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Persian Medicinal Plants as Antidiabetic Agents: Mechanisms and Evidence from Bench to Bedside

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ABSTRACT

The use of medicinal plants by diabetic patients dates back to ancient times. In recent years, numerous reports have been published on the efficacy and safety of many medicinal plants in the treatment of diabetes through various mechanisms. This review highlights the up-to-date proposed mechanisms of action of the most common antidiabetic herbs used in Persian medicine, comprising *Cinnamomum zeylanicum, Trigonella foenum-graecum, Urtica dioica, Nigella sativa, Citrullus colocynthis, Silybum marianum, Zingiber officinale, Punica granatum, Salvia officinalis, Vaccinium arctostaphylos, and Momordica charantia*, with support from clinical and experimental studies. Clinical research has shown significant reductions in blood glucose levels and insulin resistance, as well as improvements in diabetes-related symptoms, including digestive disorders and lipid dysregulation, accompanied by negligible adverse effects. Continuing to study how these plants work and how effectively they treat diabetes is important for using these natural treatments in modern medicine, offering affordable and safe options for diabetes patients. ***DOI: 10.61882/ibj.5073***

Keywords: Diabetes mellitus, Hypoglycemic agents, Persian medicinal plants, Traditional medicine

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INTRODUCTION

Medicinal plants play a significant role in the prevention and treatment of many diseases due to their popularity, low side effects, and effectiveness. Several medicinal plants have been traditionally used by diabetic patients since ancient times[1]. The efficacy and safety of self-medicating with plants in diabetic patients have drawn great attention from researchers in recent years. Interestingly, laboratory and clinical studies have demonstrated the therapeutic safety of many of these medicinal plants in the treatment of diabetes[2]. In this regard, due to the complexity and multifactorial nature of diabetes, as well as the multifaceted effects of medicinal plants, various mechanisms can be involved in the effectiveness of medicinal plants on diabetes[3]. Medicinal plants, as natural products, have numerous biological and medicinal properties, including preventive and therapeutic effects on diabetes through various cellular and molecular mechanisms[3,4]. The aim of this study was to review the mechanisms of antidiabetic effects of medicinal plants used in traditional Persian medicine, whose effectiveness has been confirmed in clinical studies.

Cinnamomum zeylanicum L. (Cinnamon)

Cinnamon is a common spice with antidiabetic properties in many traditional medicines. Its antidiabetic effect has been proven in laboratory and clinical studies[5,6]. The major cinnamon chemical components are eugenol, cinnamaldehyde, camphor, cinnamyl acetate, and copane, along with other minor constituents[7]. The hypoglycemic effect of cinnamon may be due to its multiple mechanisms of action. Cinnamaldehyde, one of the main chemical components

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of cinnamon, has antidiabetic effects by regulating glucose and blood lipids, improving insulin resistance, and promoting antioxidant activity[8]. Eugenol, another cinnamon chemical component, potentiates insulin sensitivity and promotes skeletal muscle glucose uptake in diabetic rats in addition to its anti-inflammatory and antioxidant effects[9]. It has been reported that the phytochemical composition in cinnamon facilitates the glucose entry into cells by interacting with the insulin receptor[10]. Cinnamon also increases the sensitivity of cells to insulin and stimulates cellular glucose uptake[11]. The antioxidant effects of cinnamon protect pancreatic β-cells from oxidative stress damage, and its anti-inflammatory effects have been beneficial in diabetes[12,13]. Another possible antidiabetic mechanism includes an inhibitory effect on intestinal β-glucosidase and pancreatic amylase[14] and also the ability of this plant to delay gastric emptying after meals[15]. Furthermore, it has been reported that the antidiabetic effects of cinnamaldehyde may be due to its enhancement of intestinal barrier integrity, amelioration of inflammatory responses, and remodeling of the gut microbiome[16,17].

Trigonella foenum-graecum L. (Fenugreek)

