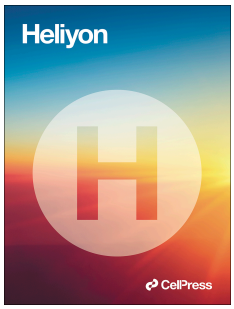

Comprehensive Review of Opportunities and Challenges of Ethnomedicinal Plants for Managing Type 2 Diabetes

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Comprehensive Review of Opportunities and Challenges of Ethnomedicinal Plants for Managing Type 2 Diabetes

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Abstract

Diabetes mellitus is a prevalent metabolic disorder worldwide. A variety of antidiabetic medications have been developed to help manage blood glucose levels in diabetic patients, but adverse reactions and efficacy loss over time have spurred research into new therapeutic agents. In view of this, investigations into the antidiabetic effect of herbal products have been encouraged due to their potential availability, inexpensiveness, and relatively minimal side effects. This review explores the antidiabetic potentials of the eight most promising medicinal plants in terms of molecular mechanisms, phytochemistry, toxicology, and efficacy. These plant extracts have gone through clinical trials and demonstrated good control of blood glucose levels by increasing serum insulin levels, enhancing tissue glucose uptake, and/or decreasing intestinal glucose uptake. Yet, medicinal plants are far from being able to replace conventional antidiabetic drugs for patient management but they have the potential for further development if rigorous clinical trials on their mechanisms, delivery, and dose regimen are performed. To date, no study has been performed to isolate and characterize active compounds in these plant extracts, suggesting that further investigations in this area would be the next step to advance this field.

Introduction

Diabetes mellitus can cause chronic or acute problems [1] through deficient action or lack of insulin. This happens when the pancreas is unable to produce enough insulin, or when body tissues do not respond to insulin. In those cases, the body cells cannot metabolize sugar properly leading to the breakdown of body fat, protein, glycogen, and the generation of by-products such as ketones [2]. Environmental and genetic factors affect onset and progression of the disease [3]. Polyuria,

thirst, weight loss, and blurring of vision are well-known symptoms [4]. Ultimately, diabetes causes organ failure leading to disability or death [5]. Impaired insulin secretion or action could lead to chronic hyperglycemia hence severity of damage is related to time with the disease and how well it has been controlled.

There are two common types of diabetes, 1 and 2: insulin-dependent and non-insulin-dependent, respectively. Type 1 occurs when pancreatic islet beta cells are destroyed so the body cannot produce insulin. This is an auto-immune disease with no cure. There is no medication other than insulin and its derivatives available for the controlling of type 1 diabetes. Type 1 patients need daily insulin to regulate their blood sugar levels [5]. Type 2 diabetes accounts for the vast majority of the diabetic people in the world, and accounts for the majority of treatable and preventable cases [6]. In type 2, insulin is produced and secreted but does not function properly due to the reduced responsiveness of the body tissue. Most currently available antidiabetic medicines control blood glucose in type 2 diabetic patients by one or more of the mechanisms shown in Fig. 1. Those drugs include sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, and non-sulfonylureas secretagogues as shown in Fig. 2.

