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Herbal therapy in diabetes mellitus: A review

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Abstract

Insulin therapy is the mainstay of treatment in patients with type 1 diabetes, while diet and lifestyle changes, and if left untreated, insulin therapy are effective in treating type 2 diabetes. Research has shown that the oldest treatment for diabetes was the use of herbs. Thus, various medicinal plants were used to relieve many of the complications of diabetes. This study aimed to assess the effectiveness of various medicinal plants in the treatment of diabetes. The data on medicinal plants and diabetes were collected from related articles published from 2014 to 2021 in reputable databases such as Cochrane, PubMed, Scopus, ScienceDirect, Embase, and SID. Data analysis showed that medicinal plants such as *Allium sativum*, *Cinnamomum verum*, *Trigonella graecum foenum*, *Silybum marianus*, *Citrullus colocynthis*, *Abelmoschus esculentus*, *Eryngium*, *Coriandrum sativum* L, and *Zingiber officinale* were the most frequently used herbs in the treatment of diabetes. Medicinal plants can reduce blood sugar in patients due to having effective medicinal compounds and natural antioxidants and due to the least side effects but longer treatment period.

Introduction

Diabetes, a disease of the endocrine system diagnosed with abnormal blood glucose levels, is one of the most common and rapidly affecting diseases worldwide and is projected to affect 693 million adults by 2045, showing a more than 50% increase compared to 2017 [1]. Diabetes is a metabolic disorder in which the body does not produce enough or respond normally to insulin, causing blood sugar (glucose) levels to be abnormally high in affected patients. Insulin is a hormone that helps stabilize blood sugar (glucose) levels by guiding cells [2]. There are several types of diabetes, including type 1, type 2 diabetes, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and diabetes induced by secondary causes such as endocrine system, steroid intake, etc. [2]. Type 1 diabetes is a form of autoimmune disease in which the cells that make insulin are destroyed by the immune system, while type II diabetes, which is more common than type I, occurs when the body does not respond to the insulin produced [3]. The global prevalence of diabetes and impaired glucose tolerance in adults have been increasing in recent decades. The changing trend in the prevalence of diabetes has increased in many countries and regions with rapid urbanization and dramatic changes in sedentary lifestyles [4]. The global diabetes epidemic now affects more than 440 million people [5]. The WHO reported a prevalence of diabetes in adults of 6.4 percent in 2010, or 285 million and 371 million in 2012, and this figure is estimated to reach 552 million by 2030 [6]. In chronic conditions, diabetes can lead to long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. A few common complications of diabetes include retinopathy, kidney failure, diabetic foot disorders (severe infection of the legs leading to amputation), and cardiovascular disease [3]. Diabetic skin ulcers appear as painful lesions with the disintegration of skin tissue, including ulcers of the epidermis, dermis, and in many cases, subcutaneous tissue. In diabetes, chronic skin lesions are common on the lower limbs, especially the feet. Diabetic foot ulcer (DFU) affects 15% of diabetic patients [7]. Until three decades ago, drug therapy for diabetes was limited to three groups of oral drugs, simple insulin, and NPH. However, in recent decades, several oral drugs have been developed to treat diabetes, and recombinant insulin has been introduced to treat patients. New drugs are more expensive and cost patients between 5-20 times more. These drugs are not affordable for all diabetic patients, except in countries with high GDP. Even in these countries, there are numerous guidelines for reducing the cost of diabetes care [8,9]. In patients with type 1 diabetes, insulin therapy is the mainstay of treatment, while diet and lifestyle changes, and if left untreated, insulin therapy are effective in treating type 2 diabetes. Research has shown that the oldest treatment for diabetes mellitus was the use of herbs. Our ancestors knew the complications of diabetes more with the general name of diabetes. Thus, they used various medicinal plants to relieve many of the complications of diabetes [10]. Medicinal plants with antidiabetic properties contain different active ingredients, not all of which are necessarily involved in this property, but one or more substances in each plant share this property.

The active ingredients in different herbs can lower blood sugar through different mechanisms. The major mechanisms involved are increased insulin secretion, activation of the glucose catabolism pathways, inhibition or inactivation of the gluconeogenesis pathway, conduction of glucose into the cell, absorption of free glucose and inhibition of its binding to proteins, increasing antioxidant capacity, and inhibiting the harmfulness of oxidants produced in various pathways that may be due to the increase of glucose and the production of glycated products of other metabolic pathways and ultimately inhibiting glucose uptake from the intestine [11].

