulin being released at all blood glucose concentrations. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal. Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people also safe and effective for health, healing, weight loss/gain/maintenance.

Herbal medicines are great body balancers that help regulate body functions, can be used to support balance process of our body and offer the nutrients that the body fails to receive due to poor diet or environmental deficiencies in the soil and air. They can be used to treat many diseases such as diabetes, asthma, eczema, premenstrual syndrome, rheumatoid

arthritis, migraine, menopausal symptoms, chronic fatigue, and irritable bowel syndrome, etc., and can be used for maintaining general health. Herbal preparations are best when taken under the guidance of a trained professional. When used correctly, herbal medicines are considered safer than conventional medications. People are greatly concerned about the efficacy and side effects of many synthetic drugs, and hence choose herbal medicines for providing a safe and natural alternative treatment for many health problems. The use is widespread and growing, In fact, herbs are always the alternative medicine and primary source.

The advantages of using herbal medicines are numerous. They tend to be more effective for long-standing health complaints that don't respond well to traditional medicine. Herbs typically have fewer side effects and may be safer to use over time [5].

Antidiabetic plants

Researchers conducted in the last few decades on plants, mentioned in ancient literature or used traditionally for diabetes, have shown an anti-diabetic property.

1. *Allium cepa* (*Onion*) and ***Allium sativum*** (*Garlic*):- (Family: ***Liliaceae***):- is an important dietary constituent. It consists of alliins, polysaccharides and saponins [16,17].

The active components are believed to be sulfur-containing compounds – allyl propyl disulfide (APDS) in onions and diallyl disulfide (allicin) in garlic.[18] In 2001, a significant decrease in glucose levels was reported in humans following garlic treatment.[19] Studies have suggested that *A. sativum* controlled the blood glucose in serum and altered the activities of liver hexokinase glucose-6-phosphatase and haemoglobin coenzyme-A reductase towards normal and administering in the concentration of 10 ml/kg/day to rabbits significantly increased liver glycogen and free amino acids, which resulted in significant decrease in fasting blood sugar, triglycerides (in serum, liver and aorta) and liver serum proteins as compared to those in sucrose-fed group.[20] Various ether soluble fractions of onion as a single oral dose (0.25 mg/kg) showed a significant hypoglycemic effect in normal fasted rabbits and was reported to decrease hyperglycaemic peak in subcutaneous glucose tolerance tests conducted in rabbits and it was suggested that it can be a useful substitute for tolbutamide in controlling alloxan diabetes in rats.[21]

2. Aegle marmelos **(Family: Rutaceae)** The main chemical constituents Mahanimbine, girinimbine, koenimbine.

The studied have reported that aqueous extract of the leaves (1 gm/kg for 30 days) significantly controlled blood glucose, urea, body weight, liver glycogen and serum cholesterol of alloxanized (60 mg/kg IV) rats as compared to controls and this effect was similar to insulin treatment. The extract was equal-effective in comparison to insulin in restoring blood glucose and body weight to normal levels[21,22].Consequently, the active principle of *A. marmelos* extract had the similar hypoglycaemic effect to that of insulin[22].

3. Murraya koeingii (Family: Rutaceae)**,** commonly known as curry leaf tree in English, is grown for its aromatic leaves and used extensively as a flavouring agent(P-gurjunene, P-caryophyllene, P-elemene and O-phellandrene.)

The Oral feeding of M. koeingii leaves diet (10% w/w) for 60 days to normal rats showed hypoglycemic effect associated with increased hepatic glycogen content due to increased glycogenesis and decreased glycogenolysis and gluconeogenesis[20,21,22]. Many enzymes of the liver including gluconeogenic, enzymes have been reported to be affected by spice both in vitro cell culture systems as well as in vivo in experimental animals [21].The studies have depicted an interesting finding that suggests M. koeingii probably prevents the destruction of b cells of islets in the pancreas, it may have antioxidant or free radical scavenger properties in preventing these changes. Thus, M. koeingii may have a role in the prevention of diabetes and its consumption should be encouraged in the early diabetic stage [23].

