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REVIEW

The Anti-Diabetic Effects of Medicinal Plants Belonging to the Liliaceae Family: Potential Alpha Glucosidase Inhibitors

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Background: Diabetes mellitus is a complex metabolic disorder that has an enormous impact on people's quality of life and health. Although there is no doubt about the effectiveness of oral hypoglycemic agents combined with lifestyle management in controlling diabetes, no individual has ever been reported to have been completely cured of the disease. Globally, many medicinal plants have been used for the management of diabetes in various traditional systems of medicine. A deep look in the literature has revealed that the *Liliaceae* family have been poorly investigated for their antidiabetic activity and phytochemical studies. In this review, we summarize medicinal plants of *Liliaceae* utilized in the management of type II diabetes mellitus (T2DM) by inhibition of α-glucosidase enzyme and phytochemical content.

Methods: The literature search was conducted using databases including PubMed, ScienceDirect, and Google Scholar to find the significant published articles about *Liliaceae* plants utilized in the prevention and treatment of antidiabetics. Data were filtered to the publication period from 2013 to 2023, free full text and only English articles were included. The keywords were *Liliaceae* OR *Alliaceae* OR *Amaryllidaceae* AND Antidiabetic OR α-glucosidase.

Results: Six medicinal plants such as *Allium ascalonicum*, *Allium cepa*, *Allium sativum*, *Aloe ferox*, *Anemarrhena asphodeloides*, and *Eremurus himalaicus* are summarized. Phytochemical and α-glucosidase enzymes inhibition by in vitro, in vivo, and human studies are reported.

Conclusion: Plants of *Liliaceae* are potential as medicine herbs to regulating PPHG and prevent the progression of T2DM and its complication. In silico study, clinical application, and toxicity evaluation are needed to be investigated in the future.

Keywords: Liliaceae, antidiabetic, phytochemicals, α-glucosidase, traditional medicine

Introduction

Changes in diets and lifestyles greatly affect the body metabolism, leading to metabolic diseases such as diabetes mellitus (DM). DM is one of the most common chronic metabolic diseases in the world with prolonged elevation of blood glucose. Carbohydrate is the main source of energy for the human body and its regulation depends on pancreatic β-cells. A high-carbohydrate diet causes an increase of blood glucose named hyperglycemia. Hyperglycemia can generate various damage and complications, such as diabetic cardiomyopathy (DCM),[1] cardiovascular disease,[2,3] heart failure and disturbance of iron metabolism,[4] cataracts,[5] nephropathy,[6] retinopathy, neuropathy, disturbance of bone metabolism,[7] and sexual dysfunction.[8]

Insulin produced by pancreatic β-cells plays a significant function in regulating and lowering levels of blood glucose in the body. Insufficient production of insulin impairs glucose homeostasis leading to hyperglycemia. Furthermore, T2DM (type 2 diabetes mellitus) occurs throughout the world. The number of people with T2DM is a concern when it comes to preventing and treating T2DM.[9] T2DM relates to blood glucose levels 2 hours after meal or postprandial blood

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glucose (PPBG).[10–12] Inhibiting the α-glucosidase enzymes plays a significant role in the progression of T2DM.[10,13–15] Inhibiting the α-glucosidase enzyme can also play a role as a prevention of cardiovascular complications.[16] An α-glucosidase inhibitor (AGI) plays a role in PPBG and relates to T2DM as reducing blood glucose drugs and cardiovascular event-preventing drugs.[16] Currently, only three AGI are established in clinical practise: acarbose, voglibose, and miglitol. The most common adverse effects are GI symptoms, including flatulence, diarrhea, and abdominal pain due to bacterial fermentation and excessive gas production in the colon, which gives the drug side-effects of the gastrointestinal tract in the form of bloating and abdominal pain.[17–19]

In recent decades, interest in natural products is increasing and therefore researcher efforts need to seek novel inhibitors from natural products with minimal side effects. The ongoing development of antidiabetic drugs underscores the paramount importance of efficacy and safety in identifying compounds with no adverse effects. Plants or herbal plants have been abundantly used as alternative medicine when chemical drugs have many side-effects. The plant contains various bioactive natural compounds that are used to pharmacological effects in the human body.[20] One group of plants that are often used is from the *Liliaceae* family, which has been reported to lower blood glucose. *Liliaceae* is one of the world most commonly utilized plant families for food and traditional medicine.[21–24] Some studies have shown its potential as a therapeutic agent against DM[12,25–29] and other disease conditions, including antioxidant,[4,20,30] antimicrobial,[31,32] antiplatelet,[33] anti-inflammation,[34–37] and others. Several studies have highlighted the presence of natural compounds such as flavonoids, phenolics, anthraquinone, and other compounds have potential for future antidiabetic agents.[12,21,23,38,39] The antidiabetic activity of plants from the *Liliaceae* family and constituents as antidiabetics have been discussed. The aim of the present study is to analyze the beneficial natural compounds of *Liliaceae* family plants for DM prevention. This review will hopefully provide enough empirical evidence of antidiabetic effectiveness and the possibility for further development and use of these *Liliaceae* plants.

Methods

From internet databases like PubMed, Science Direct, and Google Scholar, several natural sources of the *Liliaceae* family utilized in the prevention and treatment of antidiabetics were identified. All publications were assessed for in vitro, in vivo, and clinical indications of their mechanisms and therapeutic potential. Data were filtered to the publication period from 2013 to 2023, free full text and only English articles were included. Articles were filtered using keywords: *Liliaceae* AND *Antidiabetic* AND *α-glucosidase* NOT *Review*. The flow chart diagram is shown in Figure 1.

Results

Detection of α-glucosidase inhibition by natural compounds in several novel methods have been developed. The colorimetric-based quantitative method is the most common and practical approach that has been utilized for the verification of the inhibitory role of different compounds against α-glucosidase enzymes. This method is based on measuring the quantity of p-nitrophenol (pNP) released characterized by a yellow color when p-nitrophenyl-α-D-glucopyranoside (pNPG) is hydrolyzed by α-glucosidase enzyme. Enzyme isolated from yeast Saccharomyces cerevisae and rat intestinal acetone powder was mostly used in this method, with pNPG as a substrate, and measuring by spectrophotometry at wavelength 400 nm.[12,40,41]

In Vitro, In Vivo, and In Silico Studies in Humans

Natural compounds in plants have been shown to be responsible for lowering blood glucose. In the long-term, those natural compound are promising agents against management of diabetes and its complications, as well as in regulating key signaling pathways. Comprehensive studies of plants with inhibitory activity against α-glucosidase are listed in Tables 1–4, respectively.

