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Herbal Approach towards the Cure of Diabetes Mellitus— A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author JAQ designed the study and wrote the first draft of the manuscript. Authors ZM and KMM wrote the protocol and managed the analyses of the study. Author FS managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Diabetes mellitus, a silent killer, is a disease which is characterized by altered metabolism of carbohydrate, protein and lipids, classically present as raised blood glucose levels. The prevalence of diabetes mellitus in increasing rapidly in both high and low-income countries. Diabetes mellitus is characterized by uncontrolled high blood glucose levels as an outcome of deficient pancreatic insulin release or poor insulin-coordinated utilization of glucose by glucose utilizing cells. Diabetes mellitus is related to a number of metabolic manifestations like atherosclerosis, with further consequences like cardiovascular disease and stroke that can lead to premature death. Numerous therapeutic agents that are available for the treatment of diabetes however these drugs have a number of restrictions, and the whole restoration from diabetes have not been accounted up till now. Herbs have been utilized from old time to cure the humankind because of their presumed lesser adverse effects, relatively high availability and relatively low cost; herbs are admired by general public. This review high lights the role of different herbs in the treatment of diabetes mellitus along with their predicted mechanism of action in relation to clinical investigations.

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease, characterized by hyperglycemia together with impaired metabolism of carbohydrate and other energy-yielding fuels, such as lipids and proteins [1,2]. Countries which are developed or even developing are facing a significant public health issue in the form of Diabetes mellitus. It is a silent killer that kills 1 person every 8 seconds across the globe and 4 million persons during a year making it the ninth major reason of mortality [3]. Globally, diabetes mellitus is emerging as an important public health problem [4]. Diabetes mellitus is classified into two major main types i.e. insulin dependent diabetes mellitus (IDDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type II) depending upon insulin deficiency or insulin resistant of peripheral tissues respectively [5,6].

2. GLOBAL PREVALENCE

The International Diabetes Federation (IDF) reported that approximately 415 million people around the world live with diabetes mellitus and it is predicted to increase ascend to 642 million by 2040 [7]. Worldwide, every 1 individual out of 11 has diabetes mellitus, in which 90% is mainly typed II diabetes. Asia is a noteworthy continent where prevalence and complications related to chronic diabetes reaches to utmost level, with India and China are the two topmost countries [3].

3. DIABETES IN PAKISTAN

As indicated by the World Health Organization that one in four Pakistani is diabetic, and Pakistan remains at number 7 among the top ten nations having type II diabetes and it is predicted to move to number four before the end of 2030 in terms of diabetes prevalence [8].

Sindh has the highest number of diabetic patients in Pakistan and it has reached as high as 30.2%. After Sindh, Punjab and Balochistan occupied the second position incidence of diabetes, with 28.8 and 26.1 percent respectively. Khyber Pakhunkhwa was found to have the lowest prevalence of the disease, 12.9 per cent which is documented in the report of National Diabetes Survey of Pakistan 2016-17. may be due to their strenuous work and laborious lifestyle [9].

4. SYMPTOMS AND COMPLICATIONS

There are certain established sign and symptoms related to diabetes like thirst, polydipsia, polyuria along with weight reduction particularly for type I but there may be no or vague symptoms for type II diabetes. Moreover, as the disease progress, long-term complications like retinopathy, nephropathy, and neuropathy start to appear, which are high even when mild metabolic disorders continue for a longer period of time. As a result there is an increased probability of myocardial infarction, cerebral infarction, and arteriosclerosis obliterans of the lower extremities in diabetic patients. In addition, DM also causes a decrease in resistance to bacterial infection [10,11].

5. CONVENTIONAL DRUGS USED FOR TREATMENT OF DIABETES AND ASSOCIATED SIDE EFFECTS

The objective of diabetes treatment is to maintain normal blood glucose level and prevent long-term complications of uncontrolled hyperglycemia, to keep up personal satisfaction (Quality of Life), and to accomplish a life expectancy that is near to that of a healthy individual [10]. Despite the fact that insulin treatment and oral hypoglycemic drugs are the main mode of treatment for the diabetes mellitus for type I and type II respectively, they have their limitations, and these agents don't amend the course of diabetic complications [4,10].