4. *Gymnema sylvestre* (Family: Asclepiadaceae), called gurmar or Merasingi, is a woody, climbing plant, native to India. The main constituents are gymnemic acid, gurmarin, a polypeptide of 35 amino acids and saponins [24,17]. Investigation of the hypoglycaemic activity of saponin constituents from gymnemic acid, a crude saponin fraction of G. sylvestre, identified not only two new saponins, gymnemosides a and b, but also gymnemic acid V as the active principle [22]. Its triterpene glycosides isolated from plant inhibited glucose utilization in

muscles and Gymnemic fractions also inhibit glucose uptake in the intestine.

According to a study, G. sylvestre enhances the production of endogenous insulin[18]. The studies have revealed that the drug acts indirectly through stimulation in insulin secretion of the pancreas, as it has no direct action on the carbohydrate metabolism and it significantly reduced glucose levels in the hyperglycemic rats, it had no effect on normal rats. It was found that gymnemic acid molecules prevent activation of taste buds by sugar molecules, curbing the sugar craving by filling the receptor locations on the taste buds. Similarly, gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood sugar level[22].It was also found that the G. sylvestre aqueous extract of leaves stimulates insulin secretion from mouse cells and isolated human islets in vitro, without compromising cell viability and the crude extracts and its isolated compound dihydroxy gymnemic triacetate shows a hypoglycaemic effect against streptozotocin-induced diabetic rats in dose and time-dependent manner[25].

5. Ficus bengalenesis (Family: Moraceae) It yields latex containing cycloartinol (2.4%), Resin, Albumin, Cerin, Sugar and Malic acid.

A glucoside (α amyrin acetate) isolated from the bark of *F. bengalenesis* showed more potent hypoglycaemic action as compared to crude ethanolic extract and the activity was half of the tolbutamide. A glycoside of leucopelargonidin isolated from the bark of *F. bengalensis* exerts significant hypoglycaemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats with close similarities to the effects of a minimal dose of glibenclamide. In addition, pelargonidin was more potent than leucocyanidin in stimulating in vitro insulin secretion by beta cells. Leucodelphinidin (250 mg/kg) also showed hypoglycemic action equal to that of glibenclamide (2 mg/kg) in normal and alloxan-diabetic rats[21,26].

6. Ocimum sanctum (Family: *Labiatae*), commonly known as Holy basil in English, The main chemical constituent is tocotrienol.

Oral administration of an alcoholic extract of leaves of *O. sanctum* reduced glycaemia in normoglycaemic, glucose-fed hyperglycaemic and streptozotocin-induced diabetic rats. Furthermore, the extract potentiated the action of exogenous insulin in healthy rats. Administration of leaf powder to healthy and diabetic rats resulted in a reduction of fasting blood glucose after one month [20,21,27].

7. Panax ginseng (Family: Araliaceae) are slow-growing perennial plants with fleshy roots. The root of ginseng has been used for over 2,000 years in the Far East for its health-promoting properties. It is found to contain triterpene glycosides, or saponins commonly referred to as ginsenosides, *Panaxtriol germanium* polysaccharides, peptides, polyacetylenic alcohol, and fatty acids.

Ginseng polypeptide, isolated from the root of *P. ginseng*, was demonstrated to decrease the level of blood sugar and liver glycogen when injected intravenously into rats. The aqueous extract of root of *P.ginseng* showed a remarkable hypoglycemic activity on the administration to mice. It increases insulin production, reduces the death of pancreatic β-cells and insulin resistance, improves postprandial glycemia in diabetic patients. Ginseng also elevated mood, improved psychophysiological performance and physical activity, and reduced body weight[17,18,19,20,28,29].

8. Momordica charantia (Family: Cucurbitaceae), commonly known as bitter melon, bitter gourd or karela, is grown in tropical countries of Asia, Africa and South America. It is a very common folklore remedy for diabetes and the blood sugar-lowering action of the fresh juice or unripe fruit has been established in animal experimental models as well as human clinical trials. The major compounds isolated from this plant and identified as hypoglycemic agents are Charantin, momorchiarin, momordicin, polypeptide-P and vicin [20,31].

Various studies have shown a hypoglycemic effect in various animal models using an extract of fruit pulp, seed, leaves and whole plant of *M. charantia* [29,32]. Alcohol-extracted charantin from *M. charantia* consists of mixed steroids and was found to be more potent than the oral hypoglycemic agent tolbutamide in an animal study. Bitter melon also contains an insulin-like polypeptide, polypeptide- P, similar in structure to bovine insulin. It was found to decrease blood sugar levels when injected subcutaneously into type 1 diabetic patients and appears to inhibit gluconeogenesis and is believed to improve glucose tolerance in Type II diabetes [22,27,29]. Fried karela

fruits consumed as a daily supplement to the diet produced a small but significant improvement in glucose tolerance in diabetic subjects without any increase in serum insulin levels[18].

