Review

Recent Updates on Phytoconstituent Alpha-Glucosidase Inhibitors: An Approach towards the Treatment of Type Two Diabetes

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Abstract: Diabetes is a common metabolic disorder marked by unusually high plasma glucose levels, which can lead to serious consequences such as retinopathy, diabetic neuropathy and cardiovascular disease. One of the most efficient ways to reduce postprandial hyperglycemia (PPHG) in diabetes mellitus, especially insulin-independent diabetes mellitus, is to lower the amount of glucose that is absorbed by inhibiting carbohydrate hydrolyzing enzymes in the digestive system, such as α-glucosidase and α-amylase. α-Glucosidase is a crucial enzyme that catalyzes the final stage of carbohydrate digestion. As a result, α-glucosidase inhibitors can slow D-glucose release from complex carbohydrates and delay glucose absorption, resulting in lower postprandial plasma glucose levels and control of PPHG. Many attempts have been made in recent years to uncover efficient α-glucosidase inhibitors from natural sources to build a physiologic functional diet or lead compound for diabetes treatment. Many phytoconstituent α-glucosidase inhibitors have been identified from plants, including alkaloids, flavonoids, anthocyanins, terpenoids, phenolic compounds, glycosides and others. The current review focuses on the most recent updates on different traditional/medicinal plant extracts and isolated compounds’ biological activity that can help in the development of potent therapeutic medications with greater efficacy and safety for the treatment of type 2 diabetes or to avoid PPHG. For this purpose, we provide a summary of the latest scientific literature findings on plant extracts as well as plant-derived bioactive compounds as potential α-glucosidase inhibitors with hypoglycemic effects. Moreover, the review elucidates structural insights of the key drug target, α-glucosidase enzymes, and its interaction with different inhibitors.

Keywords: α-glucosidase; postprandial hyperglycemia; natural compounds; type 2 diabetes

1. Introduction

Diabetes mellitus is a metabolic condition defined by chronically high blood sugar levels [1]. The International Diabetes Federation Diabetes Atlas estimates that it affected 537 million people globally in 2021, and that number is expected to rise to 643 million by 2030 [2]. Diabetes mellitus was the ninth major cause of mortality in a worldwide study conducted by the World Health Organization (WHO) (2019), and it is projected to be the seventh leading cause of death by 2030. According to the International Diabetes Federation (IDF), 6.05 million individuals in Korea suffer from diabetes mellitus as of 2020 [3]. The insulin hormone is generated by pancreatic β-cells and plays a key role in regulating blood glucose levels. It is required for several cellular activities such as glucose absorption and transport, glycogen synthesis, protein synthesis and fatty acid synthesis. Inadequate insulin production or insulin resistance hinders proper glucose homeostasis, resulting in hyperglycemia [4]. Chronic hyperglycemia can have major long-term consequences such as cardiovascular disease nerve damage and renal failure [5]. Depending on the mechanism of its manifestation, diabetes mellitus can be categorized into three types; type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and gestational diabetes. T1DM affects roughly 5–10% of all diabetes patients and is characterized by the death...
of pancreatic insulin-producing β-cells destroyed by the immune system, resulting in an extreme shortage of insulin, hyperglycemia, inflammation, oxidative damages and other metabolic problems [6,7]. T2DM affects over 90% of diabetes people worldwide and is expected to reach 592 million by 2035 [8]. T2DM is characterized by insulin resistance resulting from insulin receptor insensitivity, persistent hyperglycemia, dyslipidemia and low-level inflammation (Scheme 1) [8,9]. Gestational diabetes occurs only during pregnancy in women and results in unfavorable clinical conditions in both the mother and her kids [10]. Hyperglycemia is the most serious criterion of all forms of diabetes, and it can lead to a variety of complications such as cardiovascular disease, neuropathy, renal failure, lipid metabolism issues and many others. Therefore, controlling blood glucose levels in diabetes individuals is very critical [11,12]. Reduced postprandial hyperglycemia is one treatment method for treating diabetes in its early stages. This is accomplished by suppressing the carbohydrate-hydrolyzing enzymes, α-glucosidase and α-amylase in the digestive system, which prevents glucose absorption. As a result, inhibitors of these enzymes slow the absorption of glucose, hence dampening the postprandial plasma glucose spike [13,14].

![Scheme 1](image)

Since the 1990s, anti-diabetic medicines with α-glucosidase inhibitory capabilities, such as acarbose, miglitol and voglibose, have been commercially accessible for treating postprandial hyperglycemia. Since their molecular structure is comparable to that of disaccharides or oligosaccharides, those antidiabetic drugs can bind to the carbohydrate-binding site of α-glucosidase. The complexes that result from such binding have a higher affinity than carbohydrate–glucosidase complexes, which consequently leads to a delay in carbohydrate digestion and absorption and thus reduces the PPHG. Nonetheless, the repeated ingestion of them causes flatulence, severe stomach discomfort, allergic responses, etc. [15–17]. Despite the commercial availability of efficient AGIs, researchers are continuously working developing novel bioactive AGIs with strong inhibitory potential and fewer adverse effects. Several bioactive compounds have been reported to alleviate various pathophysiological conditions [18–26]. Additionally, numerous attempts have been made to synthesize non-cytotoxic compounds with α-glucosidase inhibition activity [27–29]. In recent decades, there has been a surge of growing interest in using natural products as medicinal agents, particularly in the prevention and management of T2DM. Medicinal
herbs and traditional remedies have been employed throughout history to treat a wide range of medical conditions, including diabetes. This review gives an overview of the most recent plant-derived extracts as well as bioactive compounds that inhibit \( \alpha \)-glucosidase, and it emphasizes the most promising therapeutic candidates for T2DM management via \( \alpha \)-glucosidase inhibition. The most recent updates include, from various natural sources, different plant extracts, their hypoglycemic effect on animal models, phenolic compounds, flavonoids, tannins, anthocyanins and polysaccharides. The review was carried out based on published work between 2019 and 2022 by using scientific search engines such as Scopus, PubMed, Science Direct and SciFinder. The inclusion criteria were medical plants with a folklore history exhibiting \( \alpha \)-glucosidase activities.

2. Alpha-Glucosidases Structure and Mechanism of Action

Complex carbohydrates are broken down into monosaccharides in the gastrointestinal system by several breakdown processes and are absorbed in the small intestine. The digestive process starts with the production of amylases (EC 3.2.1.1), which catalyze the breakdown of starch into shorter polysaccharides and are mostly generated by the salivary and pancreatic glands [30]. When partly hydrolyzed starch enters the small intestine, it is further processed by amylases of the pancreas, which target the \( \alpha \)-1 and four linkages of carbohydrate-releasing dextrins [31]. \( \alpha \)-Glucosidases at the brush border of enterocytes mediate the last stage in glucose metabolism. The enzymes have duplicated glycoside hydrolase domains (GH31) that hydrolyze \( \alpha \)-glucosidic disaccharide and oligosaccharide bonds [32,33] (Figure 1a). These glycosidases play important roles in a variety of biological activities, including carbohydrate digestion, lysosomal glycoconjugate catabolism and post-translational glycoprotein changes. The oligosaccharides resulting from \( \alpha \)-amylase digestion are finally hydrolyzed to monosaccharides by \( \alpha \)-glucosidases; maltase glucosylase [MGAM (EC 3.2.1.20) and (EC 3.2.1.3)] and sucrose isomaltase [SI (EC 3.2.1.48) and (EC 3.2.1.10)]. MGAM (EC 3.2.1.20) are the most active of the four \( \alpha \)-glucosidases, releasing glucose from non-reducing ends of oligosaccharides [34–38].

