REVIEW PAPER

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Plants: past and present in the battle against diabetes

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ABSTRACT

From ancient times, when medicine was based on folk knowledge, to the present era of advanced science, the beneficial effects of plants on various diseases, including diabetes, have been discovered. Approximately 537 million people worldwide have diabetes, and forecasts indicate further increases. Hence, there is a need to develop new effective therapies and interventions to support diabetes treatment. Many plants impact carbohydrate metabolism, and the amount of in vitro and in vivo research on animals and humans continues to grow, updating our knowledge about their potential applications in diabetes treatment and its complications. This review discusses six plant sources with proven anti-diabetic activity. The study serves as a literature review on plants and their derived compounds that exhibit hypoglycemic effects, which are significant in managing prediabetic conditions and diagnosed diabetes.

Introduction

From ancient times, when medicine relied on folk knowledge, to the present era of advanced science, numerous plants have been studied for their beneficial impact on diabetes [1]. Both in the past and today, plants play a significant role in regulating blood sugar levels. The International Diabetes Federation reports that approximately 537 million people worldwide are living with diabetes, and it is projected that by 2045, approximately 783 million individuals will be living with diabetes [2]. Hence, there is a need for new effective therapies in the fight against diabetes and supportive interventions. Plant compounds often take the forefront in this battle, not only against diabetes itself but also against prediabetic conditions. They aim to support the patient as an adjunct to a proper diet and physical activity, serving as the first step in combating unhealthy habits that lead to later disease. We no longer rely on folklore and traditions regarding the use of herbs in specific disease entities. Contemporary scientific research focuses on identifying active plant constituents and investigating their mechanisms of action and potential applications in treating diabetes and blood sugar regulation. Some active ingredients from the plants described in this

study have been isolated and utilized to produce dietary supplements or antidiabetic medications. This review aims to systematize the current knowledge regarding selected plants and the compounds derived from them that demonstrate hypoglycemic effects. Approaching the mechanisms of action of medicinal plants in diabetes and supporting it with clinical evidence may help specialists to implement new procedures in standard diabetes therapy.

Plants with hypoglycemic properties

In this review of the latest scientific literature, we focused on the discoveries of six commonly used medicinal plants: *Aloe vera* Linnaeus, *Cinnamomumverum* J. Presl, *Momordicacharantia* Linnaeus, *Morus alba* Linnaeus, *Trigonellafoenum-graecum* Linnaeus, and *Zingiberofficinale* Roscoe. The scientific studies discussed in this work focus on identifying active plant compounds, their mechanisms of action, and potential applications in treating diabetes and blood sugar regulation. Many active plant components have been isolated and used in appropriate concentrations to produce dietary supplements and anti-diabetic medications. The discussed plant products enhance their health-promoting effects when appropriately processed and combined with other plants. Additionally, other health benefits of these mentioned plants have been highlighted. All the information has been presented clearly in **Table 1**, **Table 2**, and **Figure 1**.

Aloe vera (L) Burm. f. (syn *Aloe barbadensis Mill*), *Asphodelaceae*

Aloe verais widely distributed in hot and arid regions of North Africa, the Middle East, Asia, the southern Mediterranean, and the Canary Islands [3]. The use of *Aloe vera* dates back to ancient times when it has been utilized for generations as a medicinal and cosmetic remedy. *Aloe vera* is renowned for its application in treating various skin issues, such as burns and wounds [4].

Table 1. Phytochemicals – mechanisms of action influencing glucose metabolism of medicinal plants.

Medicinal Plants	Phytochemicals with potential action in diabetes	Potential mechanism of action in diabetes
Aloe vera	Polysaccharides Chromium Biotin	– improving glucose transport – improving the morphology and functioning of pancreatic islets [5] – reducing the toxic effect of fat on the liver [6] – improving insulin sensitivity [7]
Cinnamomum verum	Cinnamaldehyde Cinnamicacid Cinnamateesters Polyphenols	– improving insulin sensitivity [15] – increased GLUT4 translocation [16] – inhibits the production of glucose in the liver [18] – inhibition of alpha-amylase and alpha-glucosidase [19]
Momordica charantia	Charantin Polypeptide-p Lectins Momordicosides	– increased glucose uptake [28] – gluconeogenesis inhibition [29] – inhibition of alpha-amylase and alpha-glucosidase [30] – improving insulin sensitivity [29]
Morus alba	Mulberry leaf alkaloids Flavonoids 1-Deoxynojirimycin (DNJ) Chlorogenicacid	– inhibition of alpha-amylase [42,43] – improving insulin sensitivity [45] – promoting insulin secretion [46] – antioxidant properties [46–47] – protection of the liver and pancreas [46–47]
Trigonella foenum-graecum	Fenugreek saponins Fenugreek fiber Trigonelline 4-Hydroxyisoleucine	– improving the morphology and functioning of pancreatic islets [56] – improving insulin sensitivity [57] – inhibits the production of glucose in the liver [57] – stimulates the insulin signaling cascade [59] – antioxidant properties [61]
Zingiber officinale	Gingerols Shogaols Zingerone Zerumbone	– increase in the activity of glycolytic enzymes [71] – antioxidant properties [72] – increasing the expression of the glucose transporter (GLUT-4) [73]

Abbreviations: GlUT-4 – Glucose Transporter 4

Table 2. Medical plants and their impact on glucose metabolism.