Human insulin is a polypeptide and it is main stay of treatment for type I diabetes. However it is not devoid of limitation like hypoglycemia and its parenteral use. Moreover, dose of insulin differs from patient to patient which is required to control the diabetes and also varies from time to time in the same patient [12]. The hypoglycemic medications that are utilized for type II diabetes are given in Table 1 along with its mechanism of action and likely side effects [4,12-16].

6. EVOLUTION OF HERBS

The utilization and delivery of herbal prescription in treatment and forestalling of disease has a long history which began with the consumption of Mesopotamia in 2600 B.C. [17,18]. Around 21,000 plants have been recorded by the World Health Organization (WHO), which are utilized for therapeutic rationale of various diseases around the world [19].

Table 1. Conventionally used anti diabetic agents along with their mechanism of action and limitations / adverse effects

Drugs	Mechanism of action	Adverse effects
Sulfonylureas	Binds to Potassium channel on pancreatic cells, resulting in depolarization, which causes endogenous insulin secretion	Hypoglycemia, deranged LFTs, weight gain
Biguanides	Increases peripheral insulin sensitization, decreases lipogenolysis in liver, decreases intestinal absorption of glucose, Increases peripheral uptake of glucose.	Diarrhea, Abdominal Pain, weight loss, lactic acidosis, B12 deficiency
Thiazolidinediones	Activates PPAR-γ causing increase insulin sensitivity, Increase glucose uptake by peripheral tissues, decrease hepatic production	Hypoglycemia, pancreatitis, Myocardial Ischemia
GLP Analogues	Decrease gastric emptying, increase insulin secretion, decrease glucagon secretion, increase peripheral utilization	Pancreatitis, nausea, vomiting
Meglitinides	Stimulate pancreatic insulin secretion	Hypoglycemia
DPP 4 Inhibitors	Inhibit degradation of intrinsic GLP-1	Flu-like symptoms, pancreatitis
ALPHA Glucosidase Inhibitors	Inhibit brush border enzymes causing decreased carbohydrate absorption	Bloating, Flatulence
SGLT-2 Inhibitors	Increase renal excretion of glucose by blocking absorption through proximal tubules	UTI, Genital infections

7. HERBAL APPROACH TOWARDS DIABETES CURE

Medicinal plants are employed for discovery of new remedies for health problems related to mankind including diabetes. Generally, various herbs have been recognized for treatment of diabetes and their glucose lowering effects are elaborated by numerous herbalists, but limited evidence exists about their exact dose, mode of action and toxicities.

The current review is focused on the medicinal plants which have potential to lower hyperglycemia and their possible mechanism of action , supported by different experimental and clinical studies [20].

8. ADVANTAGES OF HERBS

Generally, herbal remedies are well tolerated, cost effective, easily available and safer in use and more effective for long standing of good health condition. These agents do not only have therapeutic value but also have preventive roles, more over simple herbs, such as peppermint and chamomile, can be cultivated at home [21].

9. HERBAL ANTI-DIABETICS

Some of the important anti-diabetic potential herbal plants source, their active constituents and related animal studies are given in the Table: 2.

10. CLINICAL STUDIES RELATED TO ANTI DIABETIC HERBS USED IN PAKISTAN

10.1 *Allium cepa* (Onion)

Allium cepa often recognized as onion has been used medicinally for centuries [37]. Concentrates of onion have been appeared to have hypoglycemic potential by effecting the activities of liver hexokinase, HMG coenzyme-A reductase and glucose 6-phosphatase [37]. According to a clinical trial, hypoglycemic action of *Allium cepa* was investigated in type 1 and type 2 diabetic patients. Total 42 diabetic patients were divided into two groups i.e. 21 in each group. The results demonstrated that intake of crude fresh slices of *Allium cepa* (100 g) administered orally to the patients caused a significant decrease in fasting blood glucose levels by around 89 mg/dl which

Table 2. Some important Antidiabetic herbs.