![Figure 1](image_url)

**Figure 1.** (a) Ribbon diagram of the structure of Human Nt MGAM/acarbose complex as a representative for GH31 \( \alpha \)-glucosidase. Different domains are colored as follows: N-terminal domain, blue; catalytic domain, green; subdomain b1, pale green; subdomain b2, lemon; C-terminal domain 1, red; and C-terminal domain 2, orange. (b) Human Nt MGAM/acarbose complex active site; sticks represent residues situated within a 4-A° radius of a valienamine unit. The acarbose is colored cyan and is shown as sticks and wire for a and b, respectively. (a,b) were adopted from the structure, with PDB entry code: 2QMJ [39], and were generated using PyMol [40].

The catalytic domains of MGAM and SI are duplicated, with an N-terminal membrane-adjacent domain (ntMGAM and ntSI) and a C-terminal luminal domain (ctMGAM and ctSI).
(Figures 1a, 2a and 3a). An O-glycosylated stalk produced from the N-terminal domain attaches the domains to the brush border membrane of the small intestine [41]. The N- and C-terminal domains of MGAM and SI have more sequence similarity (~60%) when compared to the N- and C-terminus domains of the same enzyme in other species (~40 percent sequence identity). This is due to the MGAM and genes evolving from a previously duplicated ancestor gene through duplication and divergence. The N- and C-terminals of MGAM and SI are members of the glycoside hydrolases (GH) 31 family. The nonreducing ends of α (1–4)-glycosidic bonds are hydrolyzed by the four domains, although they have different inclinations for malto-oligosaccharides of variant lengths [35–38]. MGAM favors α-1,4-oligosaccharides and can effectively hydrolyze lengths up to glucohexaose. α-1, 6-glycosidic linkages are hydrolyzed by MGAM at just a 2% rate compared to α-1,4-glycosidic bonding, and there is a little sum of α-1,2- and α-1,3-hydrolyzing activity. On the other hand, SI represents almost 80% of the total intestinal maltase activity (α-1,4 glycosidic linkages) and nearly all sucrase activity (α-1,2-glycosidic linkages) in the small intestine. SI may also hydrolyze isomaltose’s α-1,6-glycosidic bonds, and there is modest α-1,3-hydrolyzing activity [41,42]. The hydrolyzed glucose is then transported by glucose transporter (GLUT)-2 and sodium/glucose cotransporter-1 (SGLT1) from intestinal mucosa into the blood circulation, causing postprandial hyperglycemia (PPHG) [38].

Figure 2. (a) Ribbon diagram of Human Nt SI crystal structure in complex with kotalanol. (b) Human Nt SI important active site residues (catalysis/substrate binding). The kotalanol is colored cyan and is shown as sticks. (a,b) were adopted from the structure, with PDB entry code: 3LPP [43], and were generated using PyMol [40].

Since the inhibition of α-glucosidase enzymes results in a glucose production delay, which contributes to its therapeutic role in T2DM, the relationship between α-glucosidases’ catalytic characteristics, particularly substrate selectivity, and their structures have been the subject of much research in the past two decades. Except for CtSI, the three-dimensional structures of these subunits are now available [39,43,44]. The α-glucosidases’ structures are protein complexes containing inhibitors such as acarbose and kotalanol. (Figures 1–3). Each α-glucosidase structure consists of four main domains; an N-terminal domain, a catalytic domain of the (the (β/α)8-barrel and two C-terminal domains. Inserts 1 and 2 of the catalytic domain are located right after β-strands 3 and 4, respectively (Figure 1a). The general architectures of these subunits’ structures are almost similar, except for insert 1. Ct-MGAM insertion 1 differs from the others because it includes an additional helical segment of 21 amino acid residues [44] (Figure 3a). In the catalytic domain, the active site pocket
(Subsite-1) is formed by β-barrel loops, and the residues involved with subsite-1 formation are highly conserved among α-glucosidases’ subunits. At subsite-1, twelve residues reside within 4–Å of an acarbose valienamine unit and may contribute to enzyme/inhibitor interactions (Y299, D327, I328, I364, W406, W441, D443, M444, R526, W539, D542 and H600) (Figure 1b). D443 and D542 each supply a catalytic nucleophile and a generic acid/base. The hydroxy groups of the valienamine establish a hydrogen bond with the side chains of D327, R526 and H600 (Figure 1b). In NtMGAM, the aromatic residue of Y299 of the catalytic domain is oddly different. Both MGAM subunits feature Tyrosine residue (Y299 in NtMGAM and Y1251 in CtMGAM) (Figures 1b and 3b), and NtSI has W327 (Figure 2b). This Tryptophan residue is thought to be key in giving the α-(1→6)-specificity of NtSI [43] (Figure 2b). Mutational studies have shown that substituting Tryptophan residues for the Y299 of NtMGAM and Y1251 of CtMGAM enhances the enzyme catalytic activity for isomaltose hydrolysis [44]. The binding of α-glucosidase with isomaltose (α-(1→6) specific) was clarified using the crystal structure of α-glucosidase from Ruminococcus obeum [45]. The W169 bulky side chain appeared to impede its mobility by being opposed to the flexible α-(1→6)-glucosidic linkage with three bonds. A site-directed mutagenesis investigation demonstrated the relevance of W169 to α-(1→6)-specificity, in which the replacement of W169 with Y significantly lowered the hydrolysis activity toward isomaltose and turned the α-(1→6) specific α-glucosidase into an α-(1→4)-specific enzyme [45]. These structural insights can help us to understand α-glucosidase interactions with different AGI to produce AGI with fewer side effects.

Figure 3. (a) Ribbon diagram of the structure of human ctMGAM/acarbose complex. (b) Human ctMGAM important active site residues (catalysis/substrate binding). The acarbose is colored cyan and is shown as sticks. (a,b) were adopted from the structure, with PDB entry code: 3TOP [44], and were generated using PyMol [40].

3. Plant Extracts as α-Glucosidase Inhibitor Sources

Many herbal medications have been advocated for diabetes treatment in addition to the already available therapeutic alternatives. Traditional plant remedies are utilized all over the world to treat a variety of diabetes symptoms. The fact that plant preparations have fewer adverse reactions than current conventional medications [46–49], along with their lower cost, is encouraging both the general population and national health care organizations to examine natural medical items as alternatives to synthetic drugs [50]. As a result, research into such compounds derived from traditional medicinal herbs has become increasingly significant [51].

Cucurbitaceae family member Momordica charantia L. has been exploited as a traditional medicine for managing diabetes mellitus and other metabolic syndromes [52]. M. charantia is rich in phytoconstituents such as flavonoids, alkaloids, polysaccharides, poly peptides, glycosides phenolic and fatty acids that enhance its pharmacologic efficacy [53,54]. M.
*charantia* methanolic extract shows potent α-glucosidase inhibition activity and significantly improves fasting blood glucose levels and insulin in diabetic rats. The acarbose shows higher α-glucosidase inhibition (79.91 ± 0.77%) in vitro than *M. charantia* methanolic extract (72.30 ± 0.30%) [52].

*Artemisia absinthium* belongs to the Asteraceae family, which is considered to be the most common traditional Moroccan medicine used for diabetes [55]. The hypoglycemic effect of *A. absinthium* L. aqueous and ethyl acetate extracts have been studied in diabetic rats [56]. *A. absinthium* ethyl acetate extracts show higher α-glucosidase inhibition activity in vitro than the aqueous extract (IC$_{50}$ for ethyl acetate extract 0.155 ± 0.0009 mg/mL, aqueous extract 0.170 ± 0.0002 mg/mL as compared to acarbose 0.148 ± 0.002 mg/mL). However, in vivo, only the aqueous extract of *A. absinthium* leaves show significant hypoglycemic activity, whereas the ethyl acetate extract shows no α-glucosidase activity. Such activity could be due to the high content of polyphenols in the *A. absinthium* extract.