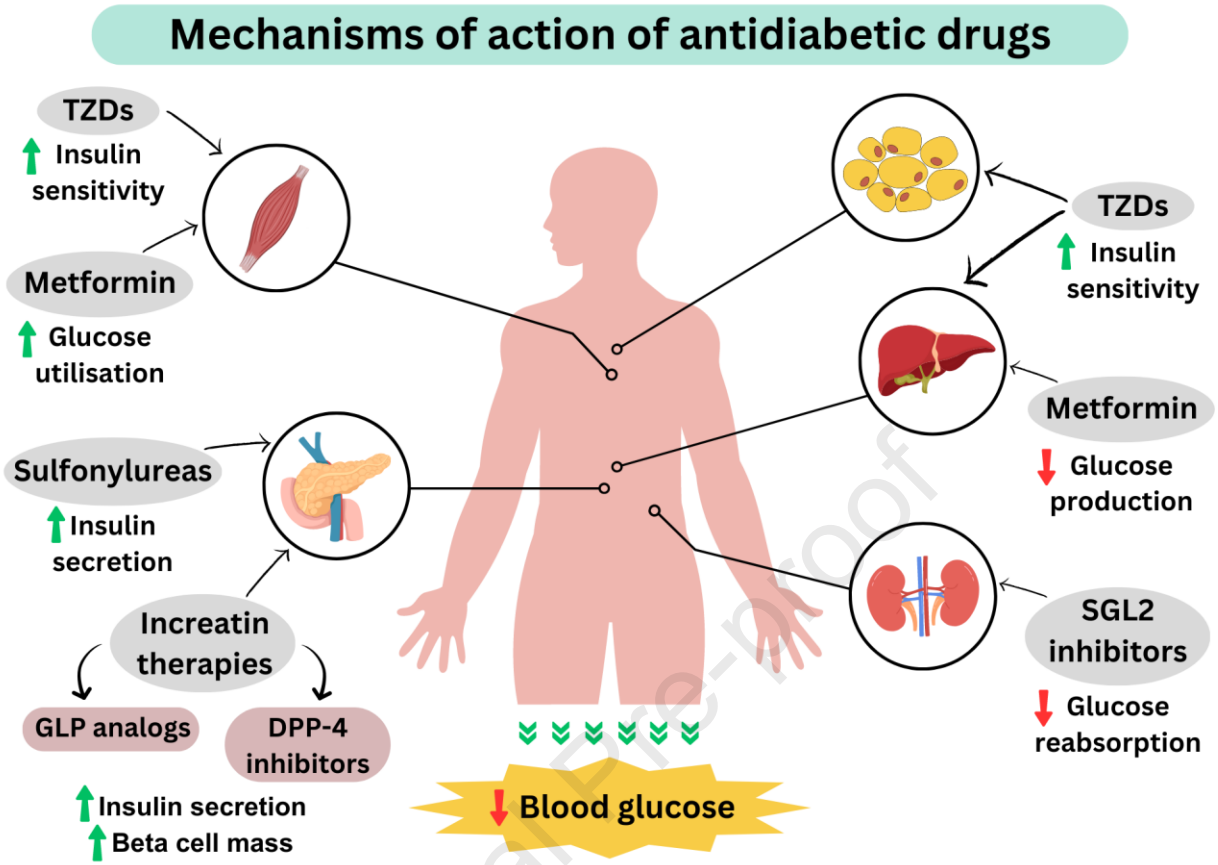


Fig. 1. Mechanisms of action of currently available antidiabetic drugs

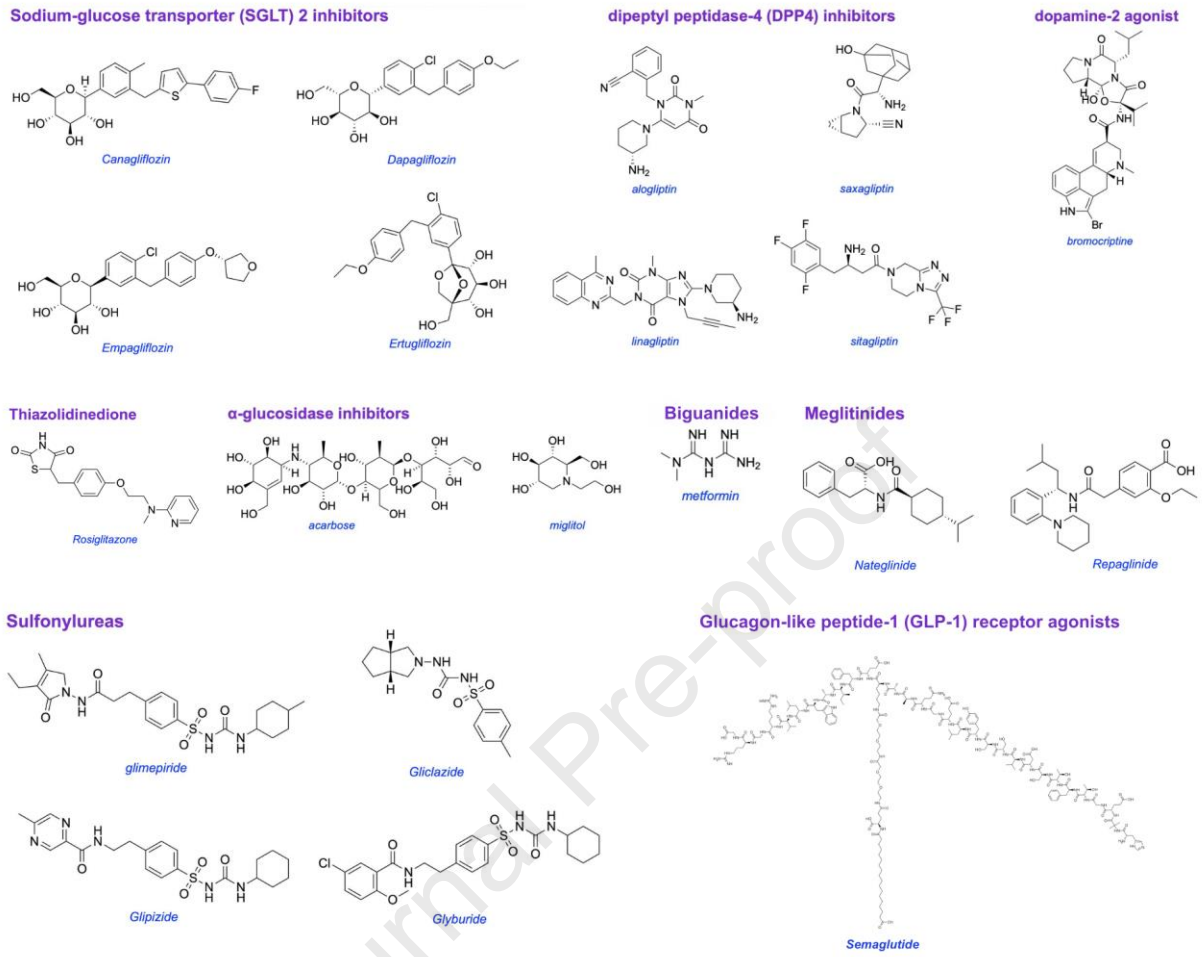


Fig. 2. Chemical structure of the different groups of antidiabetic medicine

Oral sulfonylureas such as glimepiride and glyburide work by increasing insulin secretion from the pancreas. Such drugs bind to sulfonylureas receptors on β-cells while closing adenosine triphosphate-dependent potassium channels. When this happens, the cell membrane depolarizes and insulin is secreted by the calcium influx mechanism [7,8]. The effectiveness of sulfonylureas decreases after 6 years in 44% of patients [9]. Meglitinide and repaglinide are known as non-sulfonylureas drugs which increase insulin secretion in the same way as sulfonylureas.

Biguanides drugs such as metformin lower blood glucose by reducing hepatic gluconeogenesis and insulin-stimulated uptake; drugs are not so effective in the absence of insulin [6].

Acarbose and miglitol are α-glucosidase inhibitors that inhibit pancreatic α-amylase and α-glucosidase to interfere with the digestion of carbohydrates and promote slower absorption of sugars into the body [7,10].

Pioglitazone and rosiglitazone are thiazolidinediones (TZDs) hypoglycemic agents. These act by increasing tissue sensitivity to insulin and by antagonizing nuclear peroxisome proliferator-activated receptor gamma (PPARγ), which is responsible for the transcription of insulin-responsive genes involved in the regulation of transportation, production, and glucose utilization [11].

Antidiabetic medicines such as acarbose, metformin, and sulfonylureas have common side effects and disadvantages, including gastrointestinal upset, drug resistance, diarrhea and lactic acidosis, hepatic failure, weight gain, tachycardia, and hypothyroidism [12]. More investigations are needed to discover new medicines for all forms of diabetes and natural compounds are relatively unexplored alternatives.

Antidiabetic medicinal plants

Plant based products can be relatively safe, readily available, have minimal side effects, and cheaper than synthetic drugs [13,14]. In fact, many synthetic drugs are directly or indirectly derived from medicinal plants. Medicinal plants are rich sources of bioactive chemicals with medicinal effects [15,16] due to phytoconstituents such as flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides [17]. In view of this, herbal medicines have been used as

alternative treatment for diabetes worldwide [18,19]. These plant extracts could exert hyperglycemia control by enhancing insulin secretion and sensitivity of pancreatic islets, glucose uptake by muscle cells and adipose tissues, inhibition of intestinal glucose absorption, and hepatic glycogenolysis [12,6]. Fig. 3 depicts native origin of the most commonly used medicinal plants which have gone through clinical trials for antidiabetic effect.