Medicinal plants	Authors	Features of the study	Dose	Time of taking the drug	Number of study participants	Intervention group	Control group	Results
Aloe vera	Choi et al. [10]	A randomized controlled trial	Processed aloe vera gel 147 mg/cap and aloesin powder 3 mg/cap	8 weeks	136	Allocated to experimental group: 68 Lost to follow-up: 8 Analysed: 60	Allocated to placebo group: 68 Lost to follow-up: 6 Analysed: 62	Decrease of: body weight, BFM, Insulin resistance
	Huseini et al. [11]	A randomized, double-blinded, and placebo-controlled trial	2x300 mg	2 months	60	30	30	Decrease of: FPG, HbA1c, TC, LDL-C
	Alinejad-Mofrad et al. [12]	A randomized, double-blinded, and placebo-controlled trial	n1 – 2x300 mg n2 – 2x500 mg	8 weeks	72	n1–24 n2–24	n3–24	Decrease of: FPG
Cinnamomum verum	Zare R et al. [20]	A triple-blind placebo-controlled randomized clinical trial	2x500 mg	3 months	140	BMI < 27 (n = 33) BMI ≥ 27 (n = 37, loss of 1 participant in the intervention group – leaving 36 in the intervention group)	BMI < 27 (n = 33, loss of 1 participant in the control group – leaving 32 in the control group) BMI ≥ 27 (n = 37)	Decrease of: BMI, adipose tissue, visceral fat, FPG, 2hpp, HbA1C, insulin resistance, TC, LDL-C, HDL-C
	Akilen et al. [21]	A randomized, double-blinded, and placebo-controlled trial	2 g	12 weeks	58	30	28	Decrease of: HbA1c, SBP, DBP
	Neto et al. [22]	A triple-blind placebo-controlled randomized clinical trial	3 g/day	90 days	160	Allocated to experimental group: 80 Lost to follow-up: 9 Analysed: 71	Allocated to placebo group: 80 Lost to follow-up: 11 Analysed: 69	Decrease of: HbA1C, FPG
Momordica charantia	Cortez-Navarrete et al. [34]	A randomized, double-blinded, and placebo-controlled trial	2000 mg/day	3 months	24	Allocated to experimental group: 12 Lost to follow-up: 2 Analysed: 10	Allocated to placebo group: 12 Lost to follow-up: 2 Analysed: 10	Decrease of: weight, BMI, fat percentage, WC, HbA1C, 2-h glucose in OGTT, AUC of glucose Increase of: AUC of insulin, total insulin secretion, first phase of insulin secretion
	Kim et al. [35]	A randomized, double-blinded, and placebo-controlled trial	2380 mg/day	12 weeks	96	Allocated to experimental group: 66 Lost to follow-up: 4 Analysed: 62	Allocated to placebo group: 30 Lost to follow-up: 2 Analysed: 28	Decrease of: FPG
Morus alba	Qu et al. [50]	A Multicenter, Randomized, Double-Blind, Double-Dummy, and Parallel Controlled Clinical Trial	???	24 weeks	600	360	240	Decrease of: HbA1c
	Thaipitakwong et al. [51]	A randomized controlled clinical study	12 mg/day	12 weeks	59	Allocated to experimental group: 29 Lost to follow-up: 1 Analysed: 28	Allocated to placebo group: 30 Lost to follow-up: 4 Analysed: 26	Decrease of: FPG, HbA1c, insulin resistance
Trigonella foenum-graecum	Gupta et al. [62]	A randomized, double-blinded, and placebo-controlled trial	1 gm/day hydroalcoholic extract of fenugreek seeds	2 months	25	12	13	Decrease of: (AUC) of blood glucose, TG Incrase of: insulin sensitivity, HDL-C
	Verma et al. [63]	A multicenter, randomized, placebo-controlled, double-blind, add-on clinical study	2x500 mg (Fenfuro)	90 days	154	???	???	Decrease of: FSG, FPG, HbA1c Increase of: fasting and post-prandia, l C-peptide levels
	Hadi et al.[64]	A parallel randomized clinical trial	3x5 g fenugreek seed powder	8 weeks	50	Allocated to experimental groups: 25 Lost to follow-up: 1 Analysed: 24	Allocated to placebo group: 25 Lost to follow-up: 1 Analysed: 24	Decrease of: FPG, SBP Increase of: some liver and kidney function
Zingiber officinale	Carvalho et.al. [74]	A randomized, double-blinded, and placebo-controlled trial	1,2 g	90 days	144	Allocated to experimental groups: 72 Lost to follow-up: 24 Analysed: 47	Allocated to placebo group: 72 Lost to follow-up: 15 Analysed: 56	Decrease of: FBS, TC, LDL
	El Gayar et al. [75]	A randomized, single blind, placebo-controlled clinical trial	3x600 mg	8 weeks	80	40	40	Decrease of: BMI, HbA1c, FBG, FSI, TC, LDL-C
	Mahluji et al. [76]	A randomized, double-blinded, and placebo-controlled trial	2 g	2 months	64	Allocated to experimental groups: 32 Lost to follow-up: 4 Analysed: 28	Allocated to placebo group: 32 Lost to follow-up: 2 Analysed: 30	Decrease of: LDL-C, TG, HOMA Increase of: QUICKI
	Arablou et al. [78]	A randomized, double-blinded, and placebo-controlled trial	2x800 mg	12 weeks	70	Allocated to experimental groups: 35 Lost to follow-up: 2 Analysed: 33	Allocated to placebo group: 35 Lost to follow-up: 5 Analysed: 30	Decrease of: FPG, HbA1C, insulin, HOMA, TG, TC, CRP, PGE
	Rostamkhani et al. [80]	A randomized, double-blinded, and placebo-controlled trial	2 g	8 weeks	44	Allocated to experimental groups: 22 Lost to follow-up: 2 Analysed: 20	Allocated to placebo group: 22 Lost to follow-up: 1 Analysed: 21	Decrease of: FBG, HOMA-IR, urea
	Mozaffari-Khosravi et al. [79]	A randomized, double-blinded, and placebo-controlled trial	3x1 g	8 weeks	88	Allocated to experimental groups: 44 Lost to follow-up: 4 Analysed: 40	Allocated to placebo group: 44 Lost to follow-up: 3 Analysed: 41	Decrease of: FBS, HbA1c Increase of: QUICKI