Several extracts (20) from edible spices such as mace, nutmeg, coriander, star anise and fenugreek were investigated for their anti-diabetic potential as α-glucosidase inhibitors [57]. Among them, the ethyl acetate extract of star anise has the most potent anti-α-glucosidase activity in vitro (IC$_{50}$ 4.76 ± 0.71 to 201.34 ± 20.07 µg/mL of control acarbose). The mechanism of inhibition was further investigated, and the kinetic analysis revealed the competitive and reversible binding of star anise ethyl acetate extract to α-glucosidase. The study showed that star anise ethyl acetate extract injection in hyperglycemic rabbits decreases blood glucose levels significantly and in a time-dependent manner.

*Amomum villosum* plant fruit from the Zingiberaceae family is a Korean traditional medicine used in the treatment of different digestive diseases. The fruit water extract used by healthy individuals shows a positive effect on postprandial glycemia and insulin secretion during clinical assessment [58]. *A. villosum* water extract was investigated for its α-glucosidase activity at different concentrations of 1, 3 and 5 mg/mL, which proportionally increased the inhibition against rat α-glucosidase with IC$_{50}$ of 31.99 ± 6.79%, 48.85 ± 4.75% and 62.58 ± 6.69%, respectively. Although *A. villosum* water extract has lower inhibition on α-glucosidase than the reference acarbose, it showed a considerable drop in blood glucose levels in the sucrose loading test when administered to the rats compared to the control group [59].

*Merremia tridentata* (L.) is a traditional medicinal plant used for the treatment of diabetes and several other disorders in Vietnam. The antidiabetic effect of stem-ethanol extract (SE) as well as flavonoid-rich fractions (FF) of the stem of *M. tridentata* were investigated in diabetic mice [60]. The study revealed that the daily administration of 100 mg/kg SE and 50, 75 mg/kg FF to diabetic mice for twenty days has a higher hypoglycemic effect than the reference drugs, metformin (10 mg/kg) and glibenclamide (5 mg/kg), without affecting the body weight of tested mice. Moreover, SE and FF showed decent α-glucosidase inhibition activity when compared with acarbose (IC$_{50}$ (mg/mL) 0.44 ± 0.11, 0.24 ± 0.08 and 0.29 ± 0.06, respectively) (Table 1).
Table 1. Plant extracts showing in vivo α-glucosidase inhibition activity.

| Name                        | Extract/Part Used                   | Model                  | Type of Study                  | Tested Substance Dosage | Administration Route | Assessing Criterion                      | Effect on Animal Blood Glucose Level | Ref. |
|-----------------------------|-------------------------------------|------------------------|-------------------------------|--------------------------|----------------------|------------------------------------------|--------------------------------------|------|
| *Momordica charantia*       | Methanol extract                    | Male albino Wistar rats| Alloxan-induced diabetes      | 200 mg/kg BW             | Oral                 | Fasting blood glucose (FBG) and insulin levels | Hypoglycemic                         | [52] |
| *Artemisia absinthium* L.   | Aqueous extract/leaves              | Wistar rats            | Alloxan-induced diabetes      | 200 mg/kg BW             | Oral                 | PBGL                                     | Hypoglycemic                         | [56] |
| Star anise                  | Ethyl acetate extract/fruit         | Rabbits                | Alloxan-mono-hydrate-induced diabetes | 250 mg/kg BW            | Injection            | Blood glucose levels (BGL) and body weight | Hypoglycemic                         | [57] |
| *Amomum villosum*           | Water extracts/fruit                | Male SD rats           | Sucrose loading test (SLT) (2 g/kg BW) | 200 mg/kg BW            | Oral                 | BGL                                      | Hypoglycemic                         | [59] |
| *Merremia tridentata* (L.)  | Ethanol extract (SE) and flavonoid-rich fraction (FF)/stem | Mice                   | Alloxan-induced diabetic      | SE (100 mg/kg BW) and FF (50, 75 mg/kg BW) | Oral                 | BGL and body weight                      | Hypoglycemic                         | [60] |
| Lu’an guapian green tea     | Methanol extract                    | Male mice              | GTT and ITT                   | -                        | Oral                 | Post prandial hyperglycemia effect        | Hypoglycemic                         | [61] |
| *Amomum tsao-ko*            | Methanol extract                    | Mice                   | STZ-induced diabetes          | 100 and 200 mg/kg BW     | Oral                 | FBG                                      | Hypoglycemic                         | [62] |
| *Lactuca sativa*            | Methanol extract                    | Male SD rats           | STZ-induced diabetes          | 50, 100 and 200 mg/kg BW | Oral                 | BGL                                      | Hypoglycemic                         | [63] |
| *Allium consanguineum*      | Compounds 1 and 2 isolated from the plant | Albino mice            | Alloxan-induced diabetic oral glucose tolerance test (OGTT) | 500, 250, 125, 62.5 and 31.25 µg/kg BW | Oral                 | Postprandial effect                      | Hypoglycemic                         | [64] |
| *Amischotolype mollissima*  | Ethanolic leaves extract            | Swiss albino mice      | OGTT (2 gm/kg BW)             | 250 and 500 mg/kg BW     | Oral                 | No cytotoxicity of the extract until 4000 mg/kg BW | Hypoglycemic                         | [65] |
| *Descurainia sophia*        | Methanolic flower extract           | Male Wistar rats       | Alloxan-induced diabetic      | 2.25 and 4.50 g/kg BW    | Oral                 | Blood glucose level                      | Hypoglycemic                         | [66] |
| Catechin and epicatechin    | Phenolic extract                    | Male SD rats           | SLT (2 g/kg BW)               | 20 mg/kg BW              | Oral                 | PBGL level                               | Hypoglycemic                         | [67] |
| *Zanthoxylum armatum*       | Aqueous leaves extract              | Female Swiss albino mice| Alloxan-induced diabetes      | 100–4000 mg/kg BW        | Oral                 | Hypoglycemic activity                    | Hypoglycemic                         | [68] |
|                            |                                     |                        |                               |                          |                      | Lethal dose LD₅₀ 5000 mg/kg               |                                      |      |
| *Cajanus cajan* (L.)        | Ethanol extract                     | Wistar rats            | Methylglyoxal (MGO)-induced insulin resistance | 10, 50 and 100 mg/kg BW | Oral                 | (OGTT), (ITT)/BGL                        | Hypoglycemic/ dose-dependent         | [69] |
| *Rhodiola crenulata*        | Ethanol extract/ root               | Male SD Rat/male Kunming (KM) mice | Alloxan-induced diabetes in mice/OSTT in mice | 100–4000 mg/kg BW        | Oral                 | Post carb. glucose level                 | Hypoglycemic                         | [70] |
| Name                        | Extract/Part Used                              | Model                  | Type of Study | Tested Substance Dosage | Administration Route | Assessing Criterion                  | Effect on Animal Blood Glucose Level | Ref.     |
|-----------------------------|-----------------------------------------------|------------------------|---------------|--------------------------|----------------------|---------------------------------------|--------------------------------------|---------|
| *Amomum tsao-ko* Crevost and Lemarie | Methanol extract flavonoid constituent         | Male SD Rats           | STZ-induced diabetes | 100 mg/kg BW             | Oral                 | Postprandial glucose level (OGTT)/FBG | Hypoglycemic                        | [71]    |
| *Terfezia claveryi*         | Aqueous extract Phenolic content              | Male BALB/c mice       | High-fat diet alloxan-induced diabetic mice | 250 and 500 mg/kg BW | Oral                 | Blood glucose level                   | Hypoglycemic/dose-dependant          | [72]    |
| *Paonia species*           | Ethanol extract (resveratrol derivatives (vateriferol or VT and trans-ε-viniferin or VF))/Seed coats | Male KM mice           | Alloxan-induced diabetic mice | 5, 15 and 30 mg kg BW  | Oral                 | Oral starch tolerance test for PBG level | Hypoglycemic/dose-dependent          | [73]    |
| *Ammodaucus leucotrichus Coss. and Durieu* | Aqueous extract/fruit                           | Albino Wistar rats     | Alloxan diabetic rats | 150 mg/kg BW             | Oral                 | OGTT                                  | Hypoglycemic                        | [74]    |
| *Salvia polystachya Cav.*   | Ethanolic extract/Terpenoid content           | BALB/c mice            | streptozocin-nicotinamide (STZ-NA) induced diabetes | 50, 100 and 200 mg/kg BW | Oral                 | Oral sucrose and starch tolerance tests (OSuTT and OStTT)/OGTT and galactose tolerance test (OGaTT)/glucose load (1.5 g/kg⁻¹) | Hypoglycemic/dose-dependent          | [75]    |
| *Agathophora alopecuroides* | Methanol extract                               | BALB/c male albino mice | STZ-induced diabetic mice | 100 and 200 mg/kg BW     | Oral                 | RBGL and FBGL                        | Hypoglycemic                        | [76]    |
| *Lonicera caerulea L.*      | Blue honeysuckle extract                       | Male mice              | Oral starch and maltose (2 g kg⁻¹) tolerance assay | 100 and 200 mg kg BW   | Oral                 | PBG level                             | Hypoglycemic                        | [77]    |
| *Ganoderma lucidum*        | Aqueous extract of fruiting bodies (FYGL)     | BKS-db (db/db) diabetic mice | OSTT (2.5 g/kg sucrose) | 225, 450 and 900 mg/kg bw FYGL | Oral                 | PBG concentration                     | Hypoglycemic                        | [78,79] |
| *Colvillea racemosa*       | Ethanol extract (n-butanol fraction)/leaves    | Male albino rats       | STZ-induced diabetes | 500 mg/kg BW             | Oral                 | FBG                                   | Hypoglycemic                        | [80]    |
| *Artemisia roxburghiana*    | Aqueous ethanol extract/aerial parts           | Wistar rats            | STZ-NA-induced diabetes | 200 and 400 mg/kg BW     | Oral                 | BGL                                   | Hypoglycemic/dose-dependent          | [81]    |
| *Breynia distachia*         | Methanol extract/aerial parts                  | SD rats                | Alloxan-induced diabetes | 150 and 300 mg/kg BW    | Oral                 | BGL                                   | Hypoglycemic                        | [82]    |
| *Rhodomyrtus tomentosa*     | Methanol extract/Leaf                          | Male albino Wistar rats | STZ-induced diabetes | 200, 400 and 600 mg/kg BW | Oral                 | BGL                                   | Hypoglycemic/dose-dependent          | [83]    |
Several medicinal plant extracts have been recently reported to exhibit potent α-glucosidase inhibitory activity and hypoglycemic effects in animal models. For one of the most famous and commercial green teas in China (Lu’an guapian green tea (LGGT)), its methanol extract shows α-glucosidase inhibition activity, and when supplemented with the diet, it improves insulin sensitivity and glucose tolerance in mice [61]. For another edible spice/medicinal herb from China, Amomum tsao-ko, its methanol extract shows hypoglycemic activity in a dose-dependent manner while treating STZ-induced diabetic mice as well as in vitro [62]. After six weeks of treatment, the extract significantly decreases the fasting blood glucose in diabetic mice. The study identifies bioactive constituents from methanol extracts such as phenols, flavonoids, oligosaccharides, coumarins and others that could be responsible for α-glucosidase inhibition/hypoglycemic activity. Recently, edible and hydroponically grown Lactuca sativa soil have been reported to substantially reduce blood glucose levels in diabetic rats besides in vitro α-glucosidase inhibition activity [63]. The crude extract and two isolated compounds Coniferol (1) and dillapiole (2) (from chloroform phyto-fractions) of Allium consanguineum were investigated for their hypoglycemic effects [64]. The in vivo studies revealed that two compounds, coniferol and dillapiole, substantially lower blood glucose levels in albino mice. The ethanolic leaves extract of Amischolype mollissima has shown α-glucosidase enzymatic activity in addition to the antihyperglycemic effect that was observed in the swiss albino mice oral glucose tolerance test in a dose-dependent manner [65]. The methanolic flower extract of Descurainia sophia showed in vitro α-glucosidase activity with mixed (competitive/non-competitive) inhibition [66]. Moreover, consuming the flower extract reduced blood glucose levels in the male rats when compared to the control group. The authors propose that the hypoglycemic effect of the D. sophia flower extract is due to flavonoid and phenolic phytochemical contents in the extract (Table 1).