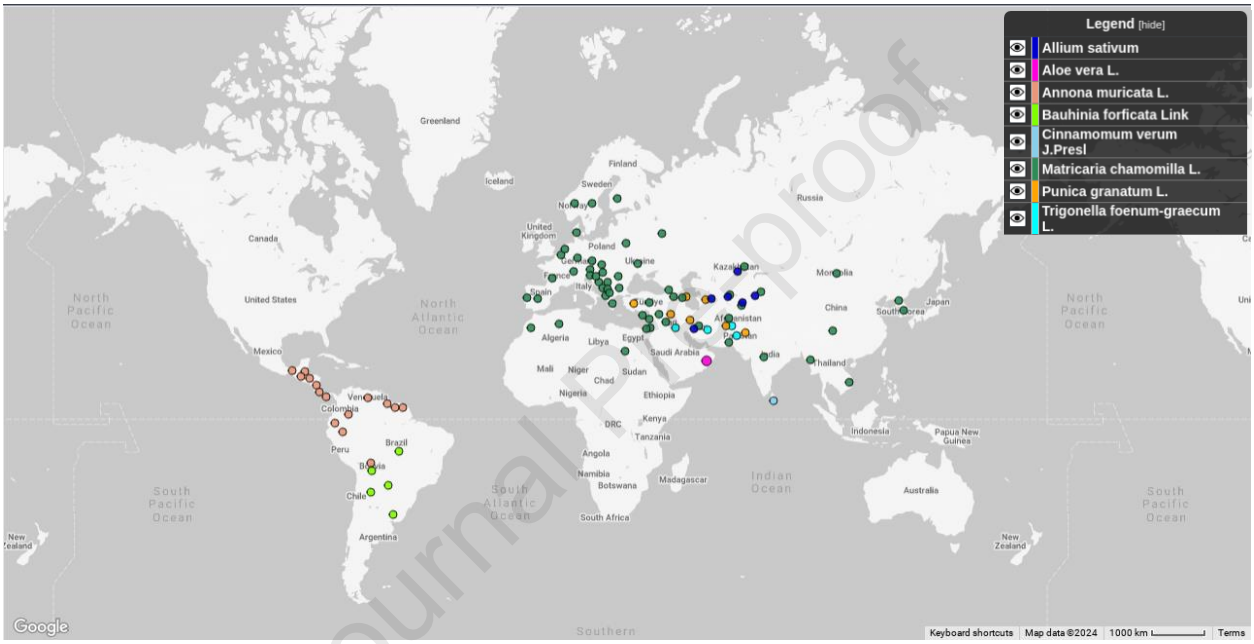


Fig. 3. Map showing native origin of the medicinal plants [20]

Most Promising Antidiabetic Phytochemicals and Plant Extracts

Allium sativum L.

Native origin

Allium sativum L. (garlic) belongs to the Amaryllidaceae family, an aromatic herbaceous annual spice that has been used as a medicine for a long time [21,22]. The native range of garlic stretches from the rocky valleys and riverbeds of Iran to the stream beds and ravines of Kazakhstan. Allium species have been found to possess antidiabetic properties, prevent cardiovascular disorders, and strengthen the immune system [23].

Major compound and mechanistic action

As shown in Table 1, Garlic bulbs and their products contain sulfur compounds (ajoenes, allicin, vinyldithiins, and sulfides), flavonoids (quercetin), and Alliin (the main precursor of allicin) [24,25]. Garlic ethanolic extract improves the complication of diabetes in STZ/alloxan-induced diabetic rats by increasing insulin secretion from pancreatic β-cells [26]. Allyl propyl disulfide, allicin, cysteine sulfoxide, and S-allyl cysteine sulfoxide, were shown to be effective in reducing blood glucose, and increasing insulin secretion and insulin sensitivity. So far, similar results have been reported between glibenclamide and Aline in reducing the complications of diabetes [27,28]. Garlic oil was able to decrease the serum aspartate aminotransferase, alanine transferases, and alkaline phosphatase in diabetic rats [29]. Moreover, it has been demonstrated that garlic bioactive compounds are able to promote antioxidant synthesis and reduce oxidizer production [30]. It was stated that garlic extract increases the activity of enzymes such as hepatic superoxide dismutase in rats (SOD) [25]. Alliin, the major component isolated from garlic extract, has great antioxidant

activity through controlling ROS generation, preventing mitogen-activated protein kinase, and inhibiting NADPH oxidase 1 [31].

Clinical trial

As summarized in Table 2, a triple-blind randomized clinical trial on the antidiabetic effects of garlic involving 49 prediabetic pregnant women by Faroughi et al. reported a decrease in fasting blood sugar, cholesterol, and serum lipids [27]. The study showed the administration of 400 mg garlic pills per day for eight weeks resulted in significantly greater improvement in prediabetic symptoms than placebo patients.

***Aloe vera* L.**

Native origin

Aloe vera L. is a succulent plant from the family Aloaceae. The plant has been used by natives to treat various diseases. The genus *Aloe* originated more than 16 million years ago from Southern Africa. To date, there are over 500 species of *Aloe* where 25% of these plants were used for various therapeutic purposes [32,33].

Major compound and mechanistic action

Aloe vera L. contains 200 bioactive compounds including anthraquinones, vitamins, phytosterols, polysaccharides, carbohydrates, amino acids, and minerals [34]. A study done by Mohammed et al. showed that anthraquinones found in the latex of the plant could increase insulin sensitivity via upregulation of insulin receptor substrates-1 (IRS-1) and phosphoinositide-3-kinase (PI3Ks) [35]. Besides, oral administration of *Aloe vera* extract (300 mg/kg) prepared from the plant's gel reduced

blood glucose levels, lowered the fasting plasma, and was also able to increase the serum insulin levels from 116.5 pmol/L (1st week) to 146.1 pmol/L (3rd week) in the STZ-induced diabetic rats [36]. Furthermore, it was shown that daily consumption of *Aloe vera* at a dose of 400 mg/kg in the form of concentrated gel for 8 weeks significantly reduces blood sugar and body weight of diabetic rats [37]. Researchers stated that *Aloe vera* gel extract is able to increase an insulin secretory function parameter, the homeostasis model assessment of β-cell function (HOMA-β), which indicated a glucose tolerance with slower diabetes development [38]. In another study, the analysis of the volume, number, diameter, and area of the pancreatic islets of diabetic rats showed improvement after treatment with *Aloe vera* gel extract in diabetic rats, with 84.6% in total number of islets, 85.1% in islet diameter, 71.7% of islet area, and 60.5% of islet volume [36]. Besides, sterols isolated from *Aloe vera* gel can also activate peroxisome proliferator-activated receptors (PPAR) which play roles in regulating metabolism of carbohydrates and lipids [39,40]. Saponins are another important ingredient in *Aloe vera* leaves which regulate nutrient absorption, reduce protein digestibility, lower blood cholesterol, and have antiviral and antidiabetic properties [41,42]. In another experiment, treatment with *Aloe vera* extract had resulted in a significant decline in triglyceride and very low density lipoprotein (VLDL) levels in the blood [38]. Other than improving diabetic condition, *Aloe vera* bioactive components could exhibit a positive impact on diabetics' nerve and brain tissue complications. It is shown that *Aloe vera* possibly reduces apoptosis phenomenon by increasing the expression of nerve growth factor (NGF) and tropomyosin receptor kinase A (TrkA) in the brain. At the same time, it reduces the activity and expression of p75 neurotrophin receptors in diabetic rats which may decline the atrophy of the hippocampus by lowering the activity of this receptor in the hippocampus [37]. Similarly, another study that fed *Aloe vera* extracts in gel format to the rats showed the ability to protect the

hippocampus and have positive effects on behavioral deficits in diabetic rats due to its antioxidative and hypoglycemic properties [43]. *Aloe vera* extract could also reduce the level of mutagenic base modifications and DNA fragmentation in diabetics significantly through its antioxidant capability [44,45]. One other recent study showed that *Aloe vera* slowed down the progression of nephropathy by altering its lipids profile and decreasing kidney oxidative stress [46]. However, there are several adverse effects associated with the use of *Aloe vera*. For instance, the anthraquinone content of the extracts appear to be responsible for most allergic reactions related to *Aloe vera* [47]. Also, it could have toxic effects on the fetus when *Aloe vera* is used during pregnancy [48]. Likewise, Boudreau and Beland recommended that patients with a history of kidney or heart problems should avoid using *Aloe vera* latex [49]. Also, it was reported that *Aloe vera* juice supplementation may affect glutathione peroxidase (GPx), superoxide dismutase (SOD), and malondialdehyde (MDA) enzymes' function in the kidneys of diabetic rats [6]. This was further proven by another research team that demonstrated increased levels of glutathione and antioxidant SOD enzyme activities in diabetic rats treated with *Aloe vera* extract [50].