Various studies showed that some medicinal plants (brewed, boiled, and combined with food) are used most widely to reduce blood sugar [12]. Accordingly, the present study aimed to collect medicinal plants and assess their effectiveness in the treatment of diabetes.

Methods

Literature search and selection criteria

The research question addressed in this study was structured and written based on questionnaire. The English and Persian articles were searched for the keywords Diabetes, Diabetes Mellitus, Herbs, and Medicinal Plants, and all possible combinations of these terms with Boolean AND and OR operators from January 2016 to late February 2021. To ensure the retrieval of all relevant documents and to obtain comprehensive results by retrieving scientific products in the field of medicinal plants and diabetes, all the mentioned keywords were selected as medical subject headings (MeSH). Published articles were searched in international databases including Cochrane, PubMed, Scopus, ScienceDirect, Embase, and SID. The quality of the articles was assessed based on a 22-item STROBE checklist. To reduce bias, the articles were searched independently by two researchers, and in case of disagreement about an article, it was judged by the head of the group. In this study, all quantitative studies that addressed diabetes with herbal medicines were included in the analysis. The exclusion criteria were qualitative studies and papers presented at

conferences, seminars, letters to the editor-in-chief, irrelevant items, duplicated studies, unclear procedures, and unavailability of the full manuscript of the article. Figure 1 shows the flowchart for the selection of articles:

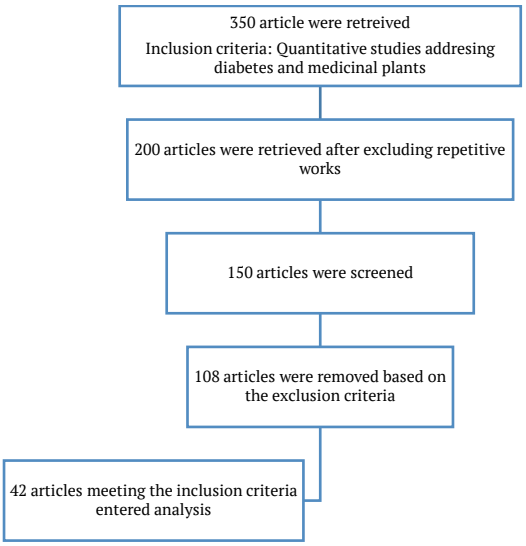

Figure 1: The procedure used to select the articles.

Discussion

Following a comprehensive review of the articles, the most widely used medicinal plants effective in lowering blood sugar were identified and discussed as follows:

Allium sativa L.

Garlic, scientifically named *A. sativum*, is a plant of the genus Asparagales, Amaryllidaceae family, and Alliaceae subfamily. vitamins B. Garlic contains sulfur and stimulates the immune system, and has a high potential for destroying cancerous tumors [13].

Effects of garlic on diabetes: The results showed that garlic alcoholic extract significantly reduced serum concentrations of glucose, triglycerides, cholesterol, urea, uric acid, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) [14].

The effect of garlic on diabetes mellitus: Garlic can lower blood sugar mainly due to the presence of allicin and sulfur compounds. Sulfur compounds include 2-propenyl disulfide and 2-propenyl propyl disulphide [15]. Garlic contains high concentrations of nonprotein sulfur amino acids, which are responsible for their medicinal properties. Co-administration of *A. sativum* extract with commercially available glibenclamide drugs resulted in weight gain and a better hypoglycemic effect in streptozotocin-induced diabetic rats [16]. The antidiabetic effect of garlic extract has been reported to be more effective than glibenclamide as a standard drug [13].

Mechanism of action of garlic on lowering blood sugar: Electrical activity and insulin release in vitro with half-maximal effective concentration (EC_{50}) are reported to be about 1/mmol, 12 glucoses outside the physiological range. S-methylcysteine sulfoxide and S-allyl cysteine sulfoxide are known as active antidiabetic components in onion (*Allium cepa*) and garlic (*Allium sativum*), respectively [21-25]. These compounds have potent antioxidant activity, normalizing the activity of hepatic hexokinase enzymes, glucose 6-phosphatase, HMG COA reductase, and stimulating glucose-dependent insulin secretion [17-21].