9. Eugenia jambolana (Family: Myrtaceae)**,** commonly known as Jamun or black plum, is being widely used to treat diabetes by the traditional practitioners over many centuries. It is a large evergreen tree growing up to 30 m high found widely in India[17,24]. Preliminary studies on seeds and decoction of dry leaves of *E. jambolana* have shown anti-hyperglycemic activity [21, 23, 29].Chemical constituents are anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol and myrecetin.

The oral administration of the pulp extract of the fruit resulted in the enhancement of insulinemia in normoglycaemic and diabetic rats. The incubation of isolated pancreatic islet cells of normal and diabetic animals with this plant extracts resulted in increased insulin secretion. In addition, the extract inhibited insulinase activity from liver and kidney [22]. Oral administration of a dried alcoholic extract of the seeds caused hypoglycemia and reduced glycosuria. In addition, the treatment also partially restored altered hepatic and skeletal muscle glycogen content and hepatic glucokinase, hexokinase, glucose-6-phosphate and phosphofructokinase levels [21,27].

10. Picrorrhiza kurroa (Family: Scrophulariaceae), Dried rhizomes and roots of the plant are being used for medical treatment. Recently, it has been known that alloxan induces its diabetogenic activity mainly by inducing oxygen free radicals and thereby damaging the pancreas. *P. kurroa* extract was found to reduce the glucose level in normal, glucose loaded animals and in animals made diabetic with alloxan.

It was reported earlier that *P. kurroa* extract can act as a free radical scavenger in vitro and it indicates that administration of *P. kurroa* can reduce the level of serum lipid peroxides as well as ameliorate the destruction of WBC and confirms the possibility that the major function of the extract is on the protection of vital tissues including the pancreas, thereby reducing the causation of diabetes in these animals [23,27]. Alcoholic extract of *P. kurroa* (75 mg extract/kg) reduced serum glucose that was maximum 2 h after the dose. It also showed an antihyperglycemic effect in alloxanized diabetic rats. Chemical constituents are picroside I, picroside III, Kutkoside, minecoside, veronicoside, apocynine, kutkiol, D mannitol[21].

11. Psidium guajava (Family: Myrtaceae): It is found to contain a high percentage of vitamin C, carotene, Vit B1, B2, B6, and free sugars (glucose, fructose and sucrose)[17,33,34].

The oral administration of aqueous leaves extract of *P. guajava* at the dose of 500mg/kg b.w for 15days have shown beneficial effect not only on blood glucose but also on body weight, glucose and ketone level of urine and tissue of pancreas in streptozotocin-induced adult albino diabetic rats. Methanolic extract (51%) of *P.guajava* leaves showed a hypoglycemic effect in type 2 diabetes[22]. Flavonoid glycosides such as strictinin, isostrictinin and pedunculagin are the effective constituents, which have been used in clinical treatment of diabetes to improve the sensitivity of insulin. A glycoprotein was also identified as an active component for anti-diabetes[32].

12. Berberine fenurgreek (Family: Leguminosae) It is found to contain mucilages, proteins, proteinase inhibitors, steroid saponins and saponin-peptide esters, sterols, flavonoids, nicotinic acid, coumarin, trigonelline and volatile oil.

The effect of fenugreek seed on blood glucose and the serum lipid profile was reported in insulin-independent (type 1) diabetes patients. Administration of the defatted seed (1.5-2.0 g/kg daily) to both normal and diabetic dogs reduced fasting and postprandial blood levels of glucose, glucagon, somatostatin, insulin, total cholesterol, and triglycerides, and increased HDL-cholesterol levels. The intake of seed fiber of *T. foenumgraecum* reduces the rate of glucose absorption and may delay gastric emptying, thereby preventing the rise in blood sugar levels following a meal. Seed's fiber also stimulates insulin receptor sites to burn cellular glucose at high fiber diet. Mechanism of action of fenugreek seeds as an orally active hypoglycemic effect may be mediated through stimulating insulin synthesis and or secretion from the beta pancreatic cells of Langerhans. The therapeutic role of Trigonella seed powder in type 1 diabetes is due to change of glucose and lipid metabolizing enzyme activities to normal values, thus stabilizing glucose homeostasis in the liver and kidney.chemical constituents 4 hydroxy isoleucine, trigonelline, sotolone, furostan [21].