Clinical trial

The effect of drinking 250 mL of *Aloe vera* gel extract daily in a clinical trial with 53 healthy volunteers over 14 days showed increased plasma total antioxidant capacity with no reported clinical side effects [51]. According to a separate double-blind randomized controlled *in vitro* trial, 300 and 500 mg of *Aloe* emodin (commercially available leave extracts from *Aloe vera*) treatments twice a day, had successfully reduced HbA1C level in pre-diabetics, indicating its potential use to control the blood glucose level [52].

***Annona muricata* L.**

Native origin

Annona muricata L., called Graviola, is a plant of the *Annonaceae* family, which is mainly distributed in tropical and subtropical regions of the world, while it's native to the tropical Americas.

Major compound and mechanistic action

Acetogenins, flavonoids, tannins, alkaloids, and coumarins are the major bioactive components of *Annona muricata* L. leaf extract [53]. Some identified phenolic compounds of *Annona muricata* are flavonoids, phenolic acids, and gallotannins [54]. *Annona muricata* L. leaves have been reported to contain alkaloids such as aporphines, isoquinolines, imino sugars, and protoberberines [55,56]. *Annona muricata* L. leaf extract contains rutin, kaempferol-3-O-rutinoside, quercetin, kaempferol, muricoreacin, annonacin, and annonacinone. It is reported that its extract can improve metabolism of insulin and lipid, and autophagy pathways which are related to non-alcoholic fatty liver disease (NAFLD) risk in type 2 diabetes [57]. *Annona muricata* L. extract also, increased glucose uptake, improved hexokinase activity, and reduced pancreatic β-cell apoptosis via the PI3K/Akt gene upregulation. It has been shown that *Annona muricata* L. extract (100 and 200 mg/kg) reduces blood glucose levels by 31.77% and 45.77% respectively in STZ-diabetic rats [53]. Furthermore, a significant increase in protein kinase B and B-cell lymphoma 2 expression in liver and pancreas tissue, as well as a decline in insulin resistance in diabetic rats were observed using *Annona muricata* L. extract [58]. Son et al. stated that a low dose of *Annona muricata* L. extract stimulates hepatic insulin signaling-related proteins such as insulin receptor subunit (IRS)-1,

glucose transporter (GLUT) 2, and p-Akt and significantly reduces the level of triglyceride in the liver concentration [57].

Clinical trial

A clinical trial study was conducted by Arroyo et al. and 60 patients with type 2 diabetes were given either *Annona muricata* L. ethanolic extract capsules containing 5 mg of glibenclamide or only 5 mg tablets of glibenclamide for a month [59]. A decline in blood glucose was seen in groups treated with *Annona muricata* L. and glibenclamide. Having said that, 11% of them experienced side effects such as burning pain in the epigastrium and nausea. Despite the hypoglycemic effects of *Annona muricata* L., a lack of adequate clinical trials is felt and the efficacy of *Annona muricata* L. extract as a single therapy or as an adjunctive therapy should be investigated [60].

Bauhinia forficata Link

Native origin

Bauhinia forficata Link (*B. forficata*) is a species of flowering tree that is native to Argentina, Brazil, Uruguay, and Peru. *B. forficata* is often used in traditional medicine to treat type-2 diabetes [61].

Major compound and mechanistic action

Flavonoids such as kaempferitrin, kaempferol, and quercetin, are introduced as major compounds in *Bauhinia forficata* leaves [62]. Kaempferol improves insulin sensitivity by phosphorylating IRS, increases glucose uptake and adiponectin secretion [63]. The aqueous extract of *B. forficata*

leaves reduces hyperglycemia, glycosuria, uremia, lipid peroxidation, stimulates the activity of glutathione reductase, and increases hepatic glycogen [64,65]. Also it has been shown that the ethanol extract of *B. forficata* leaves inhibits α-amylase and reduces protein glycation [66]. Franco et al. showed that *B. forficata* extract is an excellent inhibitor of α-amylase, α-glucosidase, and lipase. Additionally, it is not toxic to rodents, erythrocytes, and macrophages [67]. Ajebli et al. reported that the natural alkaloids of *Bauhinia forficata* blocks protein tyrosine phosfatase 1B, deactivates dipeptydil peptidase-IV, increases insulin sensitivity, reduces oxidative stress, and inhibits glucosidase [68]. In a study it was found that *B. forficata* extract can decrease hepatic oxidative stress, MDA levels and increase catalase activity [69].

Clinical trial

In an investigation conducted by Tonelli et al., it was demonstrated that the use of *B. forficata* leaf extract capsule (300 mg) decreases plasma glucose levels and glycated hemoglobin in type II diabetics compared with the placebo group [70]. Indeed they concluded that the adjunctive use of capsules containing *B. forficata* could be beneficial if added to regular oral antidiabetics in type II diabetic patients [70]. However, the study only included 92 type 2 diabetic patients from a single center, and the experts concur that a larger trial is required to validate the findings and fully analyze the undesirable side effects.

***Cinnamomum verum* J.Presl**

Native origin

Cinnamomum verum J.Presl (Cinnamon), also known as *Cinnamomum zeylanicum* Blume, *is a* small tree belonging to the family Lauraceae. Cinnamon has various beneficial effects such as

antiemetic, antidiarrheal, and antiflatulent [71,72]. The tree is native to the island of Sri Lanka and grows in wet tropical biomes.