Fenugreek has been widely used around the world for dietary cooking purposes and also as a component in varying herbal formulations in Persian medicine for the treatment of several ailments, including diabetes, hyperlipidemia, and obesity[18,19]. Fenugreek's pharmacological effects are attributed to its bioactive compounds, such as polyphenols, steroids, lipids, alkaloids, saponins, flavonoids, hydrocarbons, carbohydrates, galactomannan fiber, and amino acids[20]. Trigonelline, 4-hydroxyisoleucine, and diosgenin are considered the most bioactive substances of fenugreek with antidiabetic activity[21]. Several experimental and clinical trials have shown that fenugreek seeds can improve most metabolic symptoms associated with both type 1 and type 2 diabetes in animals and humans[22,23] In a systematic review study including 43 trials with 2,334 participants, the beneficial effects of fenugreek seed consumption on glycemic control and metabolic syndrome have been documented[24]. Multiple mechanisms have been proposed to explain the metabolic and antidiabetic effects of fenugreek and its components**.** Clinical evidence indicates that its consumption improves glycemic control primarily by enhancing insulin sensitivity and reducing insulin resistance[25,26]. Other studies have reported that consuming fenugreek can increase insulin secretion through the direct effects of Langerhans cells or by reducing oxidative stress on beta cells to restore their function[27], and improve glucose absorption in the peripheral tissues by directly targeting adipose tissue[28]. In an in vitro study, fenugreek leaf extract inhibited α-amylase and α-glucosidase activity[29]. In addition, the high fiber content of fenugreek seeds has delayed effects on carbohydrate digestion due to prolonged gastric emptying time, which reduces glucose absorption in the small intestine[30]. Furthermore, the significant reversed dysbiotic effect of fenugreek on gut microbiota is correlated with overall glucose metabolism and its hypoglycemic action[31].

Urtica dioica L. (Nettle)

Globally, traditional medicine uses nettle to treat various ailments. In Persian medicine, nettle leaf distillate has been widely used as an antihyperglycemic agent[32]. The plant root and aerial part contain many phytochemical compounds, such as phenolic compounds, sterols, fatty acids, alkaloids, terpenoids, flavonoids, and lignans[33]. The nettle's hypoglycemic effects have been reported in several studies. In an experimental animal study, treatment of diabetic rats with aqueous extract of nettle leaves showed a strong glucose-lowering effect[34]. The antihyperglycemic effects have also been confirmed in several clinical trials. In a three-month randomized, double-blind, placebo-controlled clinical trial, 1,500 mg of nettle leaf extract improved glycemic control in patients with advanced type 2 diabetes[35]. In another two clinical trials, significant decreases in insulin resistance indices were reported in type 2 diabetic patients treated with nettle leaf extract[36,37]. Furthermore, a 90-day clinical trial study indicated the antihyperglycemic effects of an herbal formulation containing a mixture of *Boswellia serrata* resin, *Silybum marianum* seeds, and nettle leaf extract[38]. The proposed mechanism for nettle hypoglycemic effects may be due to promising α-amylase and β-glucosidase inhibition[39], enhanced glucose uptake by skeletal muscles and adipose tissues[40], enhanced glucose uptake by creating glucose-permeable pores[41], decreased insulin resistance, and increased insulin secretion by Langerhans islets[42,43], augmented GluT2 gene expression[44], and regeneration of pancreatic beta cells[45]. Nettle contains several antioxidant components, making it an effective approach to controlling diabetes and reducing associated complications[46]. The effects on gut microbiota composition and alterations in amino acid metabolism by nettle may also contribute to the mechanisms by which nettle improves metabolic health[47].

Nigella sativa L. (black seed)

Black seed is widely used for its culinary and medicinal properties, especially in North Africa, the

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Middle East, Europe, and Asian countries. The seeds and their oil also have a long history of use in traditional medicine in almost all countries to treat a variety of ailments, including obesity and diabetes[48]. Many active compounds, including thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, α-pinene, thymol, niglycymine, and niglycine, have been identified in black seed. These compounds are responsible for many pharmacological effects of black seed, including antidiabetic, anti-inflammatory, antioxidant, and immunomodulatory properties, which have been published in various studies[49]. Numerous laboratory and clinical studies have confirmed its antidiabetic effect. In experimental studies, the administration of an aqueous extract of black seed or its oil improved blood insulin levels, hyperglycemia, and lipid profiles[50]. In two clinical trial studies, hypoglycemic and metabolic benefits were observed in type 2 diabetic patients taking 2.5 ml of black seed oil twice daily for three months[51]. In two other clinical trial studies, antidiabetic effects were reported in patients taking 500 mg and 2 g of black seed powder daily for two months[52] and 12 weeks, respectively[53]. Researchers have proposed various mechanisms for the antidiabetic activity of black seed. In experimental and clinical studies, black seed improves insulin secretion and hepatic glycogen storage[54], prevents β-cell damage[55], inhibits α-glucosidase and α-amylase enzyme activity[56], reduces the body's inflammatory and oxidative stress markers[57], increases pancreatic islet cell regeneration[58], inhibits intestinal glucose absorption[59], increases glucose uptake in skeletal muscles[60], and modulates the disturbed gut microbiota[61].

