Recent Progress on Natural α-glucosidase Inhibitors Derived from the Plants and Microorganisms

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Abstract: α-Glucosidase inhibitors (AGIs) showcase versatile biochemical activities with respect to antidiabetic, anticancerous, antiobese and antiviral effects. They have drawn a great deal of attention from the scientific community. While α-glucosidase inhibitors are mostly discovered from plants and microorganisms, the recent advance in natural α-glucosidase inhibitors over the past five years has been reviewed in this article, and 139 distinct α-glucosidase inhibitors from the plants and microorganisms were classified into ten groups based on their chemical structures, including flavonoids (34), xanthones (6), alkaloids (8), benzopyrones / benzofuranones (8), terpenes (23), saponins (8), phenols / alcohols (25), esters (18), chalcone (5) and other compounds (4). In this review, we mainly focused on the novel chemical structures and the various biological activities of theses natural AGIs. Some of the selected natural compounds exhibit powerful α-glucosidase inhibitory activity and anti-tumor activity, may hold promise to become the candidate drugs for treating type II diabetes and cancer in future.

Keywords: α-glucosidase inhibitors; diabetes mellitus; anticancer; flavonoid; biological activity; hypoglycemic

1 INTRODUCTION

Diabetes is one of the most common metabolic diseases in the world and is a disease that causes blood sugar levels to rise due to abnormal insulin operation, leading to various complications and developing into more severe diseases[1-4]. According to the International Diabetes Federation (IDF) reported in their 2021 Diabetes Atlas, there were a total of 537 million diabetes cases worldwide[5-8]. It is predicted that because of many people's unhealthy lifestyles, the global incidence of diabetes is rapidly increasing and it is estimated that the number of diabetes cases will reach 578 million by 2030[9-11]. Diabetes is caused by insufficient insulin secretion from pancreatic B cells or damage to normal glucose homeostasis on account of insulin resistance. Patients generally have serious complications, including cardiovascular disease, neuropathy, retinopathy, and renal failure[12-14]. In addition, diabetes patients have a higher risk of developing tumors than people without diabetes[15], indicating that diabetes poses a serious threat to human health[16-18].

In clinical practice, diabetes can be classified into type I and type II. Type I diabetes, also known as insulin-dependent diabetes, mainly occurs in children and adolescents[19]. Type II diabetes is characterized by impaired B-cell function and insulin secretion, high blood sugar, and insulin resistance, resulting in insufficient insulin secretion and the onset of the disease[20-22]. Type II diabetes accounts for 90-95% of all cases, and obesity, lack of exercise, and Vitamin D deficiency are major risk factors for its onset and progression[23]. So far, scientists have not yet found a clear treatment for diabetes and an effective mechanism to regulate metabolic disorders related to diabetes. Traditional drugs for type II diabetes include sulfonylureas such as Glimepiride, Metformin from the biguanide class, and thiazolidinediones such as Pioglitazone. Although these drugs can effectively control the postprandial blood sugar level of diabetic patients, some of them also have obvious side effects[24, 25]. For instance, Metformin may cause digestive system reactions such as bloating and diarrhea, while sulfonylureas may lead to low blood sugar and weight loss. Later, α-glucosidase inhibitors such as Acarbose (**1**), Miglitol (**2**), and Voglibose (**3**) were developed and used in the treatment of type II diabetes (Figure 1) [26, 27]. As shown in Figure 1, Acarbose is a pseudotetrasaccharide, while both Miglitol and Voglibose are iminosugars. Among them, though Acarbose only exhibits a medium inhibitory activity against α-glucosidase, it is also usually utilized as a major clinical drug for treating type II diabetes, demonstrating the bright prospect of α-glucosidase inhibitors in developing hypoglycemic therapeutic agents. Unlike the aforementioned antidiabetic agents having apparent adverse effects, these drugs only delay, rather than block the absorption of carbohydrates from food intake by inhibiting α-glucosidase, which decreases postprandial blood glucose and insulin peak levels[28]. They are consequently considered as relatively safer and ideal therapeutic agents. However, long-term use of these drugs can also cause gastrointestinal undesirable effects such as diarrhea, bloating, and abdominal discomfort[29]. Therefore, developing more α-glucosidase inhibitors with fewer adverse effects is of great practical significance.