Allium Ascalonicum

Allium ascalonicum, generally known as shallot, is used as a food flavor enhancer and in herbal medicines. Quercetin and its derivative (quercetin-4'-O-glucoside and quercetin-3,4'-O-diglucoside) have been identified with thin layer chromatography (TLC) of the shallot bulb[42–45] and are responsible for reduction of blood glucose.[53,62] The IC_{50} of ethyl acetate

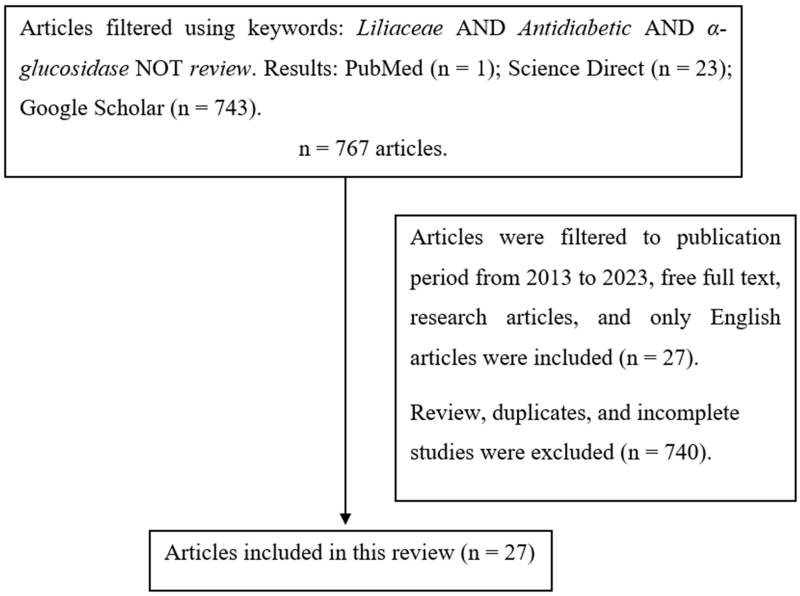

Figure 1 Flow chart diagram of the review process.

and methanol extract of *A. ascalonicum* peel for α-glucosidase inhibitory activity assay are 0.012 ± 0.002 mg/mL and 0.047 ± 0.04 mg/mL, respectively.[53] In fructose-induced insulin resistance rats, an aqueous extract dose of 500 mg/kg BW *A. ascalonicum* bulbs decrease fasting blood glucose/FBG by 24.2%, improve glucose tolerance by 32%, and fasting insulin resistance index/FIRI by 34%[56] and methanol extract dose 250 and 500 mg/kg BW significantly dropped the postprandial blood glucose (PBG) in alloxan-induced diabetic rats by 13% and 22%, respectively.[55] The hypoglycemic effect in 26 woman T2DM patients has confirmed reductions in total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), and fasting blood glucose (FBG) levels with 150 mL of low-fat yogurt (1.5% fat) + shallot (2 g/100 g yogurt).[57]

Pharmacokinetics and Bioavailability

The main compound in *A. ascalonicum* is quercetin. Quercetin from shallots may have low systemic bioavailability (0.2–12.5%) due to poor solubility and extensive first-pass metabolism. Quercetin absorbed rapidly in the intestinal epithelium and distributes to various tissues like kidney, liver, lungs, and brain. Quercetin undergoes extensive first-pass metabolism in liver by Phase II conjugating enzymes (sulfation, methylation, glucuronidation) which increases its water solubility and excretion. Quercetin rapidly eliminated via urin within 6–8 hours of first ingestion. However, pharmacokinetics study of quercetin is still needed.[45]

Table 1 Several Medicinal Plants of the *Liliaceae* Family in Antidiabetic Studies

Plant	Main Chemical Compound as Antidiabetic	Ref
A. ascalonicum	Quercetin, quercetin-4'-O-glucoside, and quercetin-3,4'-O-diglucoside	[42–45]
A. cepa	Quercetin and allyl-propyl disulfides	[12,46,47]
A. sativum	Allyl methyl trisulfide (AMS), S-allylcysteine sulfoxides (Aliin), and S-allylcysteine (SAC)	[32,48,49]
A. ferox	Phytosterols and flavonoid	[23,50]
A. asphodeloides	Sarsasapogenin and mangiferin	[6,22,35,51]
E. himalaicus	Flavonoid, anthraquinones, and coumarin	[73]

Table 2 In Vitro Study

Plant	Part Used	Solvent	IC_{50} Acarbose (μg/mL or mg/mL)	IC_{50} Extract (μg/mL or mg/mL)	Ref
A. ascalonicum	Peel	Ethyl acetate and methanol	Acarbose (0.47 ± 0.02 mg/mL)	0.012 ± 0.002 and 0.047 ± 0.04 μg/mL	[53]
A. cepa	Peel	Ethanol	Quercetin (0.15 mg/mL)	1.27 mg/mL	[12]
	Whole	Aqueous	N/A	5.87 mg/mL	[25]
	Peel	Methanol	Acarbose (10.1 ± 0.6 μg/mL)	42.8 ± 1.3 μg/mL	[30]
A. sativum	Bulb	Ethanol	Acarbose (1 mg/mL)	2 mg/mL	[27]
A. ferox	Leaves	Dichloromethane: methanol	Acarbose (<0.31 mg/mL)	0.78 mg/mL	[23]
A. asphodeloides	Rhizome	Dichloromethane	Acarbose (319.5 ± 17.3 μg/mL)	21.8 ± 1.4 μg/mL	[54]
E. himalaicus	N/A	N/A	N/A	N/A	N/A

Table 3 In Vivo Study

Plant	Dose	Duration of Treatment (Weeks)	Animal Model	Result	Ref
A. ascalonicum	0.25 and 0.5 g/kg BW	8	Alloxan-induced Wistar rats	↓Blood glucose	[55]
	0.5 g/kg BW	8	Fructose-induced Wistar rats	↓FBG 24.2%, ↓improve glucose tolerance, ↓fasting insulin resistance index	[56]
A. cepa	0.5 g/kg BW	8	Sucrose-induced Sprague Dawley rats	↓Blood glucose	[25]
	0.5 g/kg BW	8	Alloxan-induced Sprague Dawley rats	↓Blood glucose, ↑SOD, ↑GPx, ↑CAT, ↑GR, ↑GSH, ↓MDA	[47]
A. sativum	50, 100, and 200 mg/kg BW	4	STZ-induced Wistar rats	↓Blood glucose, ↑plasma insulin, ↑SOD, ↑GPx, ↑CAT, ↑GST, ↓ALT, ↓AST, ↓ALP	[34]
A. ferox	11.8%	12	Sucrose-induced Sprague Dawley rats	↓Blood glucose, ↓body weight	[23]
A. asphodeloides	20 and 60 mg/kg BW	9	STZ-induced Sprague Dawley rats	↓Blood glucose, ↓BUN, ↓Uric acid	[6]
E. himalaicus	250 and 500 mg/kg BW	N/A	Glucose-induced Wistar rats	↓Blood glucose	[28]

Allium Cepa

Allium cepa, generally known as onion, is abundantly used as a source of food and herbal medicine. Quercetin (flavonoid glucosides) and allyl-propyl disulfides (sulfur compound) present in onion are responsible for reduction of blood glucose.[12,46,47] In vitro results of *A. cepa* confirmed the IC_{50} value of ethanol extract of *A. cepa* (peel) was 1.27 mg/mL,[12] aqueous extract (whole) was 5.87 mg/mL,[25] and methanol extract (peel) was 42.8 ± 1.3 μg/mL[30] by inhibiting α-glucosidase enzyme assay. In vivo, a substantial decrease has been shown in blood glucose by ethanol extract dose 500