Citrullus colocynthis L. (Colocynth)

In Persian medicine, colocynth is used to treat several ailments, including diabetes and digestive disorders such as indigestion, constipation, and intestinal paralysis[62]. Colocynth is a source of several bioactive compounds, such as cucurbitacin, essential oils, glycosides, saponins, flavonoids, polyphenols, alkaloids, and fatty acids[63]. It exhibits several pharmacological properties, including antidiabetic, antioxidant, and anti-inflammatory effects, as well as powerful laxative and purgative effects[64]. Its hypoglycemic effect has been reported in experimental and clinical trials[65,66]. Although the exact hypoglycemic mechanism of colocynth is unclear, it has been reported that its fruit and seed extracts have an insulinotropic effect in an experimental study[67]. In an in vitro study, the hydrolysates from colocynth seed-derived proteins effectively inhibited α-glucosidase and α-amylase activity[68]. The antioxidant and anti-inflammatory effects of colocynth may play a role in restoring metabolic defects in diabetic patients[69-71]. Chronic constipation is one of the most common digestive complications of diabetic patients[72]. Colocynth has laxative and purgative properties, which may benefit diabetic patients by relieving constipation and improving digestive function[62].

Silybum Marianum L. (Milk thistle)

Milk thistle seeds have been used for centuries as an herbal medicine for various diseases, especially liver and bile problems[73]. In recent years, its seed extract has been promoted as a dietary supplement for hepatitis, cirrhosis, jaundice, diabetes, indigestion, and other conditions[74]. The Milk thistle seed extract (silymarin) contains many active constituents, including several flavonolignans, namely silibinin A, silibinin B, isosilibinin A, isosilibinin B, silychristin, and silydianin[75]. In experimental studies, the hypoglycemic effects of silymarin have been reported in different diabetic animal models[76]. Apart from experimental studies, improved hyperglycemia has been reported with a daily dose of 600 mg of silymarin in three clinical trials, including type 2 diabetic patients, type 2 diabetic patients who are candidates for insulin therapy, and first-degree relatives of type 2 diabetic patients[77-79]. The antidiabetic properties of silymarin are mediated through multiple mechanisms. These mechanisms include ameliorating insulin resistance and enhancing its secretion[80], protecting pancreatic β-cells from oxidative stress-mediated destruction[81], promoting their proliferation[82], impairing carbohydrate digestion by inhibiting α-amylase and α-glucosidase activities[83], suppressing inflammatory pathways and oxidative stress[84], regulating hepatic glucose output via the gut-brain-liver axis[85], and modulating the composition of the gut microbiota[86].

Zingiber officinale L. (Ginger)

Ginger, a most widely consumed spice worldwide, has a long history of use as an herbal medicine to treat a variety of diseases, including nausea and vomiting, constipation, indigestion (dyspepsia), pain, and cold syndromes[87]. Ginger is rich in various chemical constituents, containing phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers. The phenolic compounds are mainly gingerols, shogaols, and paradols, which are responsible for most of the bioactivities of ginger[88]. Accumulating studies have demonstrated that ginger has the potential to prevent and manage several diseases, including diabetes mellitus. In a systematic review and meta-analysis of eight randomized trials consisting of a total number of

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454 participants who underwent ginger therapy (1600-4000 mg daily), glycosylated hemoglobin levels were significantly improved, showing that this natural medicine may have an impact on glucose control in patients with type 2 diabetes[89]. The antidiabetic mechanism of ginger may be due to enhanced insulin secretion from pancreatic β-cells[90], decreased insulin resistance[91], increased glucose-stimulated insulin secretion pathway in pancreatic beta cells[92], and enhanced insulin-stimulated glucose uptake in peripheral insulin-responsive adipocytes[93]. The inhibitory potential of ginger extracts against enzymes is linked to type 2 diabetes, inflammation, and induced oxidative stress[94]. The antioxidant and anti-inflammatory effects of ginger also have the potential to prevent and reduce diabetic complications[95]. In addition, ginger improves the overall structure of intestinal microbiota by enriching effective bacteria such as Faecalibacterium and Blautia[96], with a positive impact on intestinal integrity and mitochondrial dysfunction. Furthermore, it improves glucose metabolism in the digestive system[97].