α-Glucosidase is a hydrolytic enzyme on the brush border of small intestine epithelial cells, which cleaves the α-glycosidic bond of oligosaccharides or glycoconjugates at a non-reducing end to release glucose molecules[30, 31]. It is closely related to various biochemical functions, including carbohydrate digestion and absorption, lysosomal glycocon-jugate metabolism, and processing of glycoproteins and glycolipids[32, 33]. Therefore, α-glucosidase inhibitors (AGIs) not only have significant potential in the treatment of diabetes[34-36], but also have broad application prospects in the treatment of other diseases such as obesity[37], Covid-19[38], HBV[39], and tumors[40]. For example, N-butyl-1-deoxynojirimycin (Zavesca) is a drug clinically utilized to treat lysosomal storage disorders such as Gaucher's disease and also serves as an excellent α-glucosidase inhibitor [41]. Besides anti-α-glucosidase activity, in recent years, studies have found that 1-deoxynojirimycin can inhibit the proliferation of cancer cells in a mouse model colon

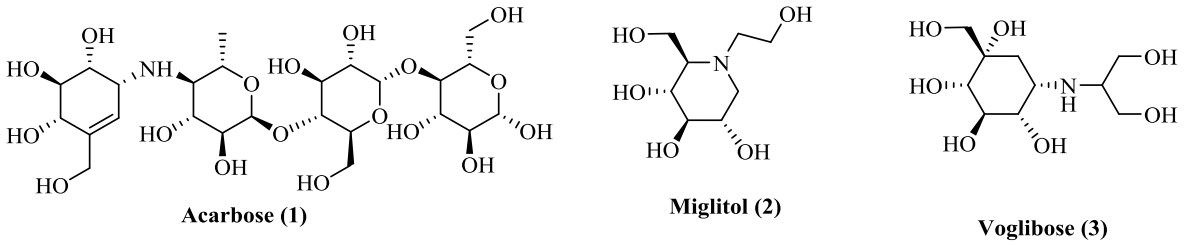


Figure 1. Chemical structures of AGIs-type hypoglycemic drugs currently available on the market (**1-3**).

cancer induced by carcinogens[42]. Therefore, discovery of new, structurally novel, and biologically active α-glucosidase inhibitors can lay the ground for the development of new therapeutic reagents for the treatment of diabetes, cancer, and other diseases.

Natural products are important sources for drug discovery, especially natural small molecules[43, 44]. According to statistics, out of the 1881 drugs newly approved by the US FDA between 1981 and 2019, 1394 were small molecule drugs, of which 431 were derived from natural products or their derivatives, accounting for 23.5% [45]. Specifically, in anti-tumor drugs, out of the 321 anti-tumor drugs approved between 1981 and 2019, 101 were derived from natural products or their derivatives, accounting for nearly one-third. In terms of antihyperglycemic drugs, of the 63 drugs approved between 1981 and 2019, 33 were derived from natural products, natural product derivatives or natural biomacromolecules, which accounted for more than a half. Therefore, natural products are the most promising way to discover new drugs, and screening new α-glucosidase inhibitors from them and developing them into therapeutic drugs makes great sense.

Currently, many studies have confirmed that compounds such as polyphenols, flavonoids, and terpenes are widely distributed in natural resources and have strong α-glucosidase inhibitory activity[46, 47]. Thus, numerous nutritionists suggest that natural α-glucosidase inhibitors in medicinal and food homologous products should be used as alternatives to those drugs having side effects for controlling postprandial hyperglycemia[48]. This article mainly reviews the chemical structures of AGIs, their *in-vitro* α-glucosidase inhibitory activity, enzyme kinetic studies, cytotoxicity of extracts from different plants and microorganisms, antioxidant activity, and summarizes 139 natural compounds from 33 plants and microorganisms having strong α-glucosidase inhibitory activity *in vitro*.