Other traditional plant extracts have been recently reported for their α-glucosidase potency, and further in vivo studies are required to verify their hypoglycemic biological effect. These studies have examined the potential role of herbal plants against α-glucosidase activity (Table 2). Among the most recent plant extract studies in the literature that are included in this review, Cerasus humilis, Gymnanthemum amygdalinum, and Paliurus spinachristi Mill have the highest α-glucosidase inhibition activities compared to the positive control acarbose. Cerasus humilis (Sok. leaf-tea) has been identified as a good source of α-glucosidase inhibitors [84]. C. humilis methanol extract with a high flavonoid/phenolic content has a substantially higher α-glucosidase inhibition activity (IC50 = 36.57 µg/mL) in comparison to acarbose (IC50 = 189.57 µg/mL). Among the phenolic compounds isolated from C. humilis methanol extract in this study, myricetin, avicularin, pruning, quercitrin, guajavarin and isoquercitrin were accountable for their α-glucosidase activity. The Paliurus spinachristi mill fruit is used as an antidiabetic traditional medicine in Turkey, and a recent study showed that n-hexane fractions derived from the methanolic fruit extract have remarkably higher α-glucosidase inhibitory effects than acarbose with IC50 of 445.7 ± 8.5 and 4212.6 ± 130.0 µg/mL, respectively [85]. The phytochemical analysis of the flower extract identified three terpenic compounds (betulin, betulinic acid and lupeol) with a higher α-glucosidase inhibitory activity than acarbose. Gymnanthemum amygdalinum (Delilee) is another folk medicine plant that has been traditionally used in Nigeria to treat diabetes, and the flavonoid-rich fractions of its leaf extract show a substantial antidiabetic effect [86]. A recent study showed that flower methanol extract also exhibits great α-glucosidase inhibitory activity with IC50 greater than the positive control [87]. The flower methanolic extract fractionation with ethyl acetate solvent yield in two flavonoid compounds with luteolin showed the highest α-glucosidase activity than 2-(3,4-dihydroxy phenyl)-5,7-dihydroxy-3-methoxy-4H-chromen-4-one compared to the positive control. Polysaccharides extracted from the water extract of Evodiae fructus, a Chinese medicinal herb, show promising α-glucosidase inhibition activity [88]. The polar extracts of Oryza sativa L. (black rice) bran possess potent α-glucosidase inhibitory activity [89]. The preliminary analysis of these
traditional medicinal plant extracts revealed promising α-glucosidase inhibition activity, and further analysis is required to support their anti-diabetic effect.