Table 4 Clinical Studies of *Liliaceae* as Antidiabetic Agent

Plants	Dosage Form	Sample Size (Patients)	Clinical Conditions	Design of Study	Length of Therapy (Weeks)	Clinical Outcomes	Adverse Effect	Ref
A. ascalonicum	Supplement	48	Female diabetic, aged 45–70 years with BMI ± 28.5 kg/m^2	Randomized controlled clinical study. **Intervention group** (n = 26) 1 group, single dose of low-fat yogurt (150 mL) mixed shallot 3 g. **Controlled group** (n = 22), 1 group, single dose of low-fat yogurt (150 mL).	10	Reduction in blood glucose and cholesterol (TG, TC, and LDL).	No AE was observed.	[57]
A. cepa	Fresh raw	56	Insulin resistance and related markers in breast cancer patients undergoing doxorubicin chemotherapy	Randomized controlled clinical study. **Intervention group** (n = 28), or high onion group, 100–160 g/day. **Controlled group** (n = 28), or low onion group, 30–40 g/day.	8	Changes in blood glucose, insulin levels, and biomarkers relating to insulin resistance and secretion.	No AE was observed.	[58]
A. sativum	Garlic tablets	60	Diabetic with blood glucose level between 100 and 130 mg/dL	Single-blind and placebo-controlled study. **Intervention group** (n = 30), garlic tablet 300 mg 3 times/day and metformin 500 mg twice daily. **Controlled group** (n = 30) placebo and metformin 500 mg twice daily.	24	Reduction in blood glucose and cholesterol (TG, TC, and LDL).	No AE was observed.	[59]
	Garlic capsule	12	Healthy, young, male participants	Single-blinded, crossover, counter balanced design. **Intervention group** (n = 12), garlic capsule 2,000 mg single one-time. **Controlled group** (n = 12), placebo.	2	Lower post-exercise blood glucose levels.	No AE was observed.	[60]
	PHF supplement	30	Diabetic patient with blood glucose level 162 ± 40 mg/dL, HbA1C 8.4%, uncontrolled lipids levels	Open-label single group study. **Intervention group** (n = 30), garlic capsule 2,000 mg single one-time. **Controlled group** (n = 0), no controlled group.	10	Reduced fasting blood glucose, HbA1c, LDL cholesterol, and triglyceride levels.	4 out of 25 patients were reported mild nausea (n = 2) and diarrhea (n = 2).	[61]
A. ferox	Capsules (*A. ferox* - Herbagetica supplement)	40	Romanian persons, aged 50–70 years, obesity with BMI ± 34.45 kg/m^2, absence of gastrointestinal disease and renal failure	Randomized placebo-controlled study, double blind. **Intervention group** (n = 20), supplements *A. ferox* 460 mg crystallized juice powder/1 gelatin capsule, given 2 capsules/day for 2 weeks, followed by a 2-week break, repeated 3 times. **Controlled group** (n = 20), placebo.	2	Reduction in fasting blood glucose, body weight, BMI, and LDL.	Diarrhea, abdominal pain, diuresis, hypokalemia while dose increased to 3 capsules/day.	[50]
A. asphodeloides	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
E. himalaicus	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: AE, adverse effect; BMI, body mass index; N/A, not applicable; PHF, polyherbal formulations; T2DM, type 2 diabetes mellitus.

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mg/kg BW in sucrose-induced rats[25] and in alloxan-induced rats.[47] Fresh raw *A. cepa* induces changes in blood glucose, insulin levels, and biomarkers relating to insulin resistance and secretion in breast cancer patients.[58]

Pharmacokinetics and Bioavailability

Flavonoids are among the largest group that exhibited alpha-glucosidase inhibitory effects, including quercetin. Quercetin can be present as the aglycone form or as glucoside derivatives. Quercetin was rapidly in intestinal and appeared in plasma in conjugated forms like glucoronides and sulfates.[63,64] Quercetin aglycone (in onion peel powder) showed higher bioavailability in plasma with peak plasma concentrations (Tmax = 0.7–1 hours) and haf-time ($T_{1/2}$= 11–28 hours) compared to quercetin glucosides (in onion peel extract). Absorption of quercetin glucosides requires hydrolysis by enzymes lactase phlorizin hydrolase or transported by sGLT1 transporters.[64,65] After absorption, quercetin undergoes phase II metabolism and is transported to the liver via the portal vein or lymphatics. It circulates in both conjugated and unconjugated forms in the bloodstream. In enterocytes and liver, quercetin is conjugated via methylation, glucuronidation, and/or sulfation before distribution. Conjugated quercetin metabolites are excreted in urine and bile.[65]

Allium Sativum

Allium sativum, also known as garlic, is abundantly used as a food flavor enhancer and herbal medicine, and is characterized by its rich content in organosulfur compound, namely as allyl methyl trisulfide (AMS), S-allylcysteine sulfoxides (Aliin), and S-allyl-L-cysteine (SAC).[32,48,49] In vitro, the IC_{50} value of ethanol extract of *A. sativum* (bulbs) was 2.54 ± 0.17 mg/mL.[27] In vivo, in STZ-induced rats, *A. sativum* doses of 50, 100, and 200 mg/kg BW can lower blood glucose levels and regulate insulin production and sensitivity in pancreatic β-cells.[34] In humans, garlic supplements can reduce blood glucose and cholesterol (TG, TC, and LDL) in diabetic patients.[59–61]

Pharmacokinetics and Bioavailability

The pharmacokinetics study of active compound (Alliin, SAC) from garlic is generally low (1–20%). Allicin bioavailability refers to its formation from alliin by alliinase, followed by absorption and metabolism to AMS. Bioequivalence refers to metabolic formation of AMS from any S-allyl compound without allinase. Allicin is rapidly metabolized with a half-life estimated to be <1 minute based on in vitro data. Allicin absorption is highly efficient after oral consumption. Allicin is rapidly metabolized, with a half-life of <1 minute when added to blood. Neither allicin nor its transformation compounds were detected in blood, urine, or stools after raw garlic consumption. The main metabolite is allyl methyl sulfide (AMS), which is detectable in breath. The major route of excretion for allicin metabolites is expiration as AMS in the breath. AMS levels in breath can be used to determine allicin bioavailability from various products. Neither allicin nor its metabolites were detected in urine or stools after raw garlic consumption. However, further research about pharmacokinetics of compound in *A. sativum* is still needed.[66]

Aloe Ferox

Aloe ferox is one of aloe species that have been used as an antidiabetic.[23,50] Phytosterols and flavonoid, the major components in *A. ferox*, exhibit strong antidiabetic activity.[23,50] An in vitro assay showed a combination of dichloromethane-methanol and aqueous extract *A. ferox* results in IC_{50} of 0.78 and 0.54 mg/mL, respectively, by inhibiting α-glucosidase.[23] The aqueous and dichloromethane-methanol extract *A. ferox* leaf confirmed a reduction in blood glucose and body weight in sucrose and high fat diet rats.[23] In obese patients, a supplement of *A. ferox* 460 mg was given as 2 capsules/day for 2 weeks and resulted in a decrease in FBG, BW, body mass index (BMI), and LDL.[50]

Pharmacokinetics and Bioavailability

The pharmacokinetic study of phytosterols in *A. ferox* is still limited. However, another compound such as aloe-emodin is also present in this plant and reports low bioavailability (1–2%). Like other plants, it has low bioavailability due to its absorption in the intestines and it undergoes extensive first-pass metabolism in the liver and gut wall. After absorption, it is widely distributed to organs like the liver, kidneys, and lungs. It is metabolized to its metabolites (glucoronide and sulfate) by Phase I and Phase II CYP450 and sulfotransferase. Half-time was 1–2 hours in rats and less than 1% was excreted unchanged in urine and feces.[67,68]

Anemarrhena Asphodeloides

Anemarrhena asphodeloides is a Chinese herb still consumed as a supplement to lower blood glucose levels.[6,69] Sarsasapogenin (steroid saponins) and mangiferin (polyphenols) are the main compounds from *A. asphodeloides* responsible for reduction of blood glucose.[6,22,35,51] The IC_{50} value of dichloromethane extract *A. asphodeloides* rhizome was 21.8 ± 1.4 μg/mL by α-glucosidase enzyme inhibition.[54] In STZ-induced rats, aqueous extracts of 20 and 60 mg/kg BW were reported as lowering blood glucose.[6] No clinical trials were observed.