Cinnamomum Verum

Cinnamon with the scientific name of *C. Verum* is a shrub of the genus Lurales (Lauraceae) native to Sri Lanka and southern India. The bark of the shrub is used as a spice. Cinnamon has been approved for the treatment of human immunodeficiency virus (HIV-1) and the substance produced from cinnamon extract has been shown to improve Alzheimer's disease in rats [22].

The effect of cinnamon on diabetes mellitus: Safdar et al. (2004) examined the effect of cinnamon on the treatment of type 2 diabetes in 60 men and women with a mean age of 48 years. The treatment lasted up to 60 days. The results showed that cinnamon reduces the serum glucose level in the fasting state [23]. Similarly, other findings indicated that cinnamon bark is effective in the treatment of type 2 diabetes [24].

Several polyphenols were isolated from cinnamon including rutin (90.06%), catechin (1.90%), quercetin (0.17%), kaempferol (0.02%), and isorhamnetin (0.10%) [25-27]. Several reports indicated that cinnamon has blood glucose and cholesterol-lowering activities [27-29]. Cinnamon polyphenols have been reported to have antidiabetic activity by a mechanism that involves regulating glucose levels, lipid metabolism, repairing pancreatic beta cells in STZ-induced high-fat diabetic rats, and inhibiting iNOS and NF-κB activation [30].

Trigonella Graecum Foenum

Fenugreek with the scientific name *T. Graecum-Foenum* is a plant of the Leguminosae family. This plant is native to the Mediterranean region and is widely cultivated in Ukraine, India, and China. It is also used in the form of paste and ointment in the treatment of pimples, burns, inflammation, and eczema [31].

The effect of fenugreek on diabetes mellitus: The first group received 1 mg of aqueous-alcoholic extract of

fenugreek seeds as capsules per day and the second group received the same amount of placebo. After 2 months, the results showed that insulin sensitivity increased and blood glucose decreased in the first group treated with fenugreek extract [32].

Mechanism of action of fenugreek on diabetes mellitus: The chemical compounds in fenugreek seeds include volatile oils, alkaloids, saponins, flavonoids, and mucilage [33]. Consumption of fenugreek seeds eliminates these disorders by reducing free radicals [34-36].

Mechanism of action of fenugreek on diabetes: There are two types of dietary fiber: Insoluble fibers such as cellulose and lignin, and soluble fibers such as hemicellulose and pectin. Both soluble fiber-rich and insoluble fiber-rich diets have been shown to significantly reduce postprandial plasma glucose concentrations compared to low-fiber diets [37]. The active hypoglycemic component of fenugreek [38], barley [39], and *Rhynchelytrum repen* [39,40].

***Silybum marianus* (L.) Gaertn.**

This plant grows on its own and in Iran mostly in Haraz Valley, Moghan Plain, parts of Khuzestan, and Kelardasht. Milk thistle is effective in treating various diseases including liver, gallbladder, spleen, and colic diseases caused by gallstones and jaundice. The healing parts of this plant are its seeds and leaves, and its active ingredient is a compound called silymarin [41,42].

The effect of milk thistle on diabetes mellitus: Experimental studies have suggested that milk thistle extract reduces insulin resistance and the need for external insulin in people with diabetes. Silymarin is also helpful in lowering blood cholesterol. The second group received only the same amount of placebo. Finally, fasting blood glucose, midday blood glucose, and glycosylated hemoglobin were measured. The results showed that fasting blood glucose levels, midday glucose, and glycosylated hemoglobin decreased after 4 months of treatment with milk thistle [43].

Mechanism of action of milk thistle on diabetes mellitus: The active ingredients in milk thistle seeds, including flavonoids and antioxidants, stabilize the cell membrane. Milk thistle with its strong antioxidant properties counteracts oxidative reactions and improves metabolic disorders caused by diabetes. Milk thistle increases the function of free radical scavenging enzymes (superoxide dismutase, glutathione peroxidase, and catalase) in the liver [44,45]. This plant inhibits insulin resistance by inhibiting insulin secretion in response to glucose stimulation [46]. Milk thistle, as a potent inhibitor of lipoperoxidation, lowers blood glucose levels. This plant also enhances liver function and has positive effects on glucose and lipid metabolism [47,48].