***Punica granatum* L**. (**Pomegranate**)

In Persian medicine, the pomegranate is known to tonify the stomach and liver and prevent bleeding, as well as heal wounds. The different parts of plants, such as flowers, fruits, stems, leaves, and roots, have antioxidant, antidiabetic, antihyperlipidemic, anti-inflammatory, anticarcinogenic, antimicrobial, and antidiarrheal properties[98]. So far, many phytochemicals have been identified in pomegranate. Anthocyanins in the seeds, along with flavonoids and hydrolysable tannins (such as gallotannins, ellagitannins, punicalgin, and punicalin) found in the leaves, bark, and fruits, are responsible for the potential health benefits of pomegranate[99]. The hypoglycemic effects of pomegranate leaves, flowers, peels, and juice have been reported in several experimental and clinical studies[100]. In a clinical trial, administration of 50 g of pomegranate juice per day to type 2 diabetic patients for three months reduced glucose level, total cholesterol, and LDL cholesterol content[101]. Multiple mechanisms of action have been proposed for the hypoglycemic effect of different parts of pomegranate. In clinical studies, the consumption of pomegranate seed juice has been shown to suppress reactive oxygen, reduce insulin resistance, and enhance β-cell function[102,103]. Pomegranate flower extract contains a large number of polyphenols with potent anti-inflammatory and antioxidant effects[104,105]. In an experimental study, the improvement of insulin sensitivity and inhibition of α-glucosidase activity were reported in diabetic rats treated with pomegranate flower extract[106,107]. Furthermore, it has been reported that the antidiabetic effects of pomegranate flowers may be due to their prebiotic and stimulatory effects on gut bacteria growth[108].

***Salvia officinalis* L. (Sage)**

Sage has a long history in medicinal and culinary uses. It has been utilized in folk medicine for its digestive, carminative, antispasmodic, sedative, analgesic, tonic, and diuretic properties, as well as for the treatment of functional gastrointestinal disorders, since ancient times[109]. Sage essential oil contains a large number of chemical constituents, which consist of borneol, camphor, caryophyllene, cineole, elemene, humulene, ledene, and pinene, while its extract contains phenolic compounds, alkaloids, and waxes[110]. Sage is claimed to be beneficial for diabetic patients, and several experimental studies and clinical trials have confirmed its hypoglycemic effects[111]. In experimental studies, the blood sugar-lowering effects of sage extract and its essential oil have been reported in both healthy and diabetic rats[112]. The antidiabetic effect of sage was also confirmed in clinical trials. In a two-month clinical trial study, the effect of daily administration of 1500 mg of sage on lowering blood sugar and blood lipids in type 2 diabetic patients was reported[113]. Researchers have proposed a few mechanisms for the hypoglycemic effects of sage. In a laboratory study, the inhibitory effects of sage on intestinal glucose absorption were suggested to be due to its α-amylase and α-glucosidase inhibitory properties[114]. Another laboratory study found that sage essential oil inhibited gluconeogenesis and enhanced the sensitivity of liver cells to insulin. In the same study, sage decoction increased glucose uptake capacity and decreased gluconeogenesis in cultured hepatocytes in response to glucagon[115]. The anti-inflammatory and antioxidant effects of sage are also involved in metabolic abnormalities due to its hyperglycemic property[116]. Furthermore, a study on adipocyte cells found that sage extract increased insulin sensitivity and decreased lipogenesis[117]. Sage also modulates the gut microbiota, which may support a healthier gut microbiome and improve glucose metabolism[118].

***Vaccinium arctostaphylos* L. (Caucasian whortleberry)**

Caucasian whortleberry leaves and fruits have long been used by traditional medicine healers to treat blood sugar, blood pressure, fever, along with bladder and urinary tract diseases[19]. Many compounds, such as polyphenols and anthocyanins, including delphinidin 3-O-β-glucoside, petunidin 3-O-β-glucoside, and malvidin 3-O-β-glucoside, have been identified in the leaves and fruits of this plant[119]. The findings of

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experimental and clinical studies have shown that the fruit and leaves of Caucasian whortleberry have antidiabetic effects. In a study on living animals, administering Caucasian whortleberry fruit extract to diabetic rats resulted in lower blood sugar and fat levels after eating[119]. In a clinical trial, diabetes improvement was reported in type 2 diabetic patients who were resistant to conventional oral antihyperglycemic drugs following the administration of a Caucasian whortleberry fruit extract[120]. Another study reported that administering Caucasian whortleberry leaf extract to diabetic patients with high blood pressure had antiglycemic and lipid-lowering effects[121]. In this regard, fasting blood glucose, two-hour postprandial glucose, and insulin resistance were also significantly reduced in diabetic patients treated with Caucasian whortleberry[122]. Since few studies have been performed on this plant, the published mechanisms of its antidiabetic effects remain limited. In an experimental study, the administration of Caucasian whortleberry fruit extract to diabetic rats increased the activity of hepatic glucokinase, glucose-6-phosphate dehydrogenase, and glycogen concentration[123]. In another experimental study, it was suggested that Caucasian whortleberries blood sugar, likely through blocking α-glucosidase in the intestine, boosting glucose transporter protein in muscle tissues, and increasing the expression of insulin genes in the pancreas[124]. The glucose transporter protein is a protein that enhances insulin-regulated glucose uptake into muscle and fat cells[125]. Other studies have reported that the antidiabetic effects of Caucasian whortleberry may be due to its antioxidant, α-glucosidase inhibitory, anti-inflammatory, and DNA protective properties[126,127].