Pharmacokinetics and Bioavailability

Sarsasapogenin is a natural steroidal sapogenin (metabolite of Timosaponin AIII) molecule mainly obtained from the rhizomes of *A. asphodeloides*. Sarsasapogenin pharmacokinetics was studied in vivo in rats after oral (50 mg/kg) administration. The molecule is rapidly absorbed, metabolized (hydrolysis) in the gastrointestinal tract, through first-pass metabolism, and distributed in rats, and its bioavailability was found to be low (9.1%). The oral administration of sarsapogenin resulted in a lower concentration of its metabolite (Cmax = 14.8 ng/mL) with peak plasma levels (Tmax was 1.5 hours). It is also known to have low permeability across the intestinal epithelium and high efflux by intestinal P-glycoproteins, leading to typically low oral bioavailability (1–10%). More research is still needed to characterize its pharmacokinetics and clinical trials need to be performed.[70]

In additional, mangiferin is also reported prominently in *A. asphodeloides*. Mangiferin is a natural xanthone polyphenolic compound and has low oral bioavailability (5%) due to its extensive first-pass metabolism. Interestingly, after oral administration of mangiferin, it will be metabolized to its metabolite, norathyriol, through deglycosylation and the methylation process (phase II) by intestinal microbiota. It will distribute to various organs like the intestines, spleen, lungs, kidney, and heart, and the metabolites of mangiferin predominantly find their way out of the body via urine. The half-time ($T_{1/2}$) was 4–8 hours.[71,72]

Eremurus Himalaicus

Eremurus himalaicus is commonly used in traditional medicine and exhibits antidiabetic activity.[28] Flavonoid, anthraquinones, and coumarin are present in *E. himalaicus*.[73] The ability to reduce blood glucose by *E. himalaicus* has been reported in ethyl acetate, methanol, and aqueous extract of *E. himalaicus* root at doses of 250 and 500 mg/kg BW, resulting in good lowering of blood glucose in glucose-induced rats by up to 20%.[28] No clinical trials were observed.

Pharmacokinetics and Bioavailability

Pharmacokinetic studies on *Eremurus himalaicus* adducts are very limited and the pharmacokinetics properties of anthraquinone still need to be investigated.[74] A previous study reported the absorption of anthraquinone mainly in small intestines and it being widely distributed in blood flow-rich organs and tissues like the intestines, stomach, liver, lungs, and kidneys. Anthraquinone is metabolized by intestinal flora and liver enzyme with hydrolysis, glucoronidation, and sulfation pathways. Generally, anthraquinone is known to have low bioavailability due to many factors including extensive first-pass metabolism.[52] Further research is still needed.

Discussion

Structure and Active Site of α-Glucosidase

In the digestion system, complex carbohydrates (starch) are multiple hydrolyzed into monosaccharides which are absorbable in the small intestine (Figure 2). The process begins with starch hydrolyzed into shorter polysaccharides by α-amylase (an enzyme produced by salivary glands and the pancreas) in saliva.[12,75] Partially hydrolyzed starch (polysaccharides) enters the small intestine and pancreatic amylase breaks down the α-1,4 glucosidic linkage and releases dextrin (an oligosaccharide). A further process mediated by α-glucosidase enzyme in the brush border of the small intestine to break downs the linkages of α-glucosidic in oligo/disaccharides.[10,23,76] α-glucosidase belongs to the glycoside hydrolases (GH) families 13 and 31 and contains three main domains, A, B, and C, that works via a retaining mechanism. This means it retains the anomeric configuration of the substrate during catalysis. Domain A is a catalytic domain formed by $(\beta/\alpha)_8$-barrelsfold, with a general acid/base catalytic (Glu) residue at the C-terminal end of the fourth β-strand and a

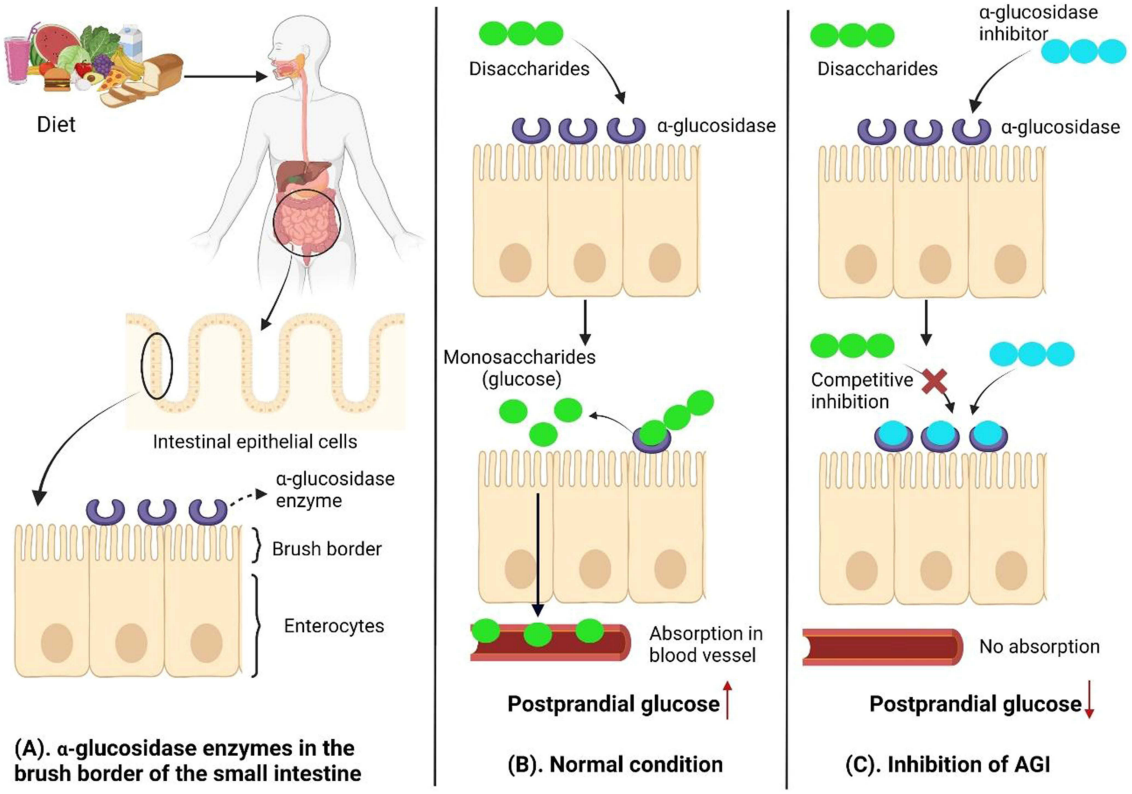

Figure 2 Mechanism of α-glucosidase inhibition. (**A**). α-glucosidase enzymes in the brush border of the small intestine; (**B**). normal condition of α-glucosidase enzymes without inhibition of AGI; (**C**). condition of α-glucosidase enzyme inhibited by AGI. Created with BioRender.com.[84,85]

catalytic nucleophile (Asp) on the fifth strand. Domain B contains multiple α-helices and β-strands, is inserted between the third β-strand and the third α-helix of the A domain, and forms part of the active site pocket wall. Domain C is formed by anti-parallel β-sheets, and follows the A domain. In addition, these enzymes have two extra α-helices on the β→α loop 8 of A domain, the main parts of the B' domain that interact with the substrate and B domain. Due to the presence of B' domain, "pocket-shaped substrate-binding sites" are formed.[15,77–80]

α-glucosidase contains 16 amino acid residues and the two main acidic residues on the active site of the enzyme are Glu233 and Glu410, which act as catalytic acid/base pairs during the reaction. While a carbohydrate substrate such as maltose (two molecules of glucose) enters the active site, Glu233, acting as an acid, donates a proton to the glycosidic hydrogen-oxygen (OH) bond in maltose, promoting the cleavage of the glycosidic bond resulting in a covalently bound alpha-glucosyl enzyme intermediate and a glucose molecule. Glu410 then acts as a base to extract a proton from glucose, releasing it, and activates water for hydrolysis of the glycosidic bond.[81–83]