Abbreviations: BFM – body fat mass; FPG – fasting plasma glucose; HbA1c – Glycated Hemoglobin; TC – triglicerydes; LDL-C – low density lipoprotein cholesterol; BMI – Body Mass Index; 2hpp – Two hours postprandial glucose; HDL-C – high density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; WC – Waist Circumference; AUC – Area Under the Curve; TG – triglycerides; FSG-fasting serum glucose; FBS – fasting blood sugar; FSI – fasting serum insulin; HOMA-IR – homeostatic model assessment; QUICKI – Quantitative Insulin Sensitivity Check Index; PGE – Prostaglandin E2

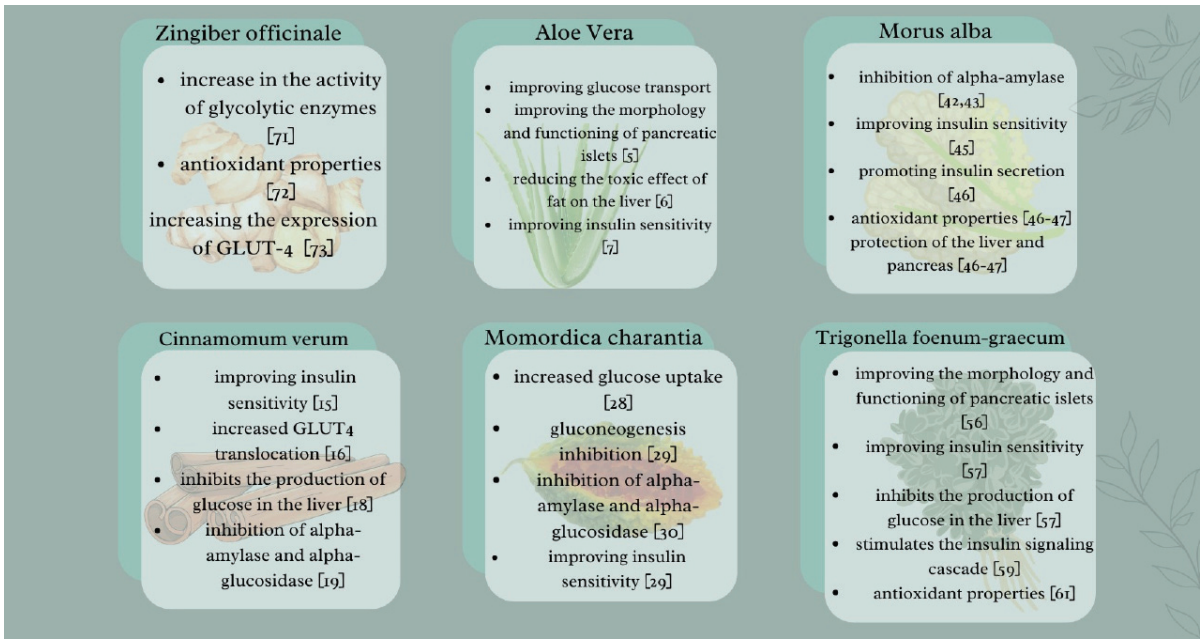

Figure 1. Plants – graphical summary of their impact on glucose metabolism.