Table 2. Summary of an in vitro α-glucosidase inhibition assay for plant extracts.

| Name of Plants/Compounds | Extract/Class | Source | IC₅₀ of Positive Control (Acarbose) | Mode of Type of Inhibition | Ref. |
|--------------------------|--------------|--------|------------------------------------|-----------------------------|-----|
| Chenopodium quinoa Willd. | Ethanolic extract | Gossypium hirsutum (seeds) | 0.049 ± 0.01 mg/mL. | - | [80] |
| Symplocos cochinchinensis | Ethanolic extract | Symplocos cochinchinensis (leaves) | 17.2 ± 1.5 mg/mL. | - | [82] |
| Paliurus spina-christi Mill. | Ethanolic extract | Paliurus spina-christi (seeds) | 0.08 ± 0.002 mg/mL. | - | [81] |
| Crepap consolida-xx | Methanolic extract | Crepat consolida (whole plant) | 107 μg/mL. | - | [84] |
| Cinnamomum zeylanicum | Ethanolic extract | Cinnamomum zeylanicum (leaves) | 25 μg/mL. | - | [85] |
| Adenosma bracteosum | Ethanolic extract | Adenosma bracteosum (seeds) | 1.873 μg/mL. | - | [91] |
| Crataegus pinnatifida | Acetone extract | Crataegus pinnatifida (fruits) | 42.35 ± 0.01 mg/mL. | - | [103] |
| Conyza canadensis | Methanolic extract | Conyza canadensis (flowers) | 36.57 ± 0.01 mg/mL. | - | [87] |
| Lepisanthes fruticosa | Methanolic extract | Lepisanthes fruticosa (flowers) | 48.5 ± 0.01 mg/mL. | - | [89] |
| Washingtonia filifera | Methanolic extract | Washingtonia filifera (leaves) | 336.25 ± 0.01 mg/mL. | - | [90] |
| Undaria pinnatifida | Chloroform residue | Undaria pinnatifida (fruits) | 23.83% at 0.8 mg/mL | - | [90] |
| Zanthoxylum armatum | Ethanolic extract | Zanthoxylum armatum (fruits) | 45% at 50 μg/mL | - | [90] |
| Cyclanthera pinnatifida | Ethanolic extract | Cyclanthera pinnatifida (fruits) | 99.66% at 4 mg/mL | - | [90] |
| Potentilla anserine | Ethanolic extract | Potentilla anserine (fruits) | 94.6% at 50 μg/mL | - | [90] |
| Nelumbo nucifera | Methanolic extract | Nelumbo nucifera (leaves) | 79.82% at 0.8 mg/mL | - | [90] |
| Gymnanthemum | Ethanolic extract | Gymnanthemum (leaves) | 47.7% at 50 μg/mL | - | [90] |
| Mentha arvensis | Methanolic extract | Mentha arvensis (leaves) | 68% at 50 μg/mL | - | [90] |
| Cinnamomum camphora | Ethanolic extract | Cinnamomum camphora (leaves) | 60% at 50 μg/mL | - | [90] |
| Andrographis paniculata | Ethanolic extract | Andrographis paniculata (fruits) | 47% at 50 μg/mL | - | [90] |
| Black rice | Ethyl acetate extract | Black rice bran | 2.48 µg/mL | - | [90] |
| Hexane extract | | | 52.80 ± 1.69 mg/mL | - | [90] |
| Potentilla anserine | Butyl alcohol fraction | Potentilla anserine (flowers) | 14.18 ± 0.05 mg/mL | - | [90] |
| Cyclanthera pinnatifida | Ethanolic extract | Cyclanthera pinnatifida (leaves) | 31.5 ± 1.05 mg/mL | - | [90] |
| Nelumbo nucifera | Ethanolic extract | Nelumbo nucifera (flowers) | 4.17 µg/mL | - | [90] |
| Evodiae fructus | Water extract | Evodiae fructus (fruits) | 99.6% at 4 mg/mL | - | [90] |
| Adenosma bracteosum | Ethanolic extract | Adenosma bracteosum (fruits) | 67.94 µg/mL | - | [90] |
| Leptosperum calcuttense | Ethanolic extract | Leptosperum calcuttense (fruits) | 79.82% at 0.8 mg/mL | - | [90] |
| Symplocos chinensis | Ethanolic extract | Symplocos chinensis (fruits) | 45 ± 1.2 µg/mL | - | [90] |
| Cinnamomum camphora | Ethanolic extract | Cinnamomum camphora (fruits) | 99.66% at 4 mg/mL | - | [90] |
| Palmarosa citriodora Mill. | Ethanolic extract | Palmarosa citriodora Mill. (fruits) | 99.66% at 4 mg/mL | - | [90] |
| Gymnophyllum stellatiflorum | Ethanolic extract | Gymnophyllum stellatiflorum (fruits) | 45% at 50 μg/mL | - | [90] |
| Wulinghui jujube | Methanolic extract | Wulinghui jujube (fruits) | 23.83% at 0.8 mg/mL | - | [90] |
| Costus yunnanensis | Ethanolic extract | Costus yunnanensis (fruits) | 31.7 ± 16.38 µg/mL | - | [90] |
| Cleopogon guianensis Willd. | Ethyl acetate fraction | Cleopogon guianensis Willd. (fruits) | 99.66% at 4 mg/mL | - | [90] |