Major compound and mechanistic action

Cinnamic aldehyde and Eugenol are the main constituents found in the leaf oil. Other compounds including camphor, eucalyptol, and safrol are present in cinnamon roots [73]. Eugenol, cinnamaldehyde, camphor, cinnamyl acetate, and copane are the cinnamon major components [74]. The polyphenols present in cinnamon contribute to its antidiabetic activity and mitigate pathological damage to pancreatic β-cells in STZ-diabetic mice [75]. It was shown that water extract from cinnamon stem barks had a blood glucose-lowering effect in STZ-induced rats [76]. Cinnamon extract has been reported to be effective in lowering fasting blood glucose and homeostatic model assessment for insulin resistance (HOMA-IR) levels [77,78]. Studies have reported the neuroprotective, fat-lowering, antioxidant, anti-inflammatory, and hypoglycemic effects of cinnamon so that it can be effective in preventing the onset of diabetes and cardiovascular diseases [79,80]. Cinnamon essential oil is a free radical scavenger and has a dose-dependent anti-proliferative effect on adipose-derived mesenchymal stem cells [81]. Multiple studies have reported that cinnamon extract increases insulin sensitivity and insulin secretion [82]. The usage of *Cinnamon cassia* and *zeylanicum* extracts was reported to enhance plasma insulin in rats [83]. Cinnamic acid can improve glucose tolerance and enhance insulin secretion in islet cells for both *in vivo* and *in vitro* studies [84]. Besides, cinnamon extract was revealed to have an inhibitory effect against α-glycosidase, and α-amylase, and exhibited reducing glucose manners [85,86]. An *in vitro* study showed that its extract may inhibit lipase, α-amylase, and α-glucosidase. Cinnamon aqueous extract was also reported to decrease the gene expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), thus declining hepatic

gluconeogenesis [87]. Furthermore, the aqueous extract can upregulate mitochondrial uncoupling protein 1 (UCP-1) and GLUT4 in brown adipose tissues and muscles in STZ-induced rats [88]. In another study, it was shown that cinnamaldehyde, found in cinnamon bark, upregulates the IRS1/ PI3K/AKT2 signaling pathway in STZ-induced rats [89]. Cinnamaldehyde was also revealed to activate PPARδ, PPARγ and retinoid X receptor (RXR) to enhance insulin sensitivity [90]. *Cinnamon Burmanii*, *Vietnamese*, *Loureirii*, and *Ceylon* were found to have great potential to suppress the formation of AGEs [91]. Procyanidin-B2 (PCB2), one of its bioactive compounds, also inhibits AGE accumulation and improves AGE-mediated pathogenesis of diabetic nephropathy [92].

Clinical trial

A clinical study involving 30 healthy adults was performed to investigate the side effects of taking water extracts of *C. zeylanicum* with the dose increased at monthly intervals at doses of 85, 250, and 500 mg/day. No adverse side effects were seen due to taking *C. zeylanicum* extract. It was reported that daily consumption of 1, 3, 6 g of cinnamon reduces LDL, mean TG, and TC [93]. In contrast, Markey et al. reported that no obvious differences were seen in the TC or LDL levels in a single-blinded randomized crossover study by using 3 g cinnamon and placebo [94]. Also, another trial showed that there is no significant alteration between the mentioned parameters after taking 1 g of cinnamon for 3 months [95]. Cinnamon's improving effects were clarified by multiple clinical trials through its beneficial effects on fasting blood glucose, two-hour postprandial glucose, insulin resistance, and HbA1C. Khan et al. conducted a randomized placebo controlled study, cinnamon was given at doses 1, 3, and 6 g/day to T2DM patients for 40 days [96]. Cinnamon decreased fasting blood glucose by 18 to 29%. In another clinical study, cinnamon extract (120 and 360 mg/day) decreased FBG and HbA1C levels [97]. The previous study is in contrast to

Leach and Kumar's results, who reported that cinnamon does not control blood glucose and cannot improve or prevent metabolic diseases [98].

***Matricaria chamomilla* L.**

Native origin

Matricaria chamomilla L. is one of the oldest plants with antidiabetic and anti-cancer activities. *Matricaria chamomilla* is native to most of continental Europe, northern Africa, and northern and western Asia and grows in all kinds of soils [99,100].

Major compound and mechanistic action

Flavonoids such as apigenin, quercetin, patoletin, luteolin, and their glucosides including several phenolic compounds are present in *Matricaria chamomilla* flowers [101]. The bioactive compounds of *Matricaria chamomilla* essential oil and extracts include terpenoids such as bisabolol and its oxides A and B, bisabolone oxide A, chamazulene, and farnesene [100]. The findings showed that a 12-week endurance training along with 200 mg/kg/day of *Matricaria chamomilla* flower extract reduces fasting blood glucose (FBG) and increases serum insulin levels in diabetic rats [99]. Administration of *Matricaria chamomilla* extracts caused a reduction in glycated hemoglobin and glycated serum protein (GSP) levels in diabetic rats [102]. Besides, the results showed that *Matricaria chamomilla* bioactive compounds protect pancreatic islet cells and reduces the oxidative stress occurring in hyperglycemia [103]. Hyperglycemia and oxidative stress can lead to brain damage which results in cognitive impairments. The results of crystal vessel staining in a study showed an increase in the number of necrotic cells in the hippocampus of

diabetic rats [99]. *Matricaria chamomilla* seems to be effective in controlling adverse changes in hippocampal neurons and its protective effects against the brain damage are likely due to its antioxidant activity. Asgharzade et al. reported that *Matricaria chamomilla* extract inhibits the peroxidation of brain tissue lipids and increases antioxidant capacity [104]. Heidarianpour et al. stated that exercise and consumption of *Matricaria chamomilla* extract together reduce the number of necrotic cells and MDA levels in hippocampal tissue in diabetic rats [99]. *Matricaria chamomilla* extract bioactive compounds such as α-bisabolol oxide can improve the serum level, and activity of MDA and AST of diabetic rats [99,105]. Quercetin is one of its extract flavonoids with good antioxidant properties that can change cell function. Apigenin is another flavonoid with antioxidant properties that stimulates neuronal differentiation, accelerates neurogenesis in hippocampal tissue, and improves memory and learning in rats [106].

Clinical trial

In a single-blind randomized controlled clinical trial conducted on 64 type 2 diabetic patients, the intervention group consumed 150 mL of *chamomile* flower tea three times a day after each meal, for 8 weeks. It was found that short-term intake of *M. chamomilla* tea can decrease blood glucose, and fatty acids, and increase insulin sensitivity in type II diabetes patients [107].

***Punica granatum* L.**

Native origin

Punica granatum L. (pomegranate) is a fruit native to the Middle East and used in Indian medicine to cure disease and disorders like diabetes, cardiovascular diseases, inflammation, and cancer [108,109].