Phytochemicals – Mechanisms of hypoglycemic action of Aloe vera

Among the compounds found in *Aloe vera*, notable ones include vitamins (such as vitamins A, C, E, and B12), enzymes (e.g., amylase, catalase, and peroxidase), minerals (e.g., zinc, copper, selenium, and calcium), sugars (including monosaccharides like mannose-6-phosphate and polysaccharides like glucomannans), anthraquinones (aloin and emodin), tritrpenes (f.ex. lupeol) and phytosterols (f.ex. campesterol), hormones (auxins and gibberellins), and others (like salicylic acid, lignin, and saponins) [4]. The influence of *Aloe vera* on glucose and lipid metabolism can be explained through several mechanisms. One involves the action of high-molecular-weight polysaccharides and phytosterols in the aloe gel (prepared from the leaves). These components can affect glucose transport by regulating the markers responsible for its uptake and lower cholesterol levels by reducing its absorption from the gastrointestinal tract. *Aloe vera leaf* extract has been shown to normalize fasting plasma glucose (FPG) and insulin levels in the serum of rats. Furthermore, *Aloe vera* supplementation contributed to the improvement of pancreatic islet morphology and function [5]. Another mechanism involves the reduction of the toxic effects of fat on the liver and the improvement of cellular insulin sensitivity [6–7]. Additionally, researchers suggest that *Aloe vera* may decrease adipose tissue mass and enhance insulin sensitivity by activating a muscle protein kinase known as AMP-activated protein kinase, which plays a crucial role in regulating glucose and lipid metabolism [8].

Clinical evidence of the hypoglycemic effects of Aloe vera

Aloe vera appears to possess anti-diabetic properties. Some studies have focused on *Aloe vera*, demonstrating its ability to reduce glucose and fructosamine levels [9]. A randomized controlled trial involving 136 obese patients with prediabetic conditions and early untreated diabetes confirmed that supplementation with Aloe QDM complex (comprising processed aloe gel at a dose of 147 mg/capsule and aloe powder at a dose of 3 mg/capsule) for eight weeks not only reduced insulin resistance but also body weight and adipose tissue mass [10]. A study conducted by Huseini et al. found that applying *Aloe vera* leaf gel twice daily at 300 mg for two months decreased fasting blood glucose levels, HbA1c, total cholesterol, and LDL-C [11]. Furthermore, *Aloe vera*can be used in the prevention of diabetes. Consumption of pure powdered of *Aloe vera extract* (300 mg twice daily for four weeks) reduced fasting blood glucose levels in individuals with prediabetic conditions [12].

Cinnamomum verum J. Presl (syn C. zeylanicum Blume), Lauraceae:

Cinnamon is a spice derived from the bark of trees belonging to the Cinnamomum genus. The most common species are *Cinnamomumverum* (Ceylon cinnamon) and *Cinnamomum cassia* Siebold (also known as Chinese cinnamon or cassia). Known initially primarily in Southeast Asia, the Portuguese introduced cinnamon to Europe from Sri Lanka in the early 16th century. It has been used for its health-promoting properties as a traditional remedy [13].

Phytochemicals – Mechanisms of hypoglycemic action of Cinnamomum verum

The hypoglycemic properties of cinnamon are primarily attributed to proanthocyanidins (epicatechin polymers), cinnamaldehyde, and cinnamic acid contained in the leaves and the bark [14]. Cinnamon extract regulates genes associated with insulin sensitivity, inflammation, and cholesterol metabolism/lipogenesis [15]. In a study on streptozotocin-induced diabetic rats, cinnamon extract exhibited antidiabetic effects independent of insulin. Cinnamon (aqueous cinnamon extract) upregulated mitochondrial UCP-1 and increased GLUT4 translocation in muscle and adipose tissue [16]. Cinnamaldehyde is responsible for the effect on GLUT4 [17]. Cinnamon extract (aqueous cinnamon extract and cinnamon polyphenol-enriched defatted soy flour) inhibits glucose production in the liver and reduces the expression of key regulators of gluconeogenesis in the liver, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase [18]. Additionally, cinnamon affects the absorption of carbohydrates by inhibiting the enzymes alpha-amylase and alpha-glucosidase. [19].

Clinical evidence of the hypoglycemic effects of Cinnamomum verum

In a clinical study conducted in 2019, 140 patients with type 2 diabetes were divided into four groups: cinnamon (BMI ≥ 27, BMI < 27) and placebo (BMI ≥ 27, BMI < 27). Supplementation with cinnamon (bark powder) at a dose of 500 mg twice daily for three months resulted in improvements in anthropometric parameters (BMI, adipose tissue, visceral fat), glycemic parameters (FPG, Two hours postprandial glucose -2hpp, HbA1c, fasting insulin, and insulin resistance), and lipid parameters (total cholesterol, LDL-c, and HDL-c) (except for triglyceride levels). All observed changes (except for total cholesterol and LDL-c) were significantly more pronounced in patients with higher baseline BMI (BMI ≥ 27) [20]. Another clinical study conducted by Akilen et al. with 58 patients taking 2 g of cinnamon (500 mg of bark powder four a day) or a placebo found that cinnamon supplementation resulted in a decrease in the average HbA1c values in the cinnamon group (8.22% to 7.86%) compared to the placebo group (8.55% to 8.68%). Additionally, systolic and diastolic blood pressure (HbA1c) also decreased significantly in the cinnamon group (SBP: 132.6 to 129.2 mmHg and DBP: 85.2 to 80.2 mmHg) compared to the placebo group (SBP: 134.5 to 134.9 mmHg and DBP: 86.8 to 86.1 mmHg) [21]. Beneficial effects in type 2 diabetes are also demonstrated by the results obtained by Neto et al., where after 90 days of consuming 3 g of cinnamon bark powder, patients had a statistically significant reduction in glycated hemoglobin by 0.2% and fasting venous glucose by 0.55 mmol/l compared to the placebo group [22]. However, no effect of cinnamon (3 g of cinnamon extract in wholes) intake on the reduction of NF-kB, sirtuin 1 (SIRT1), High-Sensivity C Reactive Protein (hs-CRP), IL-6, and TNF-α was found in patients with type 2 diabetes, which play a significant role in the development of atherosclerosis [23], nor on the adhesion molecules ICAM-1 and VCAM-1 [24].