***Citrullus colocynthis* (L.) Schrad.**

Colocynth with the scientific name of *C. colocynthis* is a bitter-tasting fruit of the Cucurbitales order, Cucurbitaceae family, and Citrus genus. This fruit is an anti-phlegm, a very strong laxative, used for treating liver disorders, strong antibiotics, anti-gingivitis, and treating tinnitus, epilepsy, and stroke. It is also a powerful antidote to scorpion venom [49].

The effect of colocynth on diabetes: This fruit is used for the treatment of diabetes. To determine the effect of colocynth on diabetes, researchers divided 50 patients with type 2 diabetes into two groups of 25 people. The first group received 100 mg of the fruit of the plant in capsules 3 times a day and the second group received the same amount of placebo. This treatment lasted for up to 2 months, and the patients' glycosylated hemoglobin (HbA1c) and fasting blood glucose levels were measured once a month. After two months, the results showed a significant reduction in HbA1c and fasting blood glucose [50].

Mechanism of action of colocynth on diabetes mellitus: The main chemical compounds in colocynth fruit extract include trins, alkaloids, glycosides, and saponins. Researchers have suggested that this fruit may increase insulin release by increasing the stimulation of beta cells in the islets of Langerhans, and this effect is due to compounds such as saponins, flavonoids, and glycosides contained in this fruit [51].
In diabetic patients, free fatty acid releases free radicals of oxygen, resulting in oxidative stress. These metabolic disorders directly increase insulin resistance in the body's cells and decrease insulin secretion. Antioxidant properties and inhibition of fat oxidation by colocynth may be effective in improving metabolic disorders in diabetic patients. Accordingly, it has been reported that herbs and other compounds with antioxidant properties improve metabolic disorders in diabetic patients by inhibiting free radicals and lipid peroxidation [52].

***Abelmoschus esculentus* (L.) Moench**

This vegetable is rich in valuable nutrients such as vitamins A, C, and B groups including folic acid, B5, B2, B6, and elements such as manganese, cobalt, calcium, phosphorus, potassium, dietary fiber, and viscous matter. Okra is free of saturated fats or cholesterol and

is rich in antioxidants. Thus, it has many positive effects on human health. Consumption of the fruit of this plant can be useful as a food to help treat diabetes. Diabetic rats taking okra powder showed reduced blood sugar levels, which could be due to the high content of fiber, mucilage, and other nutrients in okra fruit. Accordingly, high fiber contained in the fruit inhibits the rate of glucose absorption from the intestinal tract and thus decreases blood sugar [52].

Eryngium

The pharmacological and therapeutic effects of this plant, which is concentrated in its extract and essence, were discovered by the late Professor Badrial (a researcher of traditional medicine] in 1996 after a series of studies and clinical trials on diabetic patients. These studies showed that unlike modern medical treatments, which rely only on lowering blood sugar levels, *eryngium* extract affects activating and clearing the liver and adrenal glands and stimulating insulin secretion from the pancreas. Eryngium extract has a beneficial effect on the adrenal glands and in cooperation with the liver is useful for increasing insulin and activating the pancreas, lowering blood sugar, and treating diabetes. Diabetic people can drink a glass of Eryngium extract every 4 hours and experience the miraculous effects of reducing diabetes and treating it, and if they continue to do so, it will lower high blood sugar. The pure *eryngium* extract activates the pancreas cells and by producing natural insulin, it completely and permanently eliminates both types 1 and 2 diabetes during 6 to 8 months. However, the disease is treated faster at a younger age due to the young age of the body's cells. People with type 1 diabetes need to take into account a few important dietary points to have a faster treatment. The positive effects of treatment were confirmed in all cases, and diabetes was controlled in these people [52].

Coriandrum sativum L.

C. sativum L., a member of the Apiaceae family, is a common food that has medicinal as well as nutritional properties [53]. Administration of coriander stem and leaf ethanolic extract to alloxan-induced diabetic Wistar rats at a dose of 200 mg/kg body weight resulted in liver-protective activity, hypoglycemia, and hypolipidemia with improved antioxidant potential [54]. Sub-chronic administration of aqueous coriander seed extract to high-calorie ion-fed rats led to the normalization of blood glucose levels by improving insulin resistance and lowering total cholesterol and triglyceride levels [55]. Treatment of streptozotocin-induced diabetic rats with ethanolic extract of coriander seed (200 mg/kg body weight) decreased serum glucose and increased the insulin-releasing capacity of pancreatic beta cells [56].