Botanical name	Common name	Part used	Active constituent	Solvent system	Model used	Outcomes
Aegle marmelos	Bael	fruit	Aegelin	Aqeuous	streptozotocin-induced diabetic rats.	significant increase in insulin levels and body weight with increase in fasting blood glucose levels [22, 23]
Acacia arabica	Babool	Bark	Tanins, Quercetin	chloroform	STZ induced diabetic rats.	considerable reduction in insulin resistance, levels of serum glucose, TG, TC, and a significant elevation in HDL-C [24]
Allium cepa	Onion	Bulb	Quercetin	ethanol	STZ induced diabetic rats	helps in preservation of ß-cells function and pancreatic regeneration [25]
Allium sativum	Garlic	Bulbs	alliin, diallyl disulfide, diallyl trisulfide, allicin, diallyl sulfide,S-allyl cysteine, and allyl mercaptan	aqeous	STZ induced rats	Decrease in blood sugar levels via may be improved pancreas function with reduced serum levels of cholesterol and triglycerides and serum activities of ALT and AST [26]
Azadirachta indica	Neem	Leaf	Quercetin, rutin, and nimbidin	aqueous	alloxan induced hyperglycemic rats.	Decreased blood glucose levels [27]
Brassica juncea	Indian mustard	Seed	Isothiocyanate glycosidesingrin	methanol	glucose-loaded mice	reduced serum glucose levels [28]
Cajanus cajan	Pigeonpea	root	cajanin and concajanin	methanol	alloxan-induced diabetic Swiss albino mice.	decrease in fasting serum glucose level [29]
Eucalyptus globules	Blue gum	Leaves	Polyphenols,proanthocyanidins, anthocyanins	Aqueous	STZ induced rats	significantly increased the basal plasma insulin

Botanical name	Common name	Part used	Active constituent	Solvent system	Model used	Outcomes
						concentrations [30]
Aloe vera	Aloe	Gel from leaves	Barbaloin	Aqueous	STZ induced rats	significant increase in insulin levels, reduction in serum levels of superoxide dismutase and malondialdehyde with elevated blood glutathione [31]
Cinnamomum	Cinnamon	Bark	Cinnamaldehyde, eugenol	ethanol	high sucrose diet fed Sprague Dawley rats	Significant increase in insulin and reduction in glucose levels [32]
Olea europia	Olive	Leaf	Oleuropeoside	Aqueous	STZ induced rats	enhanced the altered levels of insulin glucose, IRA and IRS1, lipid profiles, inflammatory cardiac markers and unaltered the pancreatic histopathological changes. [33]
Ocimum sanctum	Basil	leaves	Eugenol	Aqueous	Alloxan- induced diabetic rats	significant reduction in levels of blood glucose [34]
Trigonella foenum graecum	Methi	Leaves and seeds	4-hydroxy isoleucine	ethanol	alloxan-induced diabetic rats	Significant hypoglycemic effects [35]
Zingiber Officinale	Ginger	rhizomes	gingerols, and shogaol	ethanol	STZ induced in rats and mice	dose-related, significant hypoglycaemia [36]

are compared to insulin (145 mg/dl) which eventually decreased blood glucose by 40 mg/dl, in type I diabetes, when compared with glibenclamide which reduces blood glucose level by 81mg/dl in type II diabetic patients [38].

10.2 *Allium sativum* (Garlic)

Allium sativum, normally identified as garlic, is from the family Liliaceae. Garlic has a compound allicin which has potent glucose lowering property. In recent years, it has been proved by many clinical trials that active compounds from garlic lower blood glucose levels by competing with insulin sites in the liver, which results in an increase in free insulin [39]. According to a clinical study done on the potential hypoglycemic impacts of garlic in type 2 diabetic patients which were given in the form of tablet at 300 mg thrice every day compared with Metformin for 24 weeks. The results showed that due to garlic there was a significant decrease in fasting blood glucose levels [40].