Momordica charantia L., Cucurbitaceae

Momordica charantia, also known as bitter melon or bitter gourd, is commonly cultivated in warm regions of the world, where its immature fruits are used as a vegetable [25]. In addition to its culinary uses, *Momordica charantia* has a long history in traditional medicine [26]. It is used as a remedy for digestive problems, as a laxative, and as an anthelmintic. Most importantly, it is utilized to treat diabetes and its complications.

Phytochemicals – Mechanisms of hypoglycemic action of Momordica charantia

The mechanism of hypoglycemic action of *Momordicacharantia*is multifaceted. Among the active compounds, we can distinguish polysaccharides, peptides, proteins, lipids, terpenoids, saponins, and phenols [25]. Some of these com-

pounds have hypoglycemic potential. In a study by Hsiao et al., 15 cucurbitane-type triterpenoids from bitter melon fruits were investigated in C2C12 myoblasts. At a concentration of 10 μM, two tested compounds: 25-hydroxy-5β,19-epoxycucurbita-6,23-dien-19-on-3β-ol3-O-β-D-glucopyranoside and 7β,25-dihydroxycucurbita-5,23 (E) -dien-19 -al 3-O-β-D-allopyranoside, increased glucose uptake by 50% and over 100%, respectively. The latter compound was a positive control, even more effective than insulin [27]. In a study conducted on the FL83B liver cell line, evaluating the activity of three triterpenoids isolated from the stem at a dose of 5 μg/ml, all three compounds [(23E)-cucurbita-5,23,25-triene-3β,7β-diol, 3β,25-dihydroxy-7β-methoxycucurbita-5,23 (E) -diene and 3β,7β,25-trihydroxycucurbita-5,23 (E) -dien-19-al] increased glucose uptake compared to cells treated with insulin. The mechanism of action was associated with AMPK activation [28]. AMPK has been recognized as a potential target in treating metabolic diseases, including obesity and type 2 diabetes. It is a cellular energy sensor that promotes ATP-producing catabolic pathways, such as glucose uptake, and inhibits ATP-consuming processes. Chen et al. also demonstrated the impact of cucurbitane-type triterpenoids from the fruits of *Momordica charantia* on glucose production in H4IIE liver cells. At a concentration of 100 μM, four out of the tested triterpenoids inhibited gluconeogenesis by approximately 50% [29]. In a study by Pera et al., triterpenoids isolated from the *Momordica charantia* fruits, were examined for their inhibition of α-amylase and α-glucosidase enzymes at concentrations of 0.87 mM and 1.33 mM. The compounds showed similar α-amylase inhibition activity to acarbose (0.13 mM), a positive control (68.0–76.6%). In the α-glucosidase inhibition test, karavilose VIII (56.5%) was the most active compound, while the activity of other compounds ranged from 24% to 40% [30]. So far, the inhibitory effect of several compounds contained in *Momordica charantia* on glucose absorption through the inhibition of α-amylase and α-glucosidase has been proven [30–31]. The results of a study conducted by Lee et al. suggest the influence of *Momordica charantia* on the inhibition of PTPN2, an enzyme associated with insulin resistance. At a concentration of 20 μM, nine out of the twenty-seven tested compounds from the *Momordica charantia* fruits exhibited inhibitory activity ranging from 72% to 93% [32]. Additionally, saponins contained in fruits of *Momordica charantia* can improve the morphology and viability of pancreatic β-cells and increase insulin secretion concentration-dependent. This will likely occur through the PI3K/Akt/FoxO1 signaling pathway [33].