***Momordica charantia* L. (karela)**

Apart from the use of karela in various types of Asian cuisine, its fruit has a long history in the traditional medicine of many countries[128]. Numerous studies have reported that karela fruit contains various chemical compounds, including saponins, polypeptides, flavonoids, alkaloids, polysaccharides, and sterols, which are responsible for the antioxidant, antidiabetic, hepatoprotective, anti-inflammatory, and immuno-modulatory activities[128]. Over the past several years, a large number of scientific studies, including experimental and clinical trials, have investigated the antidiabetic effects of karela fruit[129]. In an experimental study, the hypoglycemic effect of a polysaccharide isolated from karela fruit was reported when administered to diabetic mice[130]. In a clinical trial, the blood sugar-lowering effects of karela were observed in type 2 diabetic patients when its fruit extracts were administered[131]. Several mechanisms for its antidiabetic effect have been documented. As reported in diabetic patients, karela exerted hypoglycemic effects by stimulating insulin secretion[131]. In experimental studies, karela has been shown to improve insulin resistance[132], increase glucose uptake and glucose clearance through the activation of the insulin receptor signaling pathway[133], protect pancreatic cell damage[134], and inhibits α-amylase activity[135]. In addition, karela, due to its strong antioxidant and anti-inflammatory activities, improves lipid and glucose metabolism and insulin function by inhibiting inflammatory cytokines in fat tissues[136]. Karela also affects glucose absorption by improving gut metabolic disorders and microbiota defects[137].

DISCUSSION

The body maintains blood sugar homeostasis through an integrated series of processes. These processes include intestinal glucose absorption, pancreatic insulin secretion triggered by rising glucose levels, cellular glucose uptake, and the storage and release of glucose by the liver[138,139]. Any defect in these pathways can disrupt glucose metabolism, leading to increased blood sugar levels. Herbal medicines may affect one or more positions in the pathways of glucose absorption and metabolism. In this light, numerous laboratory and clinical studies have been conducted to find out the mechanism of action of antidiabetic herbal medicines in the body. In the current study, the antidiabetic mechanisms of commonly used medicinal plants, including *Cinnamomum zeylanicum, Trigonella foenum-graecum, Urtica dioica, Nigella sativa, Citrullus colocynthis, Silybum marianum, Zingiber officinale, Punica granatum, Salvia officinalis, Vaccinium arctostaphylos, and Momordica charantia*, were investigated. These plants contain many active compounds with a specific mechanism of action that can exert therapeutic effects in diabetic patients by improving body disorders[140].

One important mechanism of action reported by all the above-mentioned plants is the improvement of insulin action (Table 1). This effect was due to the improvement of body cells' sensitivity to insulin and the increase in insulin secretion caused by these plants. Impaired insulin secretion and insulin resistance are key pathophysiological features of type 2 diabetes. This condition leads to a reduced response to insulin in muscle, liver, and adipose tissue, subsequently decreasing glucose uptake into these cells[141]. Many of the existing synthetic antidiabetic drugs used in the treatment of type 2 diabetes lower blood sugar by affecting insulin activity or insulin release[142].

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Table 1. Studies conducted to evaluate the mechanism of action of antidiabetic herbal medicines