10.3 *Zingiber officinale* (ginger)

The *Zingiber officinale* Roscoe generally known as ginger is broadly utilized as a part of conventional medication. It enhances glucose uptake and GLUT4 expression and shows powerful hypoglycemic action. It possesses potential antidiabetic activity and also has been proved to have protective effects on diabetic nephropathy and retinopathy which are the atrocious complications. It also acts as an antioxidant and antiglycating agent [41]. In a unicenter clinical study, done on thirty two male diabetic patients, 3 g of dry ginger powder given for 30 days demonstrated improvement in blood glucose, triglyceride, total cholesterol, LDL, and VLDL cholesterol [42]. In a double-blind, randomized controlled clinical trial conducted on type 2 diabetes patients. Administration of 3 gm of ginger powder everyday for 12 weeks showed improved blood glucose levels [43].

10.4 *Aloe vera*

Aloe vera (Aloe vera L., Liliaceae family) has been widely used for medication purpose and cosmetic industry. It possesses antioxidant, anticancer, anti-inflammatory, laxative, anti-atherosclerosis properties. It contains 75 active compounds including vitamins, enzymes, minerals, sugars, Lignin, salicylic acid, and amino acids [44]. It enhances generation of beta cells as well as release of insulin from pancreatic beta cells [45] A double blind randomized controlled trial was done on patients with diabetes. To one group *Aloe vera* was given at a dose of 300 mg for two months and the other group was given placebo. Administration of *A.vera* demonstrated significant decrease in fasting blood glucose, HbA1C and lipid levels in test group when compared to control group [44]. In another clinical study including obese untreated DM patients, *Aloe vera* gel complex showed reduction in their body weight, body fat mass, and insulin resistance [46].

10.5 *Azadirachta indica* (Neem)

Azadirachta indica, commonly known as neem in different parts of the world is a huge evergreen tree that belongs with the family Meliaceae. Nimbin, nimbidin and nimbinene are the major constituents of the tree. The neem tree leaves contains quercetin and nimbosterol with various liminoids [47] .

A trial was conducted to assess the glucose lowering potential 70% alcoholic neem root bark extract (NRE) in diabetic patients. The results demonstrated that neem extract significantly improves blood glucose levels at 800 mg/kg dose in comparison with the standard medication glibenclamide at the dosage of 200,400 and 800 mg/kg [48].

10.6 *Eugenia jambolana* (Jamun)

Eugenia jambolana Lam., generally called black plum or “jamun” is an important therapeutic plant in herbal medicine. It is helpful in the management of diabetes mellitus, swelling, ulcers and stomach problems, attributed to saponins, glycosides, and flavonoids present [49].

The pulp extract of jamun showed potent hypoglycemic activity when administered orally to STZ induced diabetic rats , attributed to increased insulin secretion [50]. In another study, when 15 mg/kg dose of jamun was given daily for 8 weeks, led to significant fall in fasting blood glucose [51].

In a clinical trial, jamun seed powder was supplemented to Type II diabetic subjects for duration of two months both in roasted and crude forms. Results demonstrated that roasted seed powder has potent hypoglycemic and hypocholestrolemic activity when compared with the crude seed powder [52].

10.7 *Momordica charantia* (Bitter gourd)

Momordica charantia is generally utilized as an antihyperglycemic agent not only in Pakistan but also in other Asian nations without accurately measured evidence of their exact mechanism of action and proper doses. Research on its phytochemical constituents showed that it contains phenolic components like simple phenols, benzoic acid derivatives, lignans, flavonoids, phenylpropanoids, carotenoids, and tannins. [53] In a randomized placebo controlled, single blinded clinical trial, 52 people with pre-diabetes were examined after the administration of bitter gourd at 2.5 g powder supplementation for two months duration. Results showed that bitter gourd has benefits in bringing down elevated fasting plasma glucose levels in prediabetes patient [54].

10.8 *Ocimum sanctum* (Basil)

Tulsi is among the most popular herbs used in South East Asia. The leaves of the Tulsi contain fundamental oils including carvacrol, ursolic acid, eugenol and the seeds contain fixed oils, including oinoleic acid, oleic acid, palmitic acid, and stearic acid . In Asian continent, fresh leaves of this plant are most commonly used for the treatment of cough, cold, abdominal pain, skin diseases, arthritis, painful eye diseases, measles, and diarrhea [55].