Pharmacokinetics and Bioavailability of Established α-Glucosidase Inhibitors

The first α-glucosidase inhibitor drugs approved by the FDA in Europe and the US was acarbose. Acarbose is a pseudo-tetrasaccharide which is structurally similar to the typical oligosaccharides derived from starch digestion. Acarbose is naturally produced by actinomycetes (*Actinoplanes* sp) consisting of a C_7N-pseudosugar (cyclitol) moiety linked via nitrogen to isomaltotriose.[78,79] The active site of acarbose consists of a substituted cyclohexene ring and a 4,6-dideoxy-4-amino-D-glucose moiety called acarviosine (Figure 3). The secondary amino group of acarbose appears to prevent an essential carboxyl group on the α-glucosidase enzymes from protonating the glycosidic oxygen bonds of the substrate. The two glucose molecules of acarbose which are α-l,4-linked to acarviosine appear to determine the specificity of action and the optimal activity of the drug against α-glucosidases.[86]

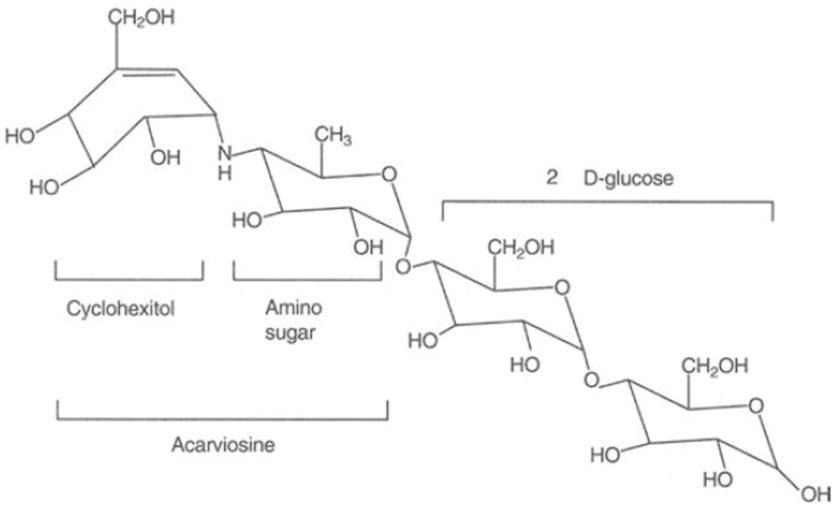

Figure 3 Structure of acarbose.

α-glucosidase inhibitors like acarbose ($C_{25}H_{43}NO_{18}$) bind reversibly and competitively to these enzyme residues (Glu233 and Glu410) at the active site through multiple hydrogen bonds that mimic the carbohydrate substrate to form multiple hydrogen bonds (4–6 H-bonds).[78,80,87] This binding causes distortion of the catalytic residue, interfering with its ability to act as an acid/base pair during the reaction, thereby blocking substrate binding and preventing the enzyme-catalyzed hydrolysis reaction from proceeding. Some inhibitors may also form additional hydrogen bonds with other adjacent amino acids like Asp349, Asn445, Arg532, Tyr547, etc to further stabilize their binding. Inhibition can be overcome by increasing the substrate concentration due to reversible binding kinetics.[88,89] Therefore, because of the reversible nature of this inhibitor–enzyme interaction, conversion of oligosaccharides to monosaccharides is only delayed rather than completely blocked.[90]

Acarbose is a drug that acts locally in the gastrointestinal (GI) tract with low systemic bioavailability less than 2% absorbed after oral administration as the active drug.[90] Acarbose exerts its effects in the small intestine; therefore, absorption is not necessary for therapeutic activity. Due to low absorption, acarbose is transported through the intestinal tract to the colon. Acarbose has limited distribution, with high concentrations generally found only in those organs associated with its absorption and elimination including small intestine mucose, colonic lumen, stomach, bladder, liver, and kidneys. Protein binding of acarbose has demonstrated concentration-dependent binding. The plasma half-life of acarbose is from 2.7 to 9 hours and increased with renal dysfunction. Acarbose is metabolized in the GI tract by intestinal bacteria and digestive enzymes to its metabolites up to 35%. Acarbose undergoes extensive degradation within the gut through two processes: 1) Hydrolysis of glucosidic linkages by intestinal enzymes produces component 1 (containing two rings, one maltose ring having been cleaved by α-amylase), which is inactive, and component 2 (containing three rings, one glucose ring having been cleaved by α-amylase), which has approximately one third the activity of the parent drug; 2) In the second, a complex mixture of acidic metabolites (mostly 4-methylpyrogallol derivatives) is formed via a sequence of biotransformation reactions by intestinal microorganisms. Elimination of acarbose occurs through the urinary and fecal routes. The kidneys filter the absorbed drug, and 51% of an oral dose gets eliminated in feces and urine.[86,90,91]

The most common adverse effects are GI symptoms, including flatulence, diarrhea, and abdominal pain. Unabsorbed oligosaccharides move towards the colon. The water-attracting nature of saccharides leads to increased bacterial fermentation and excessive gas production in the colon, which gives the drug side-effects on the gastrointestinal tract in the form of bloating and abdominal pain.[17–19]

Comparative of Pharmacological and Pharmacokinetics of Plant-Derived Vs Synthetic α-Glucosidase Inhibitors

Many factors affect the bioavailability of orally administered plant extracts or compounds, such as solubility, ability to pass through intestinal membranes, first-pass liver metabolism, etc. For plant-derived extract, the bioavailability depends on the individual bioavailabilities of the various phytochemicals/compounds present within it. Bioavailability refers to the amount of active compound entering the systemic circulation and available at the site of action. All *Lialiaceae* plants have low bioavailability in the blood due to absorption in the small intestine and it can be considered that plants from *Liliaceae* have the same bioavailability as FDA approved drugs, ie., absorption in the small intestine with lack of side-effects. Adverse effects and toxicity of plants are shown in Table 5.

In Vivo Studies

Several studies of Liliaceae plant extracts in animals and toxicity have been reported are listed in Tables 3 and 5. Among the plants studied in the papers that were included in this review, only *A. sativum* and *A. ferox* have been reported with toxic effects. The oral administration of *A. sativum* at a dose 1,000 mg/kg of body weight was found to increase oxidative stress, organ toxicity, histopathological changes, and ultrastructural damage in the liver and kidney of rats; and at a dose of 5,000 mg/kg, fatigue, udema, tachycardia, and disorientation, but no mortality, were observed.[106,107] Additionally, administration of *Aloe ferox* from acetone leaf extracts with LD_{50} >1 mg/mL and ethanol root extracts with LD_{50} <1 mg/mL show toxic effects.[110] Furthermore, mild side-effects have been reported by *A. ascalonicum*, *A. cepa*, *A. sativum*, and *A. ferox* in animals. Doses of 2,500 and 5,000 mg/kg of *A. ascalonicum* caused mild diarrhoea,[102] 500 mg/kg of *A. cepa* caused weight loss, appetite changes, normocytic anemia, and slight liver changes in rats,[104] 600 mg/kg of *A. sativum* caused raising of urea and albumin levels, and 5,000 mg/kg of *A. ferox* caused an increase of gastrointestinal motility and reduced motor activity in rats.[109] This could be due to Aloin increasing gastric motility which causes diarrhoea.[50,109] The lack of side and toxic effects shown by *Liliaceae* plants suggests that these plants are safe to use as herbal extracts and need further clinical evaluation.