Sr. No.	Herbal medicine	Proposed mechanism of action	Compound/test design	References
1	*Cinnamomum zeylanicum*	Improving insulin resistance	Cinnamaldehyde/db-db mice	[8]
		Improving SMGU; reducing OX; decreasing inflammation	Eugenol/DM rat	[9]
		Increasing CGU; exerting anti-inflammatory effects	AQ extract/3T3-L1 adipocytes	[10]
		Improving insulin sensitivity	Cinnamon/(HF/HF) fed rat	[11]
		Improving β-cell function; protecting from OX	EA fraction/β cell lines	[12]
		Exerting anti-inflammatory effects, inhibiting OX	Cinnamon extract/DM patient	[13]
		Inhibiting intestinal β-glucosidase and PA	DS extract/enzymatic	[14]
		Slowing gastric emptying	Cinnamon/healthy subjects	[15]
		Enhancing IBI; remodeling GM	Cinnamaldehyde/rats	[16]
		Changing gut microbiota	Cinnamon/diabetic patients	[17]
2	*Trigonella foenum-graecum* (fenugreek)	Improving insulin resistance	Fenugreek/DM patient	[25]
		Improving insulin sensitivity	Fenugreek seeds/healthy subject	[26]
		Stimulating glucose-induced insulin release	4-HIL/rat and human β-cell	[27]
		Reducing OX and PPARγ activity	DG and TIRG/ rat pancreas/AT	[28]
		Improving inflammation and glucose metabolism	Fenugreek/KK-Ay HFD mice AT	[29]
		Inhibiting α-amylase and β-glucosidase	AQ leaves extracts/enzymatic	[30]
		Inhibiting glucose absorption due to PGET	Fenugreek SDFF/DM rat SI	[31]
		Reversing dysbiotic effects on gut microbiota	Fenugreek/HFD mice	[32]
3	*Urtica dioica* (nettle)	Inhibiting α-amylase and β-glucosidase	UD extract/enzymatic	[39]
		Enhancing glucose uptake	UD decoction/rat SM and AT	[40]
		Decreasing insulin resistance	UD decoction/C57BL/6J mice	[42]
		Enhancing insulin secretion	UD extracts/rat β-cells	[43]
		Increasing GLUT2 gene expression in the liver	UD distillate/DM mice liver cells	[44]
		Regenerating pancreatic beta cells	UD distillate/DM rats	[45]
		Exerting antioxidant properties	UD extracts/laboratory	[46]
		Altering gut microbiota composition	UD extracts/obese mice	[47]
4	*Nigella sativa* L.	Improving insulin secretion, HG storage, and OS	TQ/DM rats	[54]
		Preventing β-cell damage	Volatile oil/DM rats	[55]
		Inhibiting α -glucosidase and α-amylase EA	NS extract/in vitro	[56]
		Reducing inflammation and OS markers	NS oil/RA patient	[57]
		Increasing pancreatic islet cell regeneration	Volatile oil/DM rats	[58]
		Inhibiting intestinal glucose absorption	NS AQ extract/in vitro	[59]
		Increasing GU in muscle cells and adipocytes	NS extract/cell line	[60]
		Restorating disturbed gut microbiota	NS oil/rat	[61]
5	*Citrullus colocynthis*	Exerting insulinotropic action	Fruit extracts/rat pancreatic islets	[67]
		Inhibiting α-glucosidase and α-amylase	Colocynth seed protein/enzymatic	[68]
		Preventing glucose toxicity	Fruit extract/ PC-12 cells	[69]
		Reducing of oxidative stress	Fruit extract/diabetic patient	[70]
		Reducing oxidative stress and inflammation	Fruit extract/rat liver damage	[71]
		Improving constipation and digestive function	Fruit powder/diabetic patient	[62]
6	*Silybum marianum*	Improving insulin resistance	Silymarin/F-DR of DM patient	[78]
		Stimulating insulin secretion	Silymarin/β-cell line	[80]
		Inhibiting OX-mediated destruction of β cells	Silymarin/invitro in rats	[81]
		Proliferating insulin-producing cells	Silymarin/AI-DM rats	[82]
		Inhibiting α-amylase and α-glucosidases	Silymarin/enzymatic	[83]
		Downregulating inflammation and OX	Silymarin/diabetic patient	[84]
		Decreasing HGP by triggering the GBLA	Silibinin/DM rats	[85]
		Modulating fecal microbiota composition	Silymarin/sows fecal microbes	[86]