Zingiber officinale Roscoe

Dietary ginger has hypoglycemia, antidiabetic, and antioxidant effects, and lowers blood cholesterol and blood lipids [57-60]. Powdered ginger supplement (3 g/day) taken for 3 months by type 2 diabetic patients improved the glycemic index and antioxidant status. In a similar study on type 2 diabetic patients, ginger supplementation (2 g/day) was found to reduce insulin levels without significant changes in fasting plasma glucose and glycosylated hemoglobin [61-63]. Ginger hydroalcoholic extract significantly reduced structural abnormalities of the heart in STZ-induced diabetic rats by improving serum leptin, apoprotein, cathepsin G, and homocysteine levels [64]. Oral ginger extract (500 mg/kg/bw) in diabetic rats facilitated peripheral glucose uptake and corrected the impairment of renal and hepatic glycolytic processes by limiting gluconeogenic formation [65].

Galega officinalis L.

Of the thousands of oral medications for diabetes, only one, called metformin (metformin with dimethylbuanidine), is derived from a plant derivative called *G. officinalis* [66-68] has been licensed for use in children [69]. Metformin relieves insulin sensitivity by lowering fasting plasma glucose but is ineffective (for example, in type 1 diabetes) in the absence of insulin. The mechanism of action of metformin in non-insulin-dependent diabetic patients is mainly attributed to decreased hepatic glucose output and increased peripheral glucose uptake [70,71]. Metformin also reduces glycogen synthesis and reduces fatty acid oxidation by 10-20% [72,73]. Indirect calorimetric methods have shown that metformin has a small effect on oxidative metabolism, meaning that it leads to a slight decrease in the oxidation of fatty acids and a slight increase in the oxidation of glucose. Metformin appears to be ineffective in insulin-insensitive tissues such as the brain, skin, and renal medulla [74,75].

Conclusions

Herbal medicines with low side effects but longer treatment cycles can lower blood sugar in diabetic patients. However, the traditional way of using herbs has changed and herbs are considered in the form of herbal medicines. The antidiabetic drug called qishen, which is made in China, contains several medicinal plants called cornus, Dioscorea, and Panax. Another Chinese medicine called jin-Yi also contains the herbs Panax and Atracyloden. In the formulation of herbal antidiabetic drugs in Russia and Ukraine, the five plant species constitute the highest percentage of

compounds, which include nettle, galega, dandelion beans, and cranberry. Glucobeet herbal medicine is made from *Syzygium cumini* by an Indian company that has anti-diabetic properties. Research has shown that glycosides, polysaccharides, sterols, terpenoids, alkaloids, saponins, flavonoids, amino acids, and their derivatives are the most active factors in controlling blood sugar in laboratory animals. The study of official herbal antidiabetic drugs in the country shows that medicinal products based on fenugreek, Galega, and milk thistle are produced in Iran. B-Glocorex tablets (manufactured by Barij Essance Company) are used for adjunctive therapy in patients with type 2 diabetes. Produced from the dried fenugreek seed extract of *Trigonella foenum* and containing 46.4 micrograms of luteolin, this pill can lower triglycerides and LDL and increase blood HDL. Galega tablets, manufactured by Dineh Company, are also adjunctive drugs for lowering blood sugar in type 2 diabetes. Made from the leaves of Galga (*Galega officinalis* L.), this pill contains saponins, phallonoids, and guanidine and alkaloid derivatives of quinazoline derivatives, such as peganin. Chronic and non-chronic, infectious and non-infectious diseases are serious health problems and cause pain and suffering to the patient, and finding a treatment solution for them seems essential [76-82]. The third most frequently used herbal antidiabetic drug in Iran is Glycogol tablet produced by Goldaro Company. This pill is prepared from the dried extract of *Salvia officinalis* L. and contains compounds such as tannins, phenolic acids, and flavonoids and essential compounds such as alpha and beta-togen, camphor, and cineole as a hypoglycemic supplement [75,76]. Today, the desire to use medicinal plants in the treatment of diseases has increased [77-79] because they are rich in secondary medicinal substances and antioxidants and improve diseases [80-82].

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