In vivo methods are often used in diabetic animals with the induction of alloxan and streptozotocin as a diabetogenic agent. Alloxan induces diabetes selectively against pancreatic β-cells that produce insulin. Alloxan will eventually damage the β-cells of the pancreas, so insulin is not produced, and type 1 diabetes (Type 1 DM) occurs.[47] Alloxan has a molecular structure similar to glucose so the body will recognize alloxan as glucose, and it will bind to and be carried by the GLUT 2 transporter (glucose transporter) into the cytoplasm of pancreatic β-cells.[29] If there is damage to the pancreatic β-cells, the risk of OS also increases.[121] Damage to pancreatic β-cells is related to DNA damage by free radicals, which also affect other organs. In addition, an imbalance in the number of higher free radicals and lower antioxidants in the body will cause a condition of SO which is the beginning of the damage and complications of other organs.[21]

Another diabetogenic agent is streptozotocin (STZ). Streptozotocin (STZ) causes damage to pancreatic β-cells.[24,122,123] Almost the same as alloxan, STZ enters pancreatic β-cells through GLUT 2.[34] STZ causes DNA damage in pancreatic β-cells and stimulates poly-adenosine diphosphate-ribose (poly-ADP-ribose), resulting in the depletion of cellular nicotinamide adenine dinucleotide (NAD+), which in turn causes a reduction in ATP (adenosine triphosphate) and ultimately inhibits insulin secretion and synthesis.[124] Furthermore, this damage causes activation of pro-inflammatory signals and changes in neuro-transmitters (decreasing glutamate and increasing GABA), and energy depletion affects behavioral complications in STZ-induced diabetic rats.[36] In addition, the toxic effect of STZ is associated with ROS formation, such as SOD, H_2O_2, OH, and others that cause oxidative damage.[24] Increased ROS causes increased DNA fragmentation and triggers changes in cells. The entry of the methyl group (alkylation) from STZ into the DNA molecule causes damage to the DNA fragment, activating ADP-ribosylation. STZ can cause toxicity of liver and kidneys.[6,124]

Clinical Studies

Clinical studies of *Liliaceae* plants as anti-diabetic agent have been reported and listed in Table 4. Six *Liliaceae* plants showed evidence of outstanding clinical outcomes in diabetic patients, with reduced blood glucose levels, weight loss,

Table 5 Adverse Effects and Toxicity of *Liliaceae*

Plant	Part Used	Dosage or Concentration	Solvent	Adverse Effect	Toxicity	Ref
A. ascalonicum	Bulb	500, 2,500, 5,000, and 10,000 mg/kg	Ethanol	Mild transient diarrhoea observed in some mice only at higher subchronic doses (2,500 and 5,000 mg/kg), no other safety concerns.	No toxic effect was observed.	[102]
	Bulb	1 g/kg BW	Aqueous	No AE was observed.	No toxic effect was observed.	[103]
A. cepa	Peel	125, 250, and 500 mg/kg	Aqueous	Mild weight loss, appetite changes, normocytic anemia, and slight liver changes observed only at the highest 500 mg/kg dose level tested in rats over the subacute period (28 days).	No toxic effect was observed.	[104]
A. sativum	Bulbs	2,000 mg/kg	Aqueous	No AE was observed.	No toxic effect was observed.	[105]
	Bulbs	250, 500, and 1,000 mg/kg BW	Aqueous	No AE was observed.	Increased oxidative stress, organ toxicity, change in histopathological and ultrastructural damage observed in the liver and kidneys of rats given the highest 1,000 mg/kg garlic dose.	[106]
	Bulbs	300, 600, 1,200, and 5,000 mg/kg	Aqueous	Lowering of ALT, total protein, direct bilirubin, and Cl-, and raising of urea and albumin levels at doses 600 and 1,200 mg/kg.	Weakness, edema, tachycardia, and disorientation, but no mortality was observed at highest doses (5,000 mg/kg)	[107]
A. ferox	Leaf	50, 100, 200, and 400 mg/kg BW	Aqueous	Inconclusive side-effects suggested such as changes to certain blood parameters, mild organ toxicity, impacts on weight, and potential pro-inflammatory or fertility effects. The causation and significance are unclear given low severity and lack of dose-dependence reported.	No toxic effect was observed.	[108]
	Resin	5,000 mg/kg	Glycerin	Increased gastrointestinal motility and reduced motor activity in Wistar rats. (Aloin increased gastric motility causing diarrhea).	No toxic effect was observed.	[109]
	Roots and leaf	0.125–2 mg/mL	Ethanol, acetone, aqueous	No AE was observed.	LD50 >1 mg/mL (acetone leaf extract), <1 mg/mL (ethanol root extract), and no toxic effects of *A. ferox* aqueous extract was observed.	[110]
	Gel	0.25%	Acetone	No AE was observed.	No toxic effect was observed.	[111]

(*Continued*)

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Table 5 (Continued).

Plant	Part Used	Dosage or Concentration	Solvent	Adverse Effect	Toxicity	Ref
A. asphodeloides	Rhizomes	250 mg/kg BW	Aqueous	No AE was observed.	No toxic effect was observed.	[112]
	Roots	500, 1,000, and 2,000 mg/kg	Aqueous	No AE was observed.	No toxic effect was observed in rats up to dose 5,000 mg/kg.	[113]
E. himalaicus	Leaves and stems	300 mg/kg BW	Ethyl acetate, methanol, aqueous	No AE was observed.	No toxic effect was observed.	[114]
	Leaves and flowers	5 g/kg BW	Methanol	No AE was observed.	No toxic effect was observed.	[115]
	Whole	2,000 mg/kg BW	Petroleum ether, ethyl acetate, methanol and aqueous	No AE was observed.	No toxic effect was observed.	[28]
	Leaves and stems	200 mg/kg BW	Methanol and aqueous	No AE was observed.	No toxic effect was observed.	[116]

Abbreviation: AE, adverse effect.

and reduced levels of triglycerides, cholesterol, and LDL cholesterol. In clinical studies in this paper review, only *A. sativum* and *A. ferox* have been reported as side-effects in humans. Supplement of *A. sativum* at doses of 2,000 mg/kg were reported to cause mild nausea and diarrhoea.[61] Supplements of *A. ferox* 460 mg while increasing the dose to 3 capsules/day caused abdominal pain, mild diarrhoea, diuresis, and hypokalemia.[50] The lack of side-effects and shown by *Liliaceae* plants suggests that these plants are safe to use as herbal extracts and need further evaluation. The recommended dosage may be adjusted to the dose used in non-toxic studies in humans. Other clinical studies of *Liliaceae* plants have been reported and listed in Table 6.