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Sr. No.	Herbal medicine	Proposed mechanism of action	Compound/test design	References
7	*Zingiber officinale (Ginger)*	Enhancing β-cells' insulin secretion	Steamed ginger/pancreatic β-cells	[90]
		Improving insulin resistance	Ginger/DM patient	[91]
		Improving GSIS in pancreatic β-cells	Gingerol/db/db DM mice β-cells	[92]
		Increasing ISGU in peripheral adipocytes	Ginger/adipocytes cell line	[93]
		Inhibiting α-amylase and α-glucosidases	Ginger extracts/enzymatic	[94]
		Exerting antioxidative and anti-inflammatory effects	Ginger/Diabetic rats	[95]
		Changing intestinal flora	Ginger Juice/healthy adults	[96]
		Improving intestinal mitochondrial function	Ginger/Diabetic rats	[97]
8	*Punica granatum* L.	Exerting antioxidant effects	Seed juice/ athletes	[102]
		Improving insulin resistance and *β*-cell function	Seed juice/DM patient	[103]
		Exerting anti-inflammatory effects	Flower extract/DM rats	[104]
		Exerting antioxidant effects	Flower extract/MCL	[105]
		Improving insulin sensitivity	Flower extract/DPPH assay	[106]
		Inhibiting α-glucosidase activity	Flower extract/DM rats/in vitro	[107]
		Stimulating gut bacteria growth	Flower extract/in vitro	[108]
9	*Salvia officinalis* L.	Inhibiting α-amylase and α-glucosidase	Sage extract/enzymatic	[114]
		Improving insulin sensitivity and inhibiting GNG	Sage EO/rat hepatocyte	[115]
		Increasing HGUC and inhibiting GNG	Sage decoction/rat hepatocyte	[115]
		Exerting anti-inflammatory and antioxidant effects	Sage extract/inflammation in rat	[116]
		Improving insulin resistance	Sage extract/HFD-IO in mice	[117]
		Modulating gut microbiota	Sage extract/sea bass	[118]
10	*Vaccinium arctostaphylos* L.	Increasing hepatic glycogen, GK, and G6PD	VA fruit extract/ DM rats	[123]
		Increasing serum insulin and adiponectin levels	VA fruit extract/ DM rats	[124]
		Inhibiting α-glucosidase activity in the intestine	VA fruit extract/ enzymatic	[124]
		Uptaking insulin-regulated glucose into cells	VA fruit extract/ enzymatic	[125]
		Decreasing oxidative stress	VA fruit extract / DM patients	[126]
		Exerting anti-inflammatory and DNA protective effects; inhibiting α-glucosidase	VA fruit extract/ enzymatic	[127]
11	*Momordica charantia* L.	Increasing insulin levels	MC extract/DM patient	[131]
		Improving insulin resistance	MC extract/HFDF mice	[132]
		Improving glucose uptake and glucose clearance	MC-IRBP/DM mice	[133]
		Protecting damage to pancreatic cells	MC polysaccharide/DM mice	[134]
		Inhibiting α-amylase	MC polysaccharide/enzymatic	[135]
		Exerting antioxidant activity	MC polysaccharide/laboratory	[136]
		Stimulating peripheral and skeletal muscle glucose utilization; modulating intestinal microbiota disorders	FMC polysaccharide/obese rats	[137]

SMGU: skeletal muscle glucose uptake; OX: oxidative stress; CGU: cellular glucose uptake; PA: pancreatic amylase; IBI: intestinal barrier integrity; db-db: leptin receptor-deficient diabetes; HF/HF: high fat/high fructose; EA: ethyl-acetate; CRP: C-reactive protein; DS: distilled water; GM: gut microbiome; CD: carbohydrate digestion; PPARγ: peroxisome proliferator-activated receptor-gamma; PGET: prolonged gastric emptying time; TIRG: trigonelline; DG: diosgenin; 4-HIL: 4-hydroxyisoleucine; HFD: high fat diet; AT: adipose tissue; AQ: aqueous; SDFF: soluble dietary fiber fraction; DM: diabetic; SI: small intestine; GLUT2: glucose transporter 2; UD: *urtica dioica*; SM: skeletal muscle; HG: hepatic glycogen; EA: enzyme activity; GU: glucose uptake; TQ: thymoquinone; NS: *nigella sativa*; RA: rheumatoid arthritis; PC12: cell line derived from a pheochromocytoma of the rat adrenal medulla; F-DR: first-degree relatives; HGP: hepatic glucose production; GBLA: gut-brain-liver axis; AI: alloxan induced; EXP: experimental; GSIS: glucose-stimulated insulin secretion; ISGU: insulin stimulated glucose uptake; MCL: macrophages cell line; DPPH: 2,2-diphenyl-1-picrylhydrazy; HGUC: hepatocyte glucose uptake capacity; GNG: gluconeogenesis; HFD-IO: high fat diet-induced obesity; EO: essential oil; LPS: lipopolysaccharide; GK: glucokinase; G6PD: glucose-6-phosphate dehydrogenase; VA: *Vaccinium Arctostaphylos*; PIGE: pancreatic insulin genes expression; GH: glucose homeostasis; HFDF: high-fat-diet; MC: momordica charantia; MC-IRBP: momordica charantia insulin receptor-binding protein; TTP: triterpenoids; FMC: fermented momordica charantia;