4. Plant-Derived Bioactive Compounds as Potential α-Glucosidase Inhibitors

There have been reports of various plants having α-glucosidase inhibition activity. Potential AGI inhibitors have been shown to exist in a wide variety of bioactive substances that fall under several classes of secondary metabolites. Numerous secondary metabolites, including flavonoids, terpenes, phenolic acids, polysaccharides, tannins, anthocyanins, stilbene and many others, have been discovered to have α-glucosidase inhibition activity (Table 3).
| Name of Plants/Compounds | Extract/Class | Source | IC$_{50}$ | IC$_{50}$ of Positive Control (Acarbose) | Mode or Type of Inhibition | Ref. |
|--------------------------|--------------|--------|----------|----------------------------------------|---------------------------|-----|
| Catechin                 | Flavonoid    | Commercial | 1.12 ± 0.03 µM  | 1250 ± 35.63 µM                        | Competitive and reversible | [67] |
| Epicatechin              | Flavonoid    | Commercial | 0.95 ± 0.02 µM  | 1250 ± 35.63 µM                        | Competitive               | [107] |
| Naringenin               | Flavonoid    | Commercial | 6.51 µM       | (1.43 ± 0.02) × 10$^{-5}$ M             | Non-competitive           | [108] |
| Apigenin                 | Flavonoid    | Commercial | (0.24 ± 0.02) × 10$^{-5}$ M | (37.65 ± 0.44) × 10$^{-5}$ M | Mixed                |       |
| Hispidulín               | Flavonoid    | Commercial | (3.21 ± 0.03) × 10$^{-5}$ M | (37.65 ± 0.44) × 10$^{-5}$ M | Non-competitive         |       |
| Nepetin                  |              |          | (1.18 ± 0.02) × 10$^{-5}$ M | (37.65 ± 0.44) × 10$^{-5}$ M | Non-competitive        |       |
| Quercetin-3-O-α-L-rhamnopyranoside-2”-gallate | Flavonoid | Potentilla anserina (rhizome) | 1.05 ± 0.03 µM  | 28.06 ± 0.82 µM                        | Competitive               | [97] |
| Quercetin-4’-O-glucoside | Flavonoid    | Allium cepa (peel) | 31.4 ± 0.8     | 51.8 ± 10.3                           |                          | [109] |
| Myricetin-3-O-(2”-O-galloyl)-α-L-rhamnoside | Flavonoid | Morella rubra (leaves) | 1.32 ± 0.17 µM | 369.15 ± 6.18 µM                       |                          | [110] |
| Myricetin-3-O-(4”-O-galloyl)-α-L-rhamnoside | Flavonoid | Rubus corchorifolius (fruit) | 4.96 ± 0.54 µM | 1.93 ± 0.08 µM                       | Non-competitive           | [111] |
| Quercetin-7-O-β-D-glucopyranoside | Flavonoid | Caesalpinia paraguariensis (bark) | 5.20 ± 0.15 µM | 1400.00 ± 0.51 µM                      | Non-competitive           | [112] |
| Vitexin                  | Flavonoid    | Natural | 52.80 ± 1.65 µM | 375 ± 12.5 µM                         | Non-competitive           | [113] |
| (-) epigallocatechin-gallate | Flavonoid | Knema globularia (stem) | 0.4 ± 0.1 µM  | 93.6 ± 0.5 µM                         | Non-competitive           |       |
| Calodenin A              | Flavonoid    |          | 0.2 ± 0.1 µM  | 2.0 ± 0.1 µM                          | Non-competitive           |       |
| Globunone A              | Flavonoid    |          | 1.6 ± 0.2 µM  | 2.9 ± 0.2 µM                          | Non-competitive           |       |
| Globunone B              |              |          |              | 3.2 ± 0.2 µM                           | Non-competitive           |       |
| Globunone C              |              |          |              | 5.6 ± 0.9 µM                           | Non-competitive           |       |
| Globunone F              |              |          |              | 3.4 ± 0.16 µM                          | Non-competitive           |       |
| Dehydrolophorine C      | Triterpenoid  | Ganoderma hainanense | 5 ± 0.15 µM  | 489.6 ± 51.4 µM                       | Non-competitive           |       |
| Lophizophore P           | Triterpenoid  | Akebia trifoliata | 9 µM       | 409 µM                                | Non-competitive           |       |
| Scolopiane A             | Triterpenoid  | Nuxia oppositifolia | 62.3 ± 2.4 µg/mL | 38.1 ± 3.1 µg/mL                      | Non-competitive           |       |
| Akebonic acid            |              | Cyclocarpha paliurus (leaves) | 2.22 ± 0.13 µM t | -                                      | Non-competitive           |       |
| 3-oxolupalen             | Triterpenoid  | Cyclocarpha paliurus (leaves) | 2.22 ± 0.13 µM t | -                                      | Non-competitive           |       |
| Katonomic acid           |              |                  |              | 248 ± 2 µM                            | Non-competitive           |       |
| Cypaliruside J           | Triterpenoid Saponin | Palium spina-christi Mill. (fruit) | 6561 ± 207 µM | -                                      | Non-competitive           |       |
| Betulin and betulinic acid mixture | Triterpenes | Palium spina-christi Mill. (fruit) | 248 ± 2 µM | 248 ± 2 µM                            | Non-competitive           |       |
| Andrographolide          | Diterpenoid   | Commercial | 11.0 ± 0.28 mg/mL | 6.2 ± 0.33 mg/mL                      | Non-competitive           |       |
| Name of Plants/Compounds                        | Extract/Class | Source                  | IC$_{50}$       | IC$_{50}$ of Positive Control (Acarbose) | Mode or Type of Inhibition | Ref. |
|-----------------------------------------------|---------------|-------------------------|-----------------|------------------------------------------|----------------------------|------|
| Ent-atisane-3-oxo-16β,17-acetonide            | Diterpenoid   | Euphorbia antiquorum    | 69.62 µM        | 332.5 µM                                  | Non-competitive            | [118]|
| Taxumariene F                                 | Diterpenoid   | Taxus mairei            | 3.7 ± 0.75 µM   | 155.86 ± 4.12 µM                         | -                          | [119]|
| Gauluecin E                                   | Diterpenoid   | Gaultheria leucocarpa var. yunnanensis | 319.3 µM | 387.8 µM                                  | -                          | [120]|
| Tergic acid dilactone                         | Polyphenols   | Eugenia jando-lana      | 5.0 ± 0.34 µM   | 289.9 ± 6.67 µM                          | -                          | [121]|
| ellagic acid                                  |               |                         | 87.30 ± 0.78 µM |                                          | Mixed                      |      |
| 3-O-methyllellagic 3,3′-O-dimethyllellagic acid|               |                         | 65.10 ± 0.56 µM |                                          | Mixed                      |      |
| 4-O-β-D-xylpyranoside                         |               |                         | 73.03 ± 0.1 µM  |                                          | Non-competitive            | [113]|
| Ellagic acid                                  | Phenolic aldehyde | Commercial            | 28.34 ± 0.89 mg/mL | 0.52 ± 0.08 mg/mL | Mixed type non-competitive | [122]|
| Vanlin                                        | Polysaccharides | Wheat bran             | 0.38 mg/mL      | 0.14 mg/mL                                | Mixed                      | [123]|
| WXN-1                                         |               |                         | 1.17 mg/mL      | 0.14 mg/mL                                | -                          |      |
| S. fusiforme polysaccharide (SFP-1)           | Polysaccharides | Sargassum fusiforme    | 0.681 mg/mL     | 1.308 mg/mL                               | Mixed                      | [124]|
| S. fusiforme polysaccharide (SFP-7-40)        | Polysaccharides | Sargassum fusiforme    | 0.304 mg/mL     | 0.657 mg/mL                               | Non-competitive            | [125]|
| Procyanidin A2                                | Tannin        | Wendlandia glabrata    | 0.47 µM         | 586.6 µM                                  | -                          | [126]|
| Dieckol                                       | Tannin        | Ecklonia cau           | 0.24 ± 0.056 mM | 1.05 ± 0.03 mM                           | -                          | [127]|
| 1,2,3-tri-O-galloyl-1-β-D-glucopyranose       | Gallotannins  | Euphorbia fischeriana  | 15.48 ± 0.60 µM |                                          | Mixed                      | [128]|
| Rhaponticin                                   | Stilbene      | Polygonum multiflorum  | 0.3 µM          | 50.04 µM                                  | -                          | [129]|
| S. fusiforme polysaccharide (SFP-7-40)        | Stilbene      | Cyperus rotundus (rhizome) | 94.3 ± 6.8 µM | 2060 ± 97.5 µM                           | -                          | [130]|
| Pelargonidin-3-O-rutinoside                   | Anthocyanin   | strawberries           | 1.69 µM         | 356.26 µM                                 | Mixed                      | [131]|
| Cynanidin                                     | Anthocyanin   | Cinnamomum camphora    | 5.291 × 10$^{-3}$ mM | 1.644 mM | Non-competitive | [132]|
| Alaternin                                     | Anthraquinone | Cassia obtusefolia    | 3.45 µM         | 191.4 µM                                  | -                          | [133]|
| Chysaladin                                    | Anthraquinone | Aloe vera              | 13.4 ± 1.5 µM   | 124.0 ± 3.1 µM                           | Competitive                | [134]|
| Parmosidone I                                 | Depsidone     | Parmotrema tsaoense    | 10.7 µM         | 449 µM                                    | -                          | [135]|
| Gymnepregoside F                             | Pregnan glycoside | Gymnema isodorum (leaves) | 63.7 ± 3.9% at 200 µM |                                          | -                          | [136]|

**Table 3. Cont.**
| Name of Plants/Compounds | Extract/Class | Source | IC$_{50}$ | IC$_{50}$ of Positive Control (Acarbose) | Mode or Type of Inhibition | Ref. |
|--------------------------|--------------|--------|-----------|-----------------------------------------|----------------------------|------|
| 3β,8β,14β,20-tetrahydroxy-(20S)-pregn-5-ene-3-O-β-D-glucopyranosyl-(1→4)-O-β-D-| Pregnane glycoside | *Caralluma hexagona* | 0.67 ± 0.01 mM | 0.81 ± 0.86 mM | - | [137] |
| 20-3-O-isoval-β-D-glucopyranoside | | | | | | |
| Mulberrofuran K | Chalcone derivatives | *Morus macroura* | 1.25 µM | 1428 µM | - | [138] |
| Mulberrofuran K | 2-(3′,4′-dihydroxyphenyl)-2,3-dihydro-4,6-dihydroxy-2-(methoxy)-3-benzofuranone | *Hylotelephium erythrostictum* | 1.8 µM | 822.9 µM | - | [139] |
| Fucoxanthin | Xanthophyll | *Undaria pinnatifida* | 0.047 ± 0.001 mg/mL | 0.6 ± 0.01 mg/mL | Mixed type | [93] |
| Mangoxanthone A | Xanthones | *Garcinia mangostana* (pericarp) | 29.06 ± 1.86 µM | - | - | [140] |
4.1. Flavonoids

Flavonoids are polyphenolic metabolites that are often present in plants as different glycosides. Typically, they consist of two phenyl rings and one heterocyclic ring in a 15-carbon phenolic structure. They include different subgroups as flavones, isoflavones, flavans, flavanones and flavonols [141]. Flavonoids play an important role in carbohydrate metabolism. Several flavonoid molecules are found to be more effective at inhibiting α-glucosidase.