2. NATURALLY OCCURRING α-GLUCOSIDASE INHIBITORS

For centuries, plant-based medicines and extracts from microorganisms have been widely adopted to treat various diseases. Plants, microorganisms and their derivatives also possess versatile pharmacological activities, such as anti-inflammatory[49], antimicrobial[50, 51], anticancer[52-54], and antidiabetic[55-57], etc. Therefore, natural plants proven to be an important source of future drugs for many diseases including diabetes[58], cancer, obesity, and these medicinal plants have become a part of primary healthcare in many developing countries due to their low side effects, easy accessibility, and low cost. It is also pivotal to note that approximately 20% of drugs worldwide come from plants and microorganisms[59], and compounds such as flavonoids, saponins, phenolic acids, terpenes, alkaloids, and lactones are often considered the primary bioactive ingredients of plants[60-62]. So far, many new, safe, and non-toxic natural compounds have been discovered from various plants or microorganisms and can be used as alternative or complementary medicines to treat various chronic diseases[63, 64]. Developing α-glucosidase inhibitors from plant sources has been reported to be more acceptable to a larger patient population and its importance continues to increase worldwide[65].

2.1 FLAVONOIDS

2.1.1 Prenylated isoflavones

Flavonoids are one of the significant types of AGIs, which are widespread in plants. While prenylated isoflavones belong to flavonoid-type AGIs, Lee et al[66] isolated 47 flavones including 16 new compounds from the leaves of *Masclura tricuspidate*. Most of the compounds exhibited strong inhibitory activity against α-glucosidase from baker's yeast, with acarbose (at IC_{50} = 78.2 μM) as a positive control.

Among them, eight new prenylated isoflavones were identified as new compounds. Cudracusisoflavone A (**4**), Cudracusisoflavone B (**5**), Cudracusisoflavone D (**6**), Cudracusisoflavone L (**7**), Cudracusisoflavone M (**8**), Cudracusisoflavone N (**9**), Cudracusisoflavone O (**10**) and Cudracusisoflavone P (**11**), Cudracusisoflavone G (**12**) exhibited powerful inhibitory activity (Figure 2). The IC_{50} values were 16.1, 18.3, 10.2, 8.9, 20.4, 13.7, 11.8 , 17.8 and 17.7 μM, respectively, and the structure-activity relationship was further analyzed through molecular docking analysis. The results showed a good correlation with the experimental results of two types of human maltase glucoamylase (NtMGAM and CtMGAM) and glucosidase, and all

the compounds exhibited strong α-glucosidase inhibitory activity. The molecular docking analysis values for NtMGAM were 5.4, 8.3, 6.8, 7.9, 5.3, 6.8, 7.1, 7.0, 6.4 and 7.0, while those for CtMGAM were 5.9, 6.5, 7.0, 7.8, 8.9, 10.1, 7.4 and 7.3. The study indicated that the leaves of *M. tricuspidate* can serve as a good source of prenylated isoflavonoids with potential blood glucose-lowering effects.

Ye et al[67] isolated 86 compounds from *liquorice stems*, among which a new compound, glycyuralin H (**13**), known compounds 6,8-diprenylgenistein (**14**) (Figure 2), showed good inhibition activity against α-glucosidase from mouse with IC_{50} values of 20.1±1.6 and 16.3±1.8 μM, respectively, using acarbose (IC_{50} = 166.4 μM) as a positive control. Besides, compounds **13** and **14** showed strong inhibition against recombinant human PTP1B enzyme with IC_{50} values of 5.9±0.8 and 2.3±0.1 μM. PTP1B plays a key role in the regulation of insulin signaling, and PTP1B inhibitors have great potential for treating type II diabetes and obesity.