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Inhibition of intestinal α-amylase and α-glucosidase activity was another important mechanism of the antidiabetic effects reported by these plants (Table 1). Intestinal α-amylase and α-glucosidase enzymes help break down carbohydrates into simple sugars, which allows glucose to be absorbed from the digestive tract. Their inhibition can significantly prevent the increase in blood sugar levels after a meal. Therefore, this therapeutic effect can be an important strategy in managing blood sugar levels in type 2 diabetic patients[143]. In addition, antioxidative and/or anti-inflammatory effects have also been reported by all the mentioned plants (Table 1). Although the direct relationship between oxidation and diabetes has not been established, it is claimed that increased oxidation contributes to insulin resistance and impaired secretion. The antidiabetic benefits of dietary antioxidants may be attributed to the regulation of insulin secretion, increased insulin sensitivity, and improved glucose metabolism[144]. For instance, in a clinical trial study, applying vitamin E improved insulin-mediated glucose uptake[145]. Chronic inflammation can be a complication of diabetes and also a risk factor for diabetes by increasing insulin resistance. In this regard, it has been determined that the antidiabetic effects of sitagliptin, a synthetic antidiabetic drug, are due to its anti-inflammatory properties, which improve insulin secretion and function[146]. Another important antidiabetic mechanism reported for most of the above plants is their influence on gut microbiota (Table 1). Alteration of the gut microbiota is an important factor associated with the development of type 2 diabetes and its complications[147]. It has been reported that decreased glucose tolerance and insulin resistance, which occur with the onset of obesity, metabolic syndrome, and type 2 diabetes, are associated with disruption of the gut microbiota[148]. However, a promising new approach to diabetes treatment has focused on modulating the gut microbiota with prebiotics and synbiotics[149]. In this regard, research has shown that one of the antidiabetic mechanisms of metformin, a widely used antidiabetic drug, is the regulation of intestinal microbiota[150].

Given the complex nature of diabetes and the diverse compounds in medicinal plants, future research should extend beyond the mechanisms discussed in this review. Key priorities include isolating bioactive compounds, standardizing extracts, and employing nanoformulations to improve bioavailability. Furthermore, in-depth mechanistic studies on insulin signaling, glucose metabolism, and gut-microbiota interactions are essential to elucidate their multi-target actions. Finally, rigorous clinical trials—focusing on dosage, safety, and potential herb-drug interactions—are crucial for validating efficacy and ensuring patient safety in insulin-resistant populations.

CONCLUSION

The findings of this review demonstrate that the antidiabetic effects of medicinal plants are mediated through multiple mechanisms, including enhancing insulin secretion, improving insulin sensitivity, promoting peripheral glucose uptake, inhibiting intestinal glucose absorption, and modulating gut microbiota. This diverse range of pharmacological actions offers fresh ideas for innovative diabetes treatment strategies, allowing for the selection and combination of medicinal plants based on their mechanisms of action. Although several medicinal plants have shown clinically significant glycemic control, first-line antidiabetic drugs such as metformin remain superior for long-term monotherapy due to their well-established efficacy, extensive safety profile, and demonstrated cardiovascular benefits. Medicinal plants are most appropriately used as adjunctive therapy rather than replacements for conventional drugs, particularly in advanced diabetes. Some botanical preparations may exhibit synergistic effects when combined with antidiabetic medications, potentially allowing for dose reduction and decreased side effects. There are several important safety considerations when using medicinal plants, including the lack of adequate safety data for medicinal plants in vulnerable populations, such as pregnant women, children, and elderly patients. In contrast, conventional antidiabetic drugs have well-documented safety profiles in these groups. Although medicinal plants show promise for managing prediabetes or as complementary therapies, they require rigorous long-term studies, product standardization, and increased safety monitoring before they can be considered real alternatives to conventional treatments. Finally, despite significant research in recent decades on antidiabetic medicinal plants demonstrating their effectiveness, there is undoubtedly a need for laboratory research and long-term clinical trials with an appropriate design to accurately determine their efficacy, safety, action mechanisms, and optimal dosing protocols.

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HFH: conceptualization, methodology, investigation, resources, data curation, writing–original draft, and project administration; MH: methodology, validation, formal analysis, data curation, writing–review and editing; SK: conceptualization, investigation, writing–review & editing; MZ: conceptualization, supervision, methodology, investigation, writing–original draft, writing–review & editing.

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