Clinical evidence of the hypoglycemic effects of Momordica charantia

Cortez-Navarrete et al. evaluated the effect of administering *M. charantia* on insulin secretion and sensitivity. The clinical study was conducted on 24 patients who received *M. charantia* (2000 mg fruit powder per day) or placebo for three months. The *M. charantia* group showed significant decreases in body weight, BMI, percentage of body fat, WC, A1C, fasting glucose, and glucose AUC. *M. charantia* administration increased the AUC of insulin, first-phase insulin secretion, and total insulin secretion [34]. In a study on 90 patients who took bitter melon extract (bitter melon powder in capsules) for 12 weeks, hypoglycemic effects were observed in patients with type 2 diabetes [35]. Furthermore, the extract from bitter melon acts synergistically with oral hypoglycemic drugs and enhances their effects on NIDDM [36]. However, the hypoglycemic effect of bitter melon is weaker, as evidenced by comparing the effects of a daily dose of 2000 mg with 1000 mg of metformin [37]. Additionally, a study comparing the effects of bitter melon and glibenclamide showed that the hypoglycemic effect of bitter melon is inferior to glibenclamide. However, bitter melon may be more effective in alleviating cardiovascular risk factors associated with diabetes [38]. Bitter melon reduces elevated fasting serum glucose levels in individuals with prediabetes. This is demonstrated by the results of a study in which the effect of consuming 2.5 g of powdered bitter melon was evaluated over eight weeks. The CROS analysis ($t = -2.23$, $p = 0.031$, $r = 0.326$) showed a significant difference in the change in FPG of 0.31 mmol/L (5.6 mg/dL) with a tendency ($R2 = 0.42387$). This indicates the potential use of *Momordica charantia* as an adjunctive therapy [39]. Additionally, changes in sialic acid were examined in patients with NIDDM after treatment with bitter melon (55 mL of juice per 24 h) and rosiglitazone (4 mg/24 h). In diabetes, there is an increase in serum sialic acid levels, which

is a strong predictor of cardiovascular mortality. Each experimental group consisted of a total of 25 patients of both genders. Patients treated with bitter melon maintained sialic acid levels comparable to healthy individuals, while rosiglitazone increased serum sialic acid levels [40].

Morus alba L., Moraceae

Morus alba, also known as white mulberry, is a fruit tree native to Asia with a long history of use in traditional medicine [41]. Its fruits, leaves, and roots have been utilized to treat various ailments. White mulberry contains diverse phytochemicals that contribute to its medicinal properties. Among them are flavonoids such as rutin, quercetin, isorhamnetin, phytosterols, and phenolic acids, including chlorogenic acid, caffeic acid, and protocatechuic acid. However, its anti-diabetic properties are attributed to moranolins, mulberrochromenes, and alkaloids [41].

Phytochemicals – Mechanisms of hypoglycemic action of Morus alba

Alkaloids from mulberry twigs (Sangzhi alkaloids [SZ-A]) consist mainly of 1-deoxynojirimycin (1-DNJ), phytomoleculefagomine (FA), 1,4-dideoxy-1,4-imino-D-arabinitol (DAB), and other polyhydroxyalkaloids. In mulberry twigs, the 1-DNJ is the dominant alkaloid, accounting for 50% of the iminosugars. In a study conducted by Ye et al., the impact of water extract of Shangzhi (SZ) on rats and mice with standard and alloxan-induced diabetes was evaluated, and the results were compared with those of acarbose, an alpha-glucosidase inhibitor. It was shown that SZ-A reduced fasting and postprandial blood glucose levels and prolonged the peak glucose concentration, similar to acarbose, indicating an impact on alpha-glucosidase [42–43]. Unabsorbed phytochemicals from *Morus alba* compete with glucose for intestinal glucose transporters [43]. Studies indicate that DNJ, besides inhibiting alpha-glucosidase, alleviates hyperglycemia by improving insulin sensitivity and affecting the activation of the PI3K/AKT insulin signaling pathway in skeletal muscles [44]. Animal experiments have shown that SZ-A improves insulin resistance, increases basal insulin levels, and enhances glucose-stimulated insulin secretion [45]. Phytochemicals (e.g., quercetin 3-(6-malonylglucoside) present in white mulberry twigs exhibit antioxidant activity, improving the oxidative state of the body and protecting liver and pancreatic cells from damage [46- 47]. Even a single intake of mulberry leaf extract (300 mg) with a meal reduces the digestion and absorption of carbohydrates [48]. In addition, a beneficial effect on the lipid profile in patients with T2DM should also be mentioned [49].

Clinical evidence of the hypoglycemic effects of Morus alba

Alkaloids from mulberry twigs (Sangzhi alkaloids [SZ-A]) demonstrate equivalent hypoglycemic effects to acarbose in patients with T2DM. In a 24-week study involving 600 patients, HbA1c decreased by 0.93% (10.2 mmol/mol), comparable to the result obtained with acarbose (50 mg three times daily). Furthermore, SZ-A administration resulted in a lower incidence of adverse effects and gastrointestinal disturbances [50]. Another study conducted by Ling et al. also recognized SZ-A as effective and safe in treating Type 2 Diabetes [51]. In a 12-week study by Thaipitakwong et al., it was determined that 12 mg of mulberry DNJ represented the minimum effective dose for alleviating postprandial hyperglycemia. Mulberry leaves reduced fasting plasma glucose (FPG) levels by 3.86 ± 5.99 mg/dL ($p = 0.002$) and glycated hemoglobin (HbA1c) by 0.11 ± 0.22% ($p = 0.011$) compared to baseline values. Additionally, mulberry leaves alleviated insulin resistance ($p = 0.057$) [52]. Furthermore, the mulberry leaf aqueous extract (dried mulberry leaves and was standardized to 3.6 mg/g of DNJ) improves postprandial glucose response in individuals with prediabetes, indicating the potential use of white mulberry in diabetes prevention [53]. In a study by Takahashi et al., the optimal timing of mulberry leaf extract (DNJ, 1 mg per tablet) intake was determined. An internal clock controls glucose tolerance and is worse in the evening. From the perspective of chrono-nutrition, the prophylaxis of diabetes requires the evaluation of the anti-diabetic effects of functional components and nutrients at different times of intake. Consuming mulberry leaf extract in the evening, but not in the morning, effectively improves glucose tolerance [54].