Major compound and mechanistic action

The beneficial effects of pomegranate are related to its bioactive compounds such as flavonoids and phenolic acids including: anthocyanin, ellagitannin, and gallotannin [110,111,112]. *In vitro* studies have shown that α-amylase and α-glucosidase are inhibited in the presence of pomegranate hydrolyzable tannins (i.e., ellagitannins and gallotannins) in its peel extract [113]. In another study which was conducted by Çam and İçyer, it was reported that the aqueous extracts of pomegranate peels inhibit the α-glucosidase (IC50 = 5.56 ± 2.23 μg/mL) [114]. The α-glucosidase inhibitory activity of pomegranate peel extracts was attributed to bioactive components such as punicalagins, ellagic acid, and anthocyanins. It was also suggested that the phenolic compounds may inhibit α-amylase and α-glucosidase activities by mechanisms like mixed/non-competitive [115]. Rock et al. reported that the activity of PON1 enzyme is increased by using pomegranate juice [116], also pomegranate flower aqueous extract enhances the activity of SOD and CAT in diabetic rats [117]. Such components exhibit metal chelation activity, so it is recommended that it can reduce ROS accumulation. It has been shown that ferrous ion chelation by pomegranate juice can reduce the production of hydroxyl radical (•OH) from hydrogen peroxide [118]. Pomegranate extract also can decrease diabetes complications due to its ROS scavenging activity [119]. *In vitro* studies have shown that pomegranate wine can inhibit NF- κB activation. Active compounds such as gallic acid which has been found in the pomegranate extract shows effects like increasing PPAR-γ activity [120]. In another study, it was stated that consumption of pomegranate juice can reduce serum resistin levels in mice [121]. Insulin-stimulated glucose uptake has been found to increase by resisting neutralization [122,123]. It was revealed that the administration of aqueous pomegranate peel extract (200 mg/kg) reduces blood glucose and LPO in cardiac, hepatic, and renal tissues

[124]. Jafri et al. reported that the use of the aqueous-ethanolic (50%, v/v) pomegranate flower extract (400 mg/kg) lowers blood glucose [125].

Clinical trial

A randomized clinical trial was conducted to find pomegranate seed oil effects on the GLUT4 gene expression in 52 obese type II diabetic patients for 8 weeks. Results showed that pomegranate seed oil decreases FBS and increases the GLUT-4 gene expression in diabetic patients without any adverse effects [126]. However, further studies, with a larger sample size and extending beyond 8 weeks, are needed to confirm the results.

Trigonella foenum-graecum L.

Native origin

Trigonella foenum-graecum L. (Fenugreek) is an annual plant, native to the Middle East region, in the family Fabaceae and used as a dietary supplement which shows its hypoglycemic effects both in insulin-dependent and non-insulin-dependent diabetes [127].

Major compound and mechanistic action

Various antidiabetic properties of Fenugreek are attributed to its bioactive compounds including steroid, saponins, trigoneosides, glycoside D, trigofoenoside A, and steroidal sapogenins such as diosgenin and yamogenin [128]. A novel amino acid, 4-hydroxyisoleucine, is shown to be present in fenugreek seed extract which facilitates insulin secretion [129]. It was also reported that fenugreek seed fibers reduce postprandial blood glucose levels and have hepatoprotective, anti-

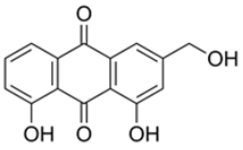
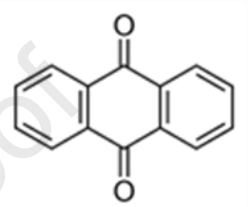
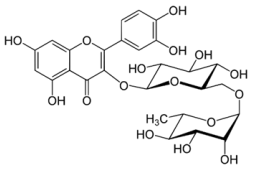
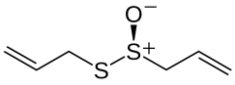
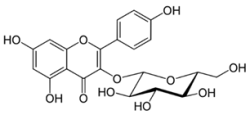
microbial, cardioprotective, and neuroprotective effects [127,130]. A study showed that blood glucose was reduced by fenugreek seed extract administration in diabetic rats [131]. Fenugreek seed is also rich in antioxidants and shows free radical scavenging activity [127]. Galactomannan, saponin, trigonelline, and 4-hydroxyisoleucine are found in fenugreek seeds and have antidiabetic and anti-cancer effects [132]. Fenugreek bioactive compounds play a role in the prevention of inflammation, controlling the cyclooxygenase enzyme inhibitory activities, and lipid peroxidation [127]. It also can reduce the glucose tolerance curve and improve glucose-induced insulin response. Such effects were attributed to its stimulatory impact on pancreatic β-cells [133]. Bafadam et al. reported that fenugreek extract at doses 50 and 100 mg/kg showed similar results to metformin in terms of catalase enzyme activity [131]. Additionally, SOD activity in groups including 200 mg/kg fenugreek extract and metformin, was higher than others.

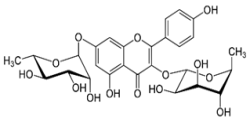
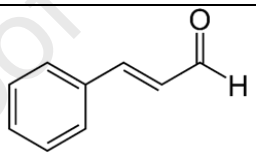
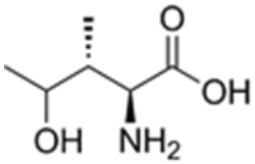
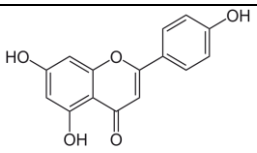
Clinical trial

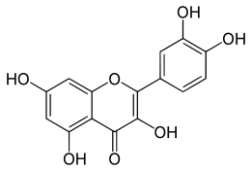
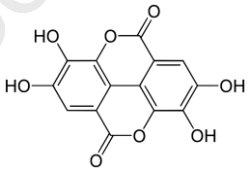
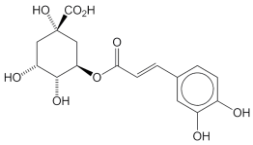
A reduction in blood glucose level, total lipid content, and serum α-amylase were seen following the use of 2.5 and 5 g/day of fenugreek seed powder for 4 weeks in 60 patients with type II diabetes [134]. A multi-site, randomized, double-blind, placebo-controlled trial was performed on 108 male and 46 female type II diabetes patients to assess fenugreek seed extract hypoglycemic activities. The fasting plasma glucose and postprandial glucose declined by 83% and 89%, respectively, while an increase in the level of fasting and postprandial C-peptide was observed [135]. Najdi et al. performed a randomized control study on 12 type II diabetes patients using 2 g of fenugreek powder per day [136]. A rise in the fasting insulin level was seen after 12 weeks. Besides, the anti-inflammatory and antioxidative effects of fenugreek seed compounds were investigated in a clinical trial study on 48 type II diabetes patients for 8 weeks [137]. A dose of 15 g/day of fenugreek seed powder enhanced the activity of SOD and reduced high-sensitivity C-reactive

protein. However, no significant effects were seen in the total antioxidant capacity, IL-6, TNF-α, and GPx activity [137]. Singh et al. designed a randomized, open-labeled, parallel-group comparative trial to evaluate the effect of fenugreek seed extract (500 mg two times a day) with glipizide (5mg/day) [138]. It was reported that the extract was not as effective as glipizide in reducing HbA1c but significantly improved blood sugar levels.