Eugenol is thought to be the most important bioactive compound among all the components for reducing blood glucose level [56].

A clinical trial was carried out to find out the antidiabetic effect of *Ocimum Sanctum* in type 2 diabetes for duration of 90 days. Patients were given a dose of 250 mg two times a day. Results showed considerable decrease in fasting blood glucose, HbA1c and post prandial blood glucose levels after 90 days [57].

10.9 *Trigonella foenum graecum:* (Fenugreek)

Fenugreek is found all over South Asia and its seeds are typically utilized as one of the traditional constituents of eastern flavors. It stimulates insulin production as well as secretion from the beta pancreatic cells of Langerhans [58]. Fenugreek seed extracts can possibly slow down the enzymatic integration of starches, diminish gastrointestinal ingestion of glucose, and subsequently decrease post-prandial glucose levels [59].

In a double blind, multi-center, randomized controlled, clinical trial, the efficacy of fenugreek seed extract (500 mg bid) was assessed in 154 subjects (25– 60 years) with Type 2 diabetes. Results showed that Fenugreek seeds caused considerable decrease in both fasting plasma and post-prandial glucose levels [60].

10.10 Cinnamomum (Cinnamon)

It has been proposed that the active ingredient through which cinnamon imparts its effects on blood glucose is cinnamaldehyde [61]. In a double blind randomized clinical trial, administration of cinnamon extract at a dose of 120 mg and 360 mg, demonstrated decrease in both fasting blood glucose levels and HbA1c in patients with type 2 diabetes [62]. In another randomized, placebo controlled clinical trial, 2 g of cinnamon was given every day for a duration of almost a year, which showed a significant decrease in the HbA1c ,BP, FBG, BMI and waist circumference [63]. Another trial demonstrated that 1g of Cinnamon brought down HbA1C when given every day for 90 days [64].

10.11 *Acacia senegal* (Gum acacia)

Gum Arabic is a water-soluble dietary fiber consisting of a blend of polysaccharides, oligosaccharides, and glycoproteins. It is exudates of Acacia senegal trees with amazing properties [65]. Type 2 diabetic patients who were given 30 g of Acacia Senegal in a double blind controlled clinical trial every day for 3 months. The outcomes demonstrated significant reduction in fasting plasma glucose (FPG) and HbA1c making it a dietary supplement for decreasing blood glucose level for type 2 diabetic patients [66].

10.12 *Nigella sativa* (Black cumin)

N. sativa commonly known as Kala Zeera and number of publications related to the beneficial effects of *N. sativa* in health and disease is now exceeding more than 500 [67]. One group of investigators reported a significant hypoglycemic effect produced by 2.5 ml of N. sativa oil which was given twice every day for a month and a half, in patients with metabolic disorder [68]. The same group of researchers reported a significant improvement in glycemic control induced by 8

weeks treatment with 500 mg/day of powder *N. sativa* capsules, as an adjuvant in patients with metabolic disorder related with type II diabetes mellitus [69]. Extended use of Nigella sativa enhances glucose utilization , antioxidant defense system and homeostasis in type 2 diabetic patients when 2g of seeds is given once every day, for one year [70].

11. CONCLUSION

Today, diabetes has turned into an appalling medical issue around the world, affecting individuals of all ages, both genders, whole ethnicities, and races. The associated complications of diabetes and failure of synthetic drugs to overcome this dilemma urge the researchers to trace natural resources which not only possess glucose lowering properties but also antioxidant and anti-inflammatory properties for a better cure, management and prevention of diabetes complications. This discussion highlights that many different plants may be used individually or in formulations for treatment of diabetes and its complications. The above-mentioned herbs have been considered for their conceivable hypoglycemic activities, and the investigators have completed some preliminary trials. It is critical to know the active ingredient and their molecular mechanisms, which will assist to examine curative efficacy and also to homogenise the product. Accomplishments are presently being made to scrutinise correct molecular mechanism of action and appropriate dosage of these plants fractions currently used in both experimental studies and clinical use.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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