Le et al. discovered six globunones A-F, two new flavonoids and nine other known compounds that displayed potent inhibition of α-glucosidase with IC$_{50}$ values between 0.4 and 26.6 µM. When compared to acarbose (IC$_{50}$ = 93.6 µM), the well-known flavonoid compound Calodenin A (Figure 4a) (IC$_{50}$ = 0.4 µM) had the greatest effect and exhibited a non-competitive mode of action during kinetic studies [114]. Similarly, Sgariglia et al. [113] isolated five polyphenolic derivatives from the bark of Caesalpinia paraguariensis. Among them, (-) epigallocatechin-gallate (Figure 4b) (IC$_{50}$ = 5.2 ± 0.15 µM) showed the most significant inhibitory effect against α-glucosidase, which was almost 270-fold higher than the control acarbose (IC$_{50}$ = 1400.0 ± 0.51 µM).

Recently, two myricetin-derived flavonols, myricetin-3-O-(2”-O-galloyl)-α-L-rhamnoside (IC$_{50}$ = 1.32 µM) (Figure 4c) and myricetin-3-O-(4”-O-galloyl)-α-L-rhamnoside (IC$_{50}$ = 1.77 µM), were isolated from Morella rubra. These compounds had a 100-fold stronger inhibitory impact on α-glucosidase enzymes than acarbose (IC$_{50}$ = 369 µM). According to the molecular docking analysis, the flavonol–enzyme binding was improved due to pi-conjugations between the galloyl functional group and key residues of α-glucosidase at the active site, which may help to explain the significantly higher activity of these two compounds [110]. Even though the in vitro α-glucosidase assay produced encouraging results, further research must be conducted on the preclinical safety and toxicity assessment of these compounds before considering them as potential anti-diabetic medication candidates.

4.2. Terpenoids

Terpenoids are vitally important plant metabolites that are required for both abiotic and biotic stress resistance as well as growth and development. The structural units of terpenoids are composed of isoprene and its derivatives [142]. Based on the isoprene unit number present in the structures, they can be categorized into monoterprenoids, diterpenoids, triterpenoids and sesquiterpenoids [143]. These terpenoids possess anti-cancer, anti-inflammatory and antimicrobial properties [144]. Terpenoid-based drugs such as Taxol (anti-cancer) and Artimesinin (anti-malarial) are commercially available. Lately, researchers have been encouraged to explore terpenoid molecules for anti-diabetic properties.

Two abietane-type diterpenoids, gauleucin E (Figure 5a) and margoclin derived from Gaultheria leucocarpa var. yunnanensis displayed α-glucosidase inhibitory efficacy with IC$_{50}$ of 319.3 and 327.9 µM, respectively [120]. Similarly, Chen and his co-workers (Chen et al.,
2020) reported seven new taxane diterpenoids, taxumarienes A–G from Taxus mairei, and assessed their α-glucosidase inhibitory activities. In comparison to the control substance acarbose (IC50 = 155.86 ± 4.12 µM), taxumariene F (Figure 5b) showed highest inhibitory effects, with an IC50 = 3.7 ± 0.75 µM. Taxumariene F’s significant inhibitory activity was ascribed to the 6/8/6 tricyclic system along with 4(20)-epoxide ring and C-9 acetoxy group. Recently, Yuca et al. evaluated the antidiabetic properties of the triterpenes isolated from Paliurus spina-christi mill fruit. Interestingly, the mixture of betulin (Figure 5c) and betulinic acid (Figure 5d) mixture (IC50 = 248 ± 12 µM) inhibited α-glucosidase 26 times better than acarbose (IC50 = 6561 ± 207 µM) [85]. In light of these findings, it may be intriguing to study the synergistic and antagonistic effects of various terpenoid compounds on α-glucosidase inhibition. Therefore, additional studies, such as kinetics studies and structure–activity relationship (SAR) studies, are essential to comprehend the underlying mechanisms for different terpenoid molecules to inhibit α-glucosidase.

Figure 5. Chemical structure of some of the reported terpenoids as α-glucosidase inhibitors; (a) Gauleucin E, (b) Taxumariene F, (c) Betulin, and (d) Betulinic acid.

4.3. Phenolic Acids and Their Derivatives

Phenolic acids are a group of bioactive molecules ubiquitous in plants. Their structure consists of functional carboxylic acid groups attached to aromatic phenols. Depending on the number and position of hydroxyl groups, phenolic acids can be classified into cinnamic and benzoic acid derivatives. These natural compounds are powerful antioxidants against free radicals and other reactive oxygen species (ROS) [145,146].

Tergallic acid dilactone isolated from Eugenia jambolana exhibit potent α-glucosidase inhibitory properties with IC50 5.0 ± 0.34 µM, which is 50 times higher than the positive control [121]. Aleixandre et al. [147] investigated the interactions between phenolic acids and α-glucosidase or the substrate by using different conditions such as the preincubation of phenolic acids with the enzyme or substrate and starch gelation in the presence of phenolic acid. Their studies revealed that, in comparison to phenolic acids with more hydroxyl groups, such as caffeic acid (Figure 6a) (IC50 = 0.39 ± 0.02 mM), phenolic acids with fewer hydroxyl groups such as vanillic acid (Figure 6b) (IC50 = 8.38 ± 0.01 mM) showed better inhibition against α-glucosidase. Similarly, Sgariglia et al. [113] reported ellagic acid and its derivatives isolated from Caesalpinia paraguariensis and performed in silico structure–activity relationship studies to evaluate the molecular interactions between α-glucosidase and the inhibitors. Ellagic acid (Figure 6c), 3-O-methyllellagic, 3,3’-O-dimethyllellagic acid and 3,3’-O-dimethyllellagic-4-O-β-D-xylopyranoside show good α-glucosidase inhibition activity with IC50 value of 87.3, 65.1, 73.03, and 263.05 µM, respectively, which are much lower than acarbose (IC50 = 1400 µM). Such promising results make them a potential candidate for lead optimization. However, further research is required to assess their toxicity.
4.4. Polysaccharides

Polysaccharides are one of the major classes of biomacromolecules, which comprises long chains of several smaller monosaccharides. They are found in a variety of plants and animals. Growing research evidence suggests that plant-derived polysaccharides exhibit a range of biological activities with low or no toxicity [148]. Additionally, the composition of monosaccharides, glycosidic linkage and molecular weight of the polysaccharides could affect their bioactivity [149,150].