DM and its complications, including insulin resistance and insufficiency, have been linked to oxidative stress (OS), thus, this disease may be related to decreased levels of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), and pancreatic β-cells are very susceptible to damage by nitric oxide and ROS.[49] In addition, levels of the enzymes ALT, AST, and ALP increase in diabetic conditions.[29] Diabetes promotes liver damage and increases liver mass, and the liver enzymes listed above are markers of liver damage.[23,125,126] One of the characteristic features of chronic disease is lipid peroxidation.[127] OS is a condition of an imbalance in the amounts of free radicals higher than anti-free radicals in the body. Glucose intake after meals triggers OS, which is the beginning of vascular inflammation and endothelial dysfunction, atherosclerosis, and cardiovascular disorders.[16] OS causes of increase in production of ROS. DM can stimulate the formation of free radicals that cause OS related to antioxidants and induce diabetic complications.[39,128] Antioxidant enzymes including CAT, SOD, and GPx play a crucial role in ROS scavenger and in the antioxidant defense system.[24,36,122] In diabetic conditions, levels of SOD and CAT decrease in number due to inactivation by H_2O_2 or glycosylated enzymes. SOD mechanism is able to protect cells from oxygen free radicals by eliminating superoxide anion (O_2^-) radical and catalyzed to H_2O_2, and CAT is converted H_2O_2 to hydroxyl radical (OH).[5,36,127] This condition is also associated with the development of diabetic complications such as hyperlipidemia.[128] Malondialdehyde (MDA) levels measured using lipid peroxidase are used to measure free radical damage. An increase in MDA levels is an indicator of increased OS. The increase in OS affects the decrease in behavior in diabetic rats.[36] When OS increases, thiobarbituric acid reactive substances (TBARS) and protein carbonyls increase, and GSH decreases.[129] Moreover, in glucose metabolism, two essential regulators are adiponectin and leptin. Both of them are hormones in the human body secreted by adipocyte tissue which plays a role in controlling the homeostasis of glucose and lipid in the body, so these two hormones can be targeted in regulating levels of blood glucose as antidiabetics.[130]

In Silico Approaches

The interaction between α-glucosidase and the major compounds found in each plant needs to be understood through in silico studies using molecular docking. Molecular docking using computational tools is often used to predict the binding affinity and activity of small molecules and drug candidates or phytoconstituents towards their target proteins. In addition, only a few molecular docking studies have been discussed and listed in Table 7.

First, quercetin in *A. ascalonicum* and *A. cepa* can be a promising agent against T2DM because it has many targets in the human body.[131] Quercetin was computationally studied to examine their binding mode to alphaglucosidase. Quercetin with binding energies (−7.6 kcal/mol) bonds with Ser420, Lys675, Gln421, Thr375, Ser422 forming hydrophobic and hydrogen bonds.[118] Another research reported quercetin has binding affinity (−8.9 kcal/mol) bonds with Asp1526, His1584, and Thr1586 forming hydrogen bonds and with Phe1560, Trp1355, and Tyr1251 forming hydrophobic bonds.[117]

Then, organosulfur compounds such as allyl methyl trisulfide (AMS), S-allylcysteine sulfoxides (Aliin), and S-allyl-L-cysteine (SAC) in *A. sativum* show the affinities. Allyl methyl trisulfide (AMS) has binding energies (−3.8 kcal/mol) with His1584, Ile1315, Ile1280, Met1421, Phe1559, Trp1355, Trp1523, and Trp1418 forming hydrophobic bonds. S-allylcysteine sulfoxides (Aliin) have binding energies (−5.2 kcal/mol) with Arg1510, Asp1157, and Asp1526 forming hydrogen bonds and with Ile1280, Trp1355, and Tyr1251 forming hydrophobic bonds. S-allyl-L-cysteine (SAC) has binding energies (−4.7 kcal/mol) with Asp1420 forming hydrogen bonds, and with Met1421, Trp1355, Phe1559, and Tyr1251 forming hydrophobic bonds. This research also reported that flavonoids and derivates, such as quercetin, rutin, myricetin, kaempferol, and apigenin, have binding affinities with α-glucosidase. Acarbose has binding energies (−15.6

Table 6 Other Clinical Studies of *Liliaceae*

Plants	Dosage Form	Sample Size (Patients)	Clinical Conditions	Design of Study	Length of Therapy (Weeks)	Clinical Outcomes	Adverse Effect	Ref
A. ascalonicum	Supplement capsules	16	Allergic rhinitis patients	Randomized, double blind, placebo-controlled clinical study. **Intervention group** (n = 8), cetirizine 10 mg once daily and shallot supplement 3 g once daily. **Controlled group** (n = 8), cetirizine 10 mg once daily and placebo.	4	Improvement in VAS, significant reduction in TNSS and TOSS	No AE was observed	[45]
A. cepa	Patch	125	Adult patients with post-surgery scars	Intra-individual randomized, observer-blinded controlled study. **Intervention group** (n = 125), patch treatment group. **Controlled group** (n = 125), patch no treatment group.	24	Improved scar appearance and healing	No AE was observed	[92]
	OPE capsule	72	Healthy overweight and obese participants	Randomized, double blind, placebo-controlled study. **Intervention group** (n = 36), OPE capsule (quercetin 100 mg)/day. **Controlled group** (n = 36), placebo.	12	Improved in FMD, endothelial function, reduced in BW and BMI	No AE was observed	[93]
	OPE capsule	68	Obese adult with prehypertension or stage 1 hypertension	Randomized, double blind, placebo-controlled crossover trial study. **Intervention group** (n = 35), OPE capsule (quercetin 162 mg)/day. **Controlled group** (n = 33), placebo.	6	Lowering ambulatory blood pressure	No AE was observed	[94]
	Tablet	22	Healthy male, aged 19–60 years old with plasma uric acid concentration of 51 μmol/L	Randomized, double blind, placebo-controlled crossover trial study. **Intervention group** (n = 22), OPE capsule (quercetin 500 mg)/day. **Controlled group** (n = 22), placebo.	4	Lowering plasma uric acid concentrations	No AE was observed	[95]

A. sativum	FGE tablet	30	Healthy adult participants, aged >19 years old	Randomized, double blind, placebo-controlled clinical study. **Intervention group** (n = 15), 450 mg FGE tablet **Controlled group** (n = 15), placebo	N/A	Decreased both systolic and diastolic blood pressure. Increased common carotid artery and internal carotid artery velocities	No AE was observed	[96]
	AGE tablet	120	Healthy adults, aged 21–50 years old	Randomized, double-blind, placebo-controlled parallel-intervention study. **Intervention group** (n = 60), 2.56 g capsules/dt **Controlled group** (n = 60), placebo.	22.5	Enhanced immune cell function, reduced severity of illness, improved antioxidant markers, and tentative evidence of reduced inflammatory response	No AE was observed	[97]
	Raw crushed garlic supplement	40	Metabolic syndrome with waist circumference >102 cm for men and >88 cm for women, systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, fasting plasma glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, and HDL cholesterol <40 mg/dL for men and <50 mg/dL for women	Non-randomized open-label study **Intervention group** (n = 40), 100 mg/kg BW twice/day. **Controlled group** (n = 0), no controlled group.	4	Reduced abdominal obesity, improved blood pressure control, decrease in fasting blood glucose levels, decrease in triglyceride levels, and increase in HDL cholesterol levels	No AE was observed	[98]
	Garlic supplement	91	Diabetic retinopathy patients with central macular edema	Double-blind randomized clinical trial. **Intervention group** (n = 45), garlic tablet 500 mg twice daily. **Controlled group** (n = 46), placebo.	4	Changes in visual acuity, macular thickness, and IOP	Single self-limited case of GI upset	[99]
A. ferox	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
A. asphodeloides	TA-III Cream	21	Female, aged 43–55 years	Randomized, placebo-controlled study, double blind. **Intervention group** 0.25% TA-III cream twice daily to the crow's feet area. **Controlled group** placebo cream.	12	Reduced skin wrinkles and photoprotecting	No AE was observed	[100]
A. asphodeloides	N/A	80	Patients with negative symptom-dominated schizophrenia	Randomized, placebo-controlled study, double blind. **Intervention group** (n = 41), sarsapogenin 200 mg/day and risperidone 2–4 mg/day. **Controlled group** (n = 39), placebo (risepridone 2–4 mg/day).	8	Changes in symptoms, cognitive function, disease severity or improvement scores, as assessed by PANSS, WMS, mWAIS, CGI and BPRS scales	No AE was observed	[101]
E. himalaicus	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: AGE, aged garlic extract; BPRS, Brief Psychiatry Rating Scale; CGI, clinical global impression; FGE, fermented garlic extract; FMD, flow-mediated dilation; IOP, intraocular pressure; mWAIS, modified Chinese version of Wechsler Adult Intelligence Scale; ND, not determined; OPE, onion peel extract; PANSS, Positive and Negative SyndromeScale; TA-III, Timosaponin A-III; TNSS, Total Nasal Ssymptom Score; TOSS, Total Ocular Symptom Score; VAS, Visual Analog Scale; VFA, visceral fat accumulation; WMS, Wechsler Memory Scale.