Trigonella foenum-graecum L., Leguminosae

Fenugreek is a native plant of Eastern Europe and parts of Asia, but it is now cultivated worldwide

for its leaves and seeds. Fenugreek seeds have traditionally been used as an expectorant, to alleviate cold symptoms, as a laxative, to aid digestion, and to support lactation [55].

Phytochemicals – Mechanisms of hypoglycemic action of Trigonella foenum-graecum

Among the most studied bioactive compounds influencing carbohydrate metabolism in fenugreek, diosgenin, 4-hydroxyisoleucine, and soluble dietary fiber fractions can be mentioned [56]. Diosgenin improves the function of pancreatic β-cells, downregulates enzymes involved in hepatic gluconeogenesis and glucose export, upregulates hepatic glucokinase, and increases the levels of hepatoprotective and antioxidant enzymes [56]. In studies on rats, 4-hydroxyisoleucine improved insulin sensitivity by increasing peripheral glucose utilization and reducing hepatic glucose production [57]. Research has shown that fenugreek's soluble dietary fiber fraction (SDF) does not exhibit hypoglycemic activity alone but acts during glucose perfusion. When SDF was administered concurrently with an oral glucose load, it significantly reduced the rise in blood glucose levels in healthy rats at 75 minutes and in rats with diabetes at 30 minutes. Additionally, SDF improved glucose uptake by adipocytes [58]. In studies conducted by Vijayakumar et al., the effect of fenugreek seed extract (FSE) (seeds were ground and dialyzed into extract) was evaluated in alloxan-induced diabetic mice, and it was found that the action of FSE was associated with the activation of the insulin signaling pathway. FSE improved GLUT4 translocation from intracellular spaces to the cell membrane [59]. Pyruvate kinase (PK) and phosphoenolpyruvate carboxykinase (PEPCK) are two key enzymes involved in glycolysis and gluconeogenesis, respectively, and their activity is impaired in diabetes. In a study by Mahammada et al., in addition to the beneficial effect on GLUT4, the influence of fenugreek (fenugreek seed powder) on the restoration of PK and PEPCK activity was demonstrated [60]. The antioxidant activity of fenugreek (25 mg of Trigonella foenum-graecum seed powder solution twice a day per 1 month) protects the liver and pancreas from oxidative damage induced by diabetes [61].

Clinical evidence of the hypoglycemic effects of Trigonella foenum-graecum

In a study conducted by Gupta et al., patients with newly diagnosed type 2 diabetes received 1 g of aqueous-alcoholic extract of fenugreek seeds daily. After two months of the study, an improvement in glycemic control and a reduction in insulin resistance was observed in the intervention group [62]. The commercial product 'Fenfuro', which contains an extract from fenugreek seeds (patented with water–ethanol extraction), lowers fasting and postprandial blood glucose levels, allowing for a reduction in the dose of anti-diabetic medications [63]. Consumption of fenugreek seeds (5 g fenugreek powder mixed with water three times daily) has a beneficial effect on fasting plasma glucose (FPG), systolic blood pressure (SBP), and certain liver and kidney function tests in patients with type 2 diabetes mellitus (T2DM) [64]. Additionally, fenugreek positively impacts lipid metabolism in patients with type 2 diabetes mellitus (DM2) [61]. Interestingly, substituting fenugreek flour for standard flour used in bread-making enables the production of bread that retains the beneficial properties of fenugreek in reducing insulin resistance [65].

Zingiber officinale Rosc., Zingiberaceae

Ginger, known as *Zingiber officinale*, has a rich history and wide medical application. Its usage dates back thousands of years and has roots in ancient China and India [66]. In traditional medicine, ginger has been widely used to treat gastrointestinal disorders such as nausea, vomiting, and indigestion. It is also appreciated for its anti-inflammatory properties and potential for pain relief and reducing inflammation [67].