13. Lawsonia inermis (Family: Lythraceae), commonly known as Henna or Mehndi, is a much branched glabrous shrub or small tree, cultivated for its leaves is found to constitute carbohydrates,

proteins, flavonoids, tannins and phenolic compounds, alkaloids, terpenoids, quinones, coumarins, xanthones and fatty acids. Main chemical components are lawsone, esculetin, fraxetin, isoplumbagin, scopoletin, betulin, betulinic acid.

Ethanol (70 %) extract of *L. inermis* showed significant hypoglycaemic and hypolipidaemic activities in alloxan-induced diabetic mice after oral administration[35]. Decreased concentration of glucose, cholesterol and triglycerides to normal was seen by feeding of 0.8 g/kg of *L. inermis* extract. Methanol (95 %) extract of leaves of *L. inermis* was found to possess significant *in-vitro* antihyperglycemic effect[24].

14. Cinnamomum zeylanicum (Family: Lauraceae), commonly known as Cinnamon, is harvested by growing the tree for two years then coppicing it. The mainly constitute volatile oils, containing cinnamaldehyde, ethyl cinnamate, eugenol (found mostly in the leaves), beta-caryophyllene, Linalool, and methyl chavicol.

Cinnamon ingestion reduced total plasma glucose responses measured by area under the curve (AUC) to oral glucose ingestion as well as improved insulin sensitivity[36].Cinnamon supplementation may thus be important to *in vivo* glycaemic control and insulin sensitivity in humans and they also appear to be sustained for 12 hours. Cinnamon also significantly delayed gastric emptying and profoundly lowered postprandial glycaemic response without any significant effect on satiety[37,17].

15. Tinospora cordifolia (Family: Menispermaceae) It is widely used in Ayurveda as a tonic, vitalizer and as a remedy for diabetes and metabolic disorders[16]. The main constituents are found to be adaptogens**,** alkaloids, diterpenoid lactones, glycosides, steroids, Sesquiterpenoid, phenolics, aliphatic compounds and Polysaccharides[40]. Leaves of this plant are rich in protein (11.2%) and are fairly rich in calcium and phosphorus[38]**.**

Oral administration of the aqueous extract of *T. cordifolia* root produced a significant reduction in blood glucose, brain lipid level, hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline and lactate dehydrogenase and increase in body weight, total haemoglobin and hepatic hexokinase in alloxanized diabetic rats[21,22].

Future Trends

Current knowledge of altered body metabolism during diabetes mellitus can be utilized for the development of new trends in herbal antidiabetic research. Polypeptides to proteins, all have an efficient antidiabetic effect. Secretions from plants that are co-secreted with insulin have demonstrated to inhibit insulin release and muscle glycogenesis. Amylin is thought to play a major role in the disturbed metabolism associated with diabetes mellitus. The search for drugs that may antagonize amylin, and thus improve metabolic control in diabetic patients, is considered as a frontier in the search for novel antidiabetic agents. Medicinal plants that have been shown to improve the diabetic state without apparent enhancement of insulin secretion may be tested for amylin antagonism[44].

Conclusion

In spite of the presence of known antidiabetic medicine in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease. Some of these combinations may also lead to potentially harmful interactions. It is believed that greater attention needs to be paid to the broader systems of environment and culture and their interconnections to understand the use of complimentary and alternative medical therapies. Many traditional plant treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic ones. Based on the WHO recommendations, hypoglycemic agents of plant originated in traditional medicine are important. The attributed antihyperglycemic effects of these plants are due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or a decrease in the intestinal absorption of glucose. Hence, treatment with herbal drugs has an effect on protecting -cells and smoothing out fluctuation in glucose levels. In general, there is very little biological knowledge on the specific modes of action in the treatment of diabetes, but most of the plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavonoids etc. that are frequently implicated as having antidiabetic effects. The research for alternate remedies (from the plant kingdom)for diabetes mellitus will continue all over the world as the disease poses many challenges not only to the physician but also to the researcher.

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Conflict of interest

The authors declare no conflict of interest.

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