Recent evidence from the literature revealed that polysaccharides from different plant species could inhibit α-glucosidase activity [88,122,151]. A polysaccharide fraction, AXA-1, isolated from wheat bran showed a potential non-competitive mode of inhibitory effects against the α-glucosidase enzyme [123]. Zheng et al. [125] investigated the α-glucosidase inhibitory activity of several polysaccharides extracted from Sargassum fusiforme at different pH conditions. According to the study, SEP-7-40, which has relatively high levels of xylose and galacturonic acid and low molecular weight, exhibits a considerable inhibitory effect ($IC_{50} = 0.304 \text{ mg/mL}$). Similarly, an acidic polysaccharide, SFP-1, isolated from Sargassum fusiforme inhibits α-glucosidase significantly ($IC_{50} = 0.681 \text{ mg/mL}$) in a mixed-type inhibition mode [124]. Such potential α-glucosidase inhibitory effects shown by polysaccharides in combination with their low toxicity could be promising in the development of drugs against diabetes mellitus. Therefore, further and more organized research work is essential to understand the therapeutic role of polysaccharides in the treatment of diabetes mellitus.

4.5. Tannins

Tannins are polyphenolic natural compounds, which play a major role in carbohydrate metabolism [152]. They can be categorized into hydrolyzable tannins and condensed tannins. Tannins have strong anti-oxidant properties that are beneficial in the dietary and healthcare industries. Tannins are widely used in the dietary, leather and chemical industries due to their abundancy in raw materials, chemical reactivity and safe extraction [153,154].

Sheikh et al. [126] studied the role of tannin, procyanidin A2 (Figure 7a) in the post-prandial management of diabetes mellitus. The study revealed that procyanidin A2 exhibits significant α-glucosidase inhibitory activities ($IC_{50} = 0.27 \pm 0.01 \mu \text{g/mL}$). It also significantly reduced elevated G-6-Pase and mRNA levels in diabetic mice. Another study conducted by Zhang et al. [128] revealed that gallotannins isolated from Euphorbia fischeriana steud have antidiabetic potential. Specifically, 1,2,3-tri-O-galloyl-β-D-glucopyranose (Figure 7b) showed the most significant and highly selective α-glucosidase inhibitory effect. Additional SAR studies have indicated that the galloyl and glucopyranosyl groups are crucial in the inhibition of α-glucosidase. Despite these promising results, more thorough research on the mechanism and in vivo evaluations are still needed. Overcoming these drawbacks is essential in developing tannin-based significant α-glucosidase inhibitors.
4.6. Other Secondary Metabolites

Besides flavonoids, terpenoids, phenolic acids, tannins and polysaccharides, there are many other classes of secondary metabolites, which have been reported with significant α-glucosidase inhibitory properties. Other bioactive molecules include stilbene, anthocyanin, anthraquinone, xanthones, chalcone derivatives, pregnane glycosides, etc. [129,131,133,136,138].

J. Chen et al. [132] investigated cyanidin and its derivatives isolated from the fruit of *Cinnamomum camphora* for in vitro α-glucosidase inhibitory activities. Significantly higher inhibition was observed with cyanidin (IC$_{50} = 5.293 \times 10^{-3}$ mM) (Figure 8a) in comparison to acarbose (IC$_{50} = 1.644$ mM). Kim et al. [134], explored aloe vera plants and isolated various bioactive metabolites using chromatographic techniques, and they investigated their inhibitory mechanism of them on α-glucosidase. Chysalodin (Figure 8b), an anthraquinone dimer, has the greatest ability to block α-glucosidase of all of them. The kinetic analysis further showed that chysalodin competes with the substrate of α-glucosidase for binding to the active region of the receptor.

Other metabolites, depsidones isolated from lichen *Parmotrema tsavoense*, have been reported to inhibit α-glucosidase. All five new depsidones, parmosidones F–J (Figure 8c), showed significantly higher α-glucosidase inhibition with IC$_{50}$ values ranging from 10.7 to 17.6 µM in comparison...
Another new pregnane glycoside compound, 3β,8β,14β,20-tetrahydroxy-(20S)-pregn-5-ene-3-O-β-D-glucopyranosyl-(1→4)-O-β-D-digitaloside-20-O-3-isoval-β-D-glucopyranoside (Figure 8d), isolated from *Camalluma hexagona* Lavranos, was found to be a good α-glucosidase inhibitor (IC$_{50} =$ 0.67 ± 0.01 µM) [137].

Another study conducted by Zaharudi and his co-workers identified fucoxanthin (Figure 8e) from *Undaria pinnatifida* as a potential α-glucosidase inhibitor, with IC$_{50}$ of 0.047 ± 0.001 mg/mL, which is 12-fold higher than that of acarbose (IC$_{50} =$ 0.6 ± 0.01 mg/mL) [93]. Similarly, Quan et al. [139] reported another potential α-glucosidase inhibitor from the perennial herb, *Hylotelephium erythrostictum*. The isolated bioactive compound, 2-(3′, 4′-dihydroxyphenyl)-2, 3-dihydro-4, 6-dihydroxy-2-(methoxy)-3-benzofuranone (Figure 8f) (IC$_{50} =$ 1.8 µM) showed 457 times more inhibition than acarbose (IC$_{50} =$ 822.9 µM) and showed a competitive mode of inhibition toward the α-glucosidase substrate. Recently, Yang et al. [140] reported new prenylated xanthone, mangoxanthone A, (Figure 8g) isolated from *Garcinia mangostana*, with moderate α-glucosidase inhibitory activity with IC$_{50}$ of 22.74 ± 2.07 µM.

These results and conclusions, however, are derived based on the reactions to α-glucosidase in vitro and may not accurately represent the processes involved in vivo. Despite the fact that numerous bioactive substances with various structural moieties display notable α-glucosidase inhibitory activity, the pharmacodynamics behind their inhibition remain unexplored. Therefore, comprehensive and detailed research is required to assess the toxicity, potential drug interactions and long-term side effects of these reported compounds to develop them as α-glucosidase inhibitors for the treatment and management of diabetes mellitus.

5. Conclusions

Diabetes mellitus is a carbohydrate metabolic disorder caused by decreased insulin production or increasing insulin resistance. Herbal remedies for diabetes have been utilized in patients with insulin-dependent and insulin-independent diabetes, diabetic peripheral neuropathy, diabetic retinopathy and other diabetic-related conditions. According to the research on their potential effectiveness against diabetes, natural compounds have a significant role to play in diabetes care, which requires additional investigation for drug development and nutraceuticals from natural plant resources. However, many herbal medicines in use today have not been well researched, and some have the capacity to induce significant adverse effects and substantial drug-to-drug interactions. To understand the pharmacological activity of herbal treatments presently being used in traditional folk medicine to treat diabetes mellitus, further study is required. Although a tremendous effort has been made by scientists to analyze the antidiabetic effects of several natural products, shortcomings are still remaining. Most of the research focuses on the in vitro studies of natural products with fewer researchers conducting in vivo studies and further pharmaceutical advanced studies. Moreover, there is a need for more structural insight into the interaction between glucosidases and the promising anti-diabetic drug targets, which can have great value in new anti-diabetic drug discoveries. The goal of this review paper is to summarize the most recent discoveries in research on natural products that act as α-glucosidase enzyme inhibitors. Indeed, reducing postprandial hyperglycemia is one therapeutic strategy for diabetes in its early stages. This is accomplished by slowing glucose absorption in the digestive system by inhibiting the carbohydrate-hydrolyzing enzymes α-glucosidases. Therefore, inhibitors of these enzymes reduce the rate of glucose absorption, hence dampening the postprandial plasma glucose spike. This study reviews over forty extracts collected using various solvents and more than fifty natural products. This review’s insight should contribute to the ultimate objective of discovering new therapeutic medications with greater efficacy and safety for the treatment of type 2 diabetes or to avoid hyperglycemia.

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