Table 1. In alphabetical orders, plants and their bioactive compounds, mechanism and structure

No	Plant	Compound (s)	Plant Part	Category	Mechanism of action	Structure	Reference
1	*Aloe vera* L.	Aloe-emodin	Latex	Anthraquinones	↓ ROS generation ↓ Pro inflammatory cytokine		[38]
		Anthraquinones	Latex	Anthraquinones	↑ IRS1 ↑ PI3Ks		
2	*Annona muricata* L.	Rutin	Leaves	Flavonoids	↓α-amylase activity ↓α-glucosidase activity ↓ Hepatic G6Pase activity ↓ Glycogen phosphorylase ↑Insulin secretion ↑ Expression of PPARγ		[139]
3	*Allium sativum* L.	Allicin	Bulb	Organosulfides	↓ Bcl-2 ↓ Fas ↓ CTGF ↓ TGFβ1		[140]
4	*Bauhinia forficata* Link	Astragalin	Leaves	Flavonoids	↓α-amylase activity ↓α-glucosidase activity ↓SERCA activity ↑Release of Ca^{2+}		[141]

					↑Ca^{2+} trough L-VDCC		
		Kaempferitrin	Leaves	Flavonoids	↑Activates PKC ↑Glucose uptake		
5	*Cinnamomum verum* J.Presl	Cinnamaldehyde	Bark	Flavonoids	↓ FBG ↑ insulin sensitivity ↑ GLUT 4 ↓ PTP-1B ↓NO		[142]
6	*Trigonella foenum-graecum* L.	4-hydroxyisoleucine	Seed	Amino acid	↑ Insulin secretion ↓ Lipid peroxidation		[143]
7	*Matricaria chamomilla* L.	Apigenin	Flower	Flavonoids	↓ α-glucosidase ↓ROS ↑SOD ↑CAT ↑GSH ↑ Insulin		[6]

		Quercetin	Flower	Flavonoids	↓ G6Pase activity ↓ PEPCK activity ↓ ALT ↓AST ↓ALP ↓GGT ↓CRE ↓BUN		[144]
8	*Punica granatum* L.	Ellagic acid	Peel & Fruit	Ellagitannins	↓ Serum resistin ↑The association of recombinant PON1 to HDL		[145]
		Chlorogenic acid	Peel	Quinic acid	↓ Hepatic G6Pase activity		[146]

ROS: Reactive oxygen species, IRS1: Insulin receptor substrate 1, PI3K: Phosphoinositide 3-kinase, Fas: Death receptor, CTGF: Connective tissue growth factor, TGFβ: Transforming growth factor beta 1, PEPCK: Phosphoenolpyruvate carboxykinase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyltransferase, BUN: Blood urea nitrogen, SERCA: Sarcoendoplasmic reticulum calcium ATPase pump, L-VDCC: L-type voltage-dependent calcium channel, PKC: Protein kinase C, SOD: Superoxide dismutases, GLUT: Glucose transporter, FBG: Fasting blood glucose, PTP-1B: Protein-tyrosine phosphatase 1B, NO: Nitric oxide, CAT: Catalase, GSH: Glutathione

Table 2. Summary of clinical trials evaluated metabolic effects of the plants for diabetes

Plant	End Product	Dose	Sample Size	Duration	Effect	Reference
Aloe vera L.	Aloe vera gel extract	250 mL/day	53 healthy individuals	14 days	↑ plasma antioxidant capacity	[51]
	Aloe emodin treatment	300 & 500 mg twice a day	-	-	↓ HbA1C ↓ TC ↓ LDL ↓ TG	[52]
Allium sativum L.	Garlic pill	400 mg/day	49 prediabetic pregnant woman	8 weeks	↓ fasting blood sugar ↓ cholesterol ↓ serum lipids	[27]
Annona muricata L.	Annona muricata capsule	180 mg/day	60 T2DM patients	1 month	↓ blood glucose ↑ nausea ↑ burning pain in abdomen	[59]
Bauhinia forficata Link	Capsule	300 mg/day	92 T2DM patients	4 months	↓ plasma glucose ↓ glycated hemoglobin	[70]
Cinnamomum verum J.Presl	CZ capsule	1, 3, 6 g/day	30 healthy adults	3 months	↓ LDL ↓ mean TG ↓ TC	[93]
	Gelatin capsule	3 g	9 healthy adults	1 day trials 28 days apart	~ TC ~ LDL	[94]
	Capsule	1 g/day	43 T2DM patients	3 months	~ TC ~ LDL ~ mean TG	[95]
	Capsule	1, 3, 6 g/day	60 T2DM patients	40 days	↓ 18 - 29% fasting blood glucose	[96]
	Tablet	120 & 360 mg/day	66 T2DM patients	3 months	↓ FBG ↓ HbA1C	[97]
	Tablet or capsule	2 g/day	577 diabetic patients	4-16 weeks	~ blood glucose	[98]
Matricaria chamomilla L.	Chamomile tea	3 g/150 mL tea three times a day	64 T2DM patients	8 weeks	↓ blood glucose ↓ fatty acids ↑ insulin sensitivity	[107]
Punica granatum L.	Pomegranate seed oil capsule	1 g/day	52 obese T2DM patients	8 weeks	↓ FBS ↓ GLUT-4 gene expression	[126]
	Fenugreek seeds	2.5 & 5 g/day	60 T2DM patients	4 weeks	↓ blood glucose ↓ total lipid content ↓ serum α-amylase	[134]

Trigonella foenum-graecum L.	Fenfuro capsule	500 mg/day	108 male T2DM patients 46 female T2DM patients	90 days	↓ 83% fasting plasma glucose ↓ 89% postprandial glucose ↑ fasting C-peptide ↑ postprandial C-peptide	[135]
	Capsule	2 g/day	12 T2DM patients	12 weeks	↑ fasting insulin	[136]
	Fenugreek seed powder dissolved in water	15 g/day	48 T2DM patients	8 weeks	↑ SOD activity ↓ high sensitivity CRP ~ total antioxidant capacity ~ IL-6 ~ TNF-α ~ GPx activity	[137]
	Capsule	500 mg twice a day	60 T2DM patients	12 weeks	~ HbA1c ↓ blood sugar	[138]

The limited clinical trial data available has been summarized by the end product of the plant used in testing (in capsule, tablet, oil, or other form), the dose and frequency, the medical status (healthy or type 2 diabetic patients), and the number of participants, duration, and main antidiabetic findings of the study. The plants are displayed in the table in alphabetical order.

Solving diabetic complications, the challenges and limitations

Complications of diabetes add another layer of complexity to the research. Diabetes is associated with a range of severe complications, including cardiovascular disease, neuropathy, nephropathy, retinopathy, and an increased risk of infections. These complications result from chronic hyperglycemia, which damages blood vessels and nerves over time. The interplay between these complications means that effective antidiabetic compounds must not only regulate blood glucose levels but also mitigate or prevent the onset of these associated conditions.

Cardiovascular complications, such as heart disease and stroke, are common in diabetic patients due to the accelerated atherosclerosis caused by prolonged high blood sugar levels. Certain flavonoids and polyphenols found in plants have been shown to possess cardioprotective properties. For example, quercetin, a flavonoid present in many fruits and vegetables, has antioxidant and anti-inflammatory effects that can help reduce the risk of atherosclerosis and improve endothelial function, thereby protecting against cardiovascular complications (Fig. 4).