Table 7 In Silico Study

Plant	Compound Name	Binding Affinity (kcal/mol)	Amino Acid Residues	Amino Acid Residues	Ref
			Involved in the Interaction (Hydrogen Bond)	Involved in the Interaction (Hydrophobic Bond)	
	Acarbose	−15.6	Arg1510, Asp1157, Asp1279, Met1421, Thr1528, and Trp1355	Asp1526 and His1584	[117]
A. ascalonicum and *A. cepa*	Quercetin	−7.6	Ser420, Lys675, Gln421, Thr375, Ser422	Ser420, Lys675, Gln421, Thr375, Ser422	[118]
	Quercetin	−8.9	Asp1526, His1584, and Thr1586	Phe1560, Trp1355, and Tyr1251	[117]
A. sativum	Allyl methyl trisulfide (AMS)	−3.8	N/A	His1584, Ile1315, Ile1280, Met1421, Phe1559, Trp1355, Trp1523, and Trp1418	[117]
	S-allylcysteine sulfoxides (Aliin)	−5.2	Arg1510, Asp1157, and Asp1526	Ile1280, Trp1355, and Tyr1251	[117]
	S-allyl-L-cysteine (SAC)	−4.7	Asp1420	Met1421, Trp1355, Phe1559, and Tyr1251	[117]
A. ferox	β-sitosterol	−8.8	Pro312	Asp352, Arg442, Leu313, Arg213, Arg315, Phe314, Tyr158, Asp69, Glu411, Tyr72, His351, His112, Asp215, Phe303, Phe178, Glu277, and Gln279	[119]
A. asphodeloides	Mangiferin	−10	Ser311, Gln279, Asp307, and Asp215	N/A	[54]
E. himalaicus	Isorutarine	−7.64	Phe490, Thr491, and Arg608	N/A	[120]
	Compound 10	−7.12	Val358, Arg608, and Tyr609	N/A	[120]
	Compound 36	−6.86	Val358 and Arg608	N/A	[120]

kcal/mol) with Arg1510, Asp1157, Asp1279, Met1421, Thr1528, and Trp1355 forming hydrogen bonds and with Asp1526 and His1584 forming hydrophobic bonds.[117]

Phytosterols in *A. ferox* can lower serum levels of free fatty acids and triglycerides, stimulating insulin sensitivity and production, and can be used to treat DM[21]. A derivate of phytosterol, β-Sitosterol, has a docking score of −16.097 and binds with amino acids of the active site of α-glucosidase enzyme Asp215, Asp352, Arg442, and Gln182. The binding interactions may be attributed by hydroxyl groups.[132] Another research reported β-Sitosterol exhibited high affinity with binding energies (−8.8 kcal/mol) and is comparable with quercetin as a positive control with binding energies (−8.8 kcal/mol). This interaction forms hydrogen bonds with Pro312 and forms hydrophobic bonds with Asp352, Arg442, Leu313, Arg213, Arg315, Phe314, Tyr158, Asp69, Glu411, Tyr72, His351, His112, Asp215, Phe303, Phe178, Glu277, and Gln279.[119]

Mangiferin in *A. asphodeloides* was reported to inhibit α-glucosidase enzyme. Mangiferin exhibited high affinity with α-glucosidase with binding energies (−10 kcal/mol) compared to acarbose (−2.3 kcal/mol). Several mangiferin and protein bonds that occur form stable complexes. Mangiferin bonds with Ser 311, Gln 279, Asp 307, and Asp 215 forming conventional hydrogen bonds, bonds with Phe 178, Tyr 158, Val 216, and Asp 352 forming T-shaped π-π bonds, π-alkyl, and π-anion, and bonds with Arg 315 forming a carbon hydrogen bond.[54]

Coumarin derivates (isorutarine, compound 10, and compound 36) in *E. himalaicus* have been reported to have affinity with α-glucosidase. Isorutarine binding energies (−7.64 kcal/mol) with Phe490, Thr491, and Arg608, compound 10 binding energies (−7.12 kcal/mol) bonds with Val358, Arg608, and Tyr609, and compound 36 binding energies (−6.86 kcal/mol) bonds with Val358 and Arg608. All of these bonds form hydrogen bonds by their oxygen atom and hydroxyl groups.[120]

Enhanced Utility and Safety of Plant-Derived α-Glucosidase Inhibitors

The primary challenge associated with therapeutic effects is related to its poor aqueous solubility and low bioavailability upon oral administration. Standardization, novel formulations, clinical trials, and combination with other therapies can enhance the safety, efficacy, and acceptability of herbal medicines. Several possible strategies can be implemented to improve the utility and safety of plant-derived α-glucosidase inhibitors: 1) ensuring consistent levels of active compounds through collection practices and standardized extraction methods, purifying, and characterizing of marker compounds this may improve efficacy and reproducibility;[133–135] 2) combination with absorption enhancers may help increase the bioavailability of poorly absorbed phytochemicals;[136] 3) in novel drug delivery systems, encapsulation in nanoparticles, liposomes, etc. can enhance intestinal permeability and protect compounds from degradation which may improve time-controlled or targeted delivery;[137–139] 4) in phase I clinical trials, proper evaluation of pharmacokinetics, dosage optimization, safety verification, and herb–drug interaction screening before longer efficacy trials is needed;[140,141] 5) combined with lifestyle interventions, integrating herbal extracts as a complement to healthy diet, and exercise plans in diabetes management helps lower medication needs and dependence;[142] and 6) in post-marketing surveillance, continuing to monitor safety and obtain long-term efficacy data after commercial market release helps to identify rare adverse effects and better establish benefits.[143]

Conclusion

Based on our findings, to prevent progression of T2DM and maintain blood glucose levels, *Allium ascalonicum, Allium cepa, Allium sativum, Aloe ferox, Anemarrhena asphodeloides*, and *Eremurus himalaicus* are responsible for curing decreasing blood glucose in vitro, in vivo, in silico, and in human studies. The development of antidiabetic drugs is complex due to pure compounds from the plant and need further research. The target of this enzyme inhibition will affect other mechanisms such as increased insulin production and sensitivity, recovered β-cell damage, and stress oxidative suppression. Furthermore, these plants can be developed to the existence of new dosage forms of herbal plants as antidiabetic agents.

Abbreviations

AGI, α-glucosidase inhibitor; ALP, alkaline phosphatase; ALT, alanine transaminase; AMS, allyl methyl trisulfide; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BG, blood glucose; BMI, body mass index; BW, body weight; CAT, catalase; DM, diabetes mellitus; FBG, fasting blood glucose; FIRI, fasting insulin resistance index; GPx, glutathione peroxidase; GSH, glutathione; H_2O_2, hydrogen peroxide; LDL, low density lipoproteins; MDA, malondialdehyde; NAD, nicotinamide adenine dinucleotide; N/A, not applicable; PPBG, post prandial blood glucose; PPHG, post prandial hyperglycemia; ROS, reactive oxygen species; SAC, S-allyl-L-cysteine; SO, stress oxidative; SOD, superoxide dismutase; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TLC, thin layer chromatography; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides.

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Disclosure

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