Phytochemicals – Mechanisms of hypoglycemic action of Zingiber officinale

[6]-Gingerol, which is one of the main components of the rhizome of *Zingiber officinale*, influences the reinforcement of the glucose-stimulated insulin secretion pathway mediated by GLP-1 in pancreatic β-cells [68]. Additionally, [6]-Gingerol increases the membrane presentation of GLUT4 transporters in the skeletal muscles of diabetic mice [68]. In a study on rats with induced type 2 diabetes, ingesting ginger extract at a 4 ml/kg body weight significantly reduced blood glucose levels after six weeks [69]. Treatment with *Zigniber officinale* significantly increases insulin levels and decreases fasting blood glucose levels in diabetic rats treated with

ginger juice [70]. In studies conducted by Abdulrazaq et al., ginger juice increased the activity of glucokinase, phosphofructokinase, and pyruvate kinase and exhibited anti-hyperglycemic effects [71]. In vitro studies on mouse myoblast and myotube cell lines demonstrated the influence of ginger extract on the increased expression of GLUT4 transporters on the cell surface compared to the control [72]. Furthermore, *Zingiber officinale* protects against diabetes-induced kidney damage by alleviating oxidative stress, inflammation, and apoptosis [73].

Clinical evidence of the hypoglycemic effects of Zingiber officinale

In a study conducted by Carvalho et al., the effectiveness of ginger in lowering blood glucose levels, total cholesterol, and LDL cholesterol (LDL-C) was demonstrated [74]. In a study conducted in 2019 on a group of newly diagnosed, obese (BMI > 30 kg/m^2) diabetic patients, El Gayara et al. showed that daily consumption of 3 capsules, each containing 600 mg of powdered ginger (dried, finely ground rhizomes of ginger in gelatin capsules), for eight weeks resulted in a reduction in BMI, HbA1c, FBG, FSI, triglycerides, TC, and LDL-C [75]. In another study, ginger supplementation (dried and ground rhizomes of ginger in tablets containing 1 g ginger in each) significantly lowered insulin levels, LDL-C, triglycerides, and HOMA index while increasing the value of the Quantitative Insulin Sensitivity Check Index (QUICKI index) compared to the control group [76]. Shidfar et al. examined the effect of administering 3 g of powdered rhizomes of ginger (in capsules) daily for three months, which resulted in improved glycemic indices, total antioxidant capacity (TAC), and PON-1 activity in patients with type 2 diabetes, confirming its antioxidant properties [77]. Further studies confirm the impact of ginger (powdered rhizomes of ginger in 800 mg capsules [78] or one-gram capsules containing ginger powder [79]) intake on reducing fasting plasma glucose levels, HbA1c, insulin, HOMA, triglycerides, total cholesterol, CRP, prostaglandin E2 (PGE_2), and improving insulin resistance indices such as the QUICKI index [78–79]. In patients with diabetes and end-stage renal disease, ginger (2000 mg of rhizomes ginger powder) lowers blood glucose levels, increases insulin sensitivity, and reduces serum urea levels [80].

Conclusions

Diabetes is a global health problem affecting millions worldwide, and forecasts indicate further increases in cases. Therefore, searching for new, effective therapies and interventions to combat this disease is necessary. The modern approach to managing diabetes increasingly turns to traditional medicine and explores the use of natural plant remedies. Scientific research focuses on identifying active plant compounds, studying their mechanisms of action, and exploring their potential applications in diabetes treatment and blood sugar regulation. Many active plant ingredients have been isolated and used to produce dietary supplements and anti-diabetic medications at appropriate concentrations. Combinations of different plant products are often used to enhance their effects synergistically [81]. The mechanisms of action of plant-derived compounds summarized in the publication represent a consolidated compilation of scientific achievements thus far regarding the anti-diabetic properties of plant preparations. They include improvements in glucose transport, influence on glucose metabolism, inhibition of carbohydrate-digesting enzymes, promotion and enhancement of insulin secretion, reduction of insulin resistance, improvement of pancreatic islet morphology and function, and liver protection. These pieces of information, presented clearly, are summarized in **Table 1**. The potential of plant-based anti-diabetic agents is only partially discovered, thereby encouraging further research and discoveries aimed at understanding their mechanisms of action and utilizing them within contemporary health movements.

Abbreviations

FPG – Fasting Plasma Glucose, HbA1c – Glycated Hemoglobin, UCP-1 – Uncoupling Protein, PEPCK – Phosphoenolpyruvate Carboxykinase, BMI – Body Mass Index, NF-kB – Nuclear Factor Kappa B, SIRT1 – Sirtuin 1, hs-CRP – High-Sensitivity C-Reactive Protein, IL-6 – Interleukin-6, TNF-α – Tumor Necrosis Factor-Alpha, ICAM-1 – Intercellular Adhesion Molecule 1, VCAM-1 – Vascular Cell Adhesion Molecule 1, AMPK – AMP-Activated Protein Kinase, WC – Waist Circumference, NIDDM – Non-Insulin Dependent Diabetes Mellitus, 1-DNJ – 1-Deoxynojirimycin, FA – PhytomoleculeFagomine, DAB – 1,4-Dideoxy-1,4-Imino-D-Arabinitol, T2DM – Type 2 Diabetes Mellitus, SZ-A – Sangzhi Alkaloids, SDF – Soluble Dietary Fiber, FSE – Fenugreek Seed Extract, PK – Pyruvate Kinase, GLP-1 – Glucagon-Like Peptide 1, FBG – Fasting Blood Glucose, TAC – total antioxidant capacity

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Conflict of interest statement
The authors declare no conflict of interest.

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