Diabetic neuropathy, resulting in nerve damage, can lead to severe pain and loss of sensation, particularly in the extremities, increasing the risk of injury and infection. Plant extracts of aloe vera and chamomile have demonstrated neuroprotective effects. These compounds help reduce oxidative stress and inflammation, which are key contributors to diabetic neuropathy, thereby alleviating pain and preventing nerve damage.

Diabetic nephropathy, or kidney damage, can progress to end-stage renal disease, necessitating dialysis or transplantation. Extracts from multiple plants such as aloe vera and cinnamon have been found to protect kidney function through alleviating oxidative stress.

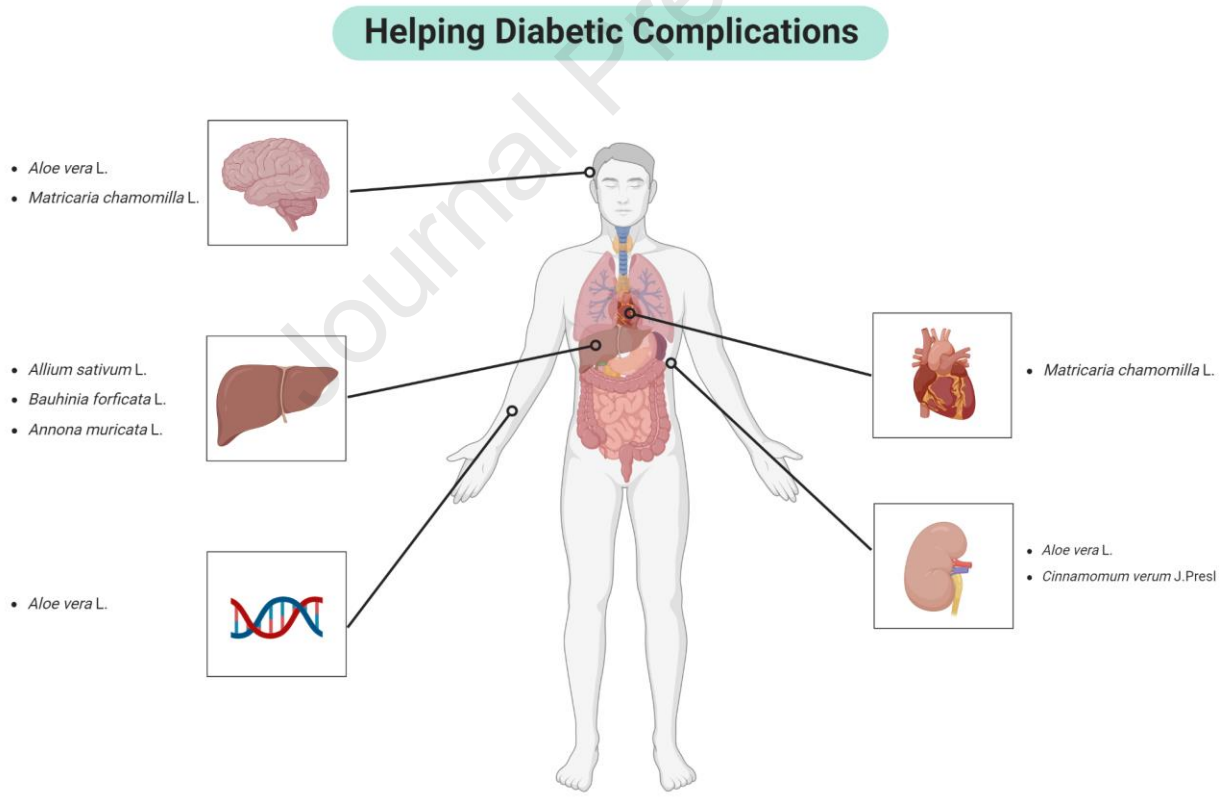


Fig. 4. Medicinal plants beneficial for diabetic complications [147]

More detailed studies must be performed before rigorous long-term clinical studies can take place. Specifically, of the 118 articles cited in this review and found on PubMed, none of the summarized studies isolate the active compounds that are primarily responsible for the antidiabetic effect, and subsequently test them in clinical trials. This could be due to multiple factors, such as the lengthy process of isolating the active compounds from the plant extracts, and the high cost of conducting clinical trials [148]. However, studies structured in this way can feature quantifiable doses of those active compounds, whereas this is impractical with plant extracts. Dose-response studies *in vitro*, in cells, and in animals are then possible, but until then they will be impractical. Further, the identification of active compounds based on data, rather than hypotheses, facilitates studies to prove mechanisms, rather than speculate on what they might be. Determining the active compounds in the extract is generally a time-consuming process and is particularly challenging for antidiabetic compounds compared to, for example, anti-cancer leads, where cytotoxicity studies can be done *in vitro* using cell lines. For antidiabetic research, the complexity is heightened due to the multifactorial nature of diabetes, involving multiple biological pathways and systems. Isolating and identifying active compounds requires extensive bioassay-guided fractionation, advanced analytical techniques, and comprehensive *in vivo* testing to assess efficacy and safety [149]. Furthermore, the lack of straightforward *in vitro* models for diabetes makes it difficult to screen for active compounds quickly, increasing the reliance on time-consuming *in vivo* models [150,151]. This intricate process demands significant resources, expertise, and time, making it a particularly daunting task for researchers in the field of diabetes.

Conclusion

Diabetes mellitus is one of the most common endocrine disorders, which affects more than 463 million people worldwide. Current drug treatments can have negative side effects, are out of reach for many people, and are expensive. As a result, numerous investigations have been and continue to be undertaken in search of effective and safe herbal treatments. In this review, we compiled information from *in vitro*, *in vivo*, and clinical studies on the eight most promising plants in controlling diabetes complications. Research into these plant extracts is abundant, but isolating the active compounds and confirming their efficacy remains a significant challenge. Nevertheless, the potential benefits are substantial, given the current global prevalence of diabetes and its complications. Effective plant-based treatments could offer a natural and complementary approach to managing diabetes and its associated health issues, underscoring the need for continued and focused research in this area.

Author contributions

V. L. Mahmoud: Writing – original draft, Visualization, Investigation, Formal analysis. **S. W. Chan:** Writing – review & editing, Project administration, Funding acquisition. **T. K. F. Y. Loh:** Visualization, Investigation. **G. Sethi:** Writing – review & editing, Formal analysis. **R. Shayesteh:** Writing – original draft, Visualization. **K. Burgess:** Writing – review & editing, Methodology. **S. H. Lee:** Writing – original draft, Investigation. **W. F. Wong:** Writing – review & editing, Methodology, Supervision, Investigation, Conceptualization, Funding acquisition, Project administration. **C. Y. Looi:** Writing – original draft, Validation, Supervision, Project administration, Conceptualization.

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Ethics declaration

Review and/or approval by an ethics committee was not needed for this study because it does not involve any animal or human experimental research.

Data availability statement

No data were used for the research described in the article.

Declaration of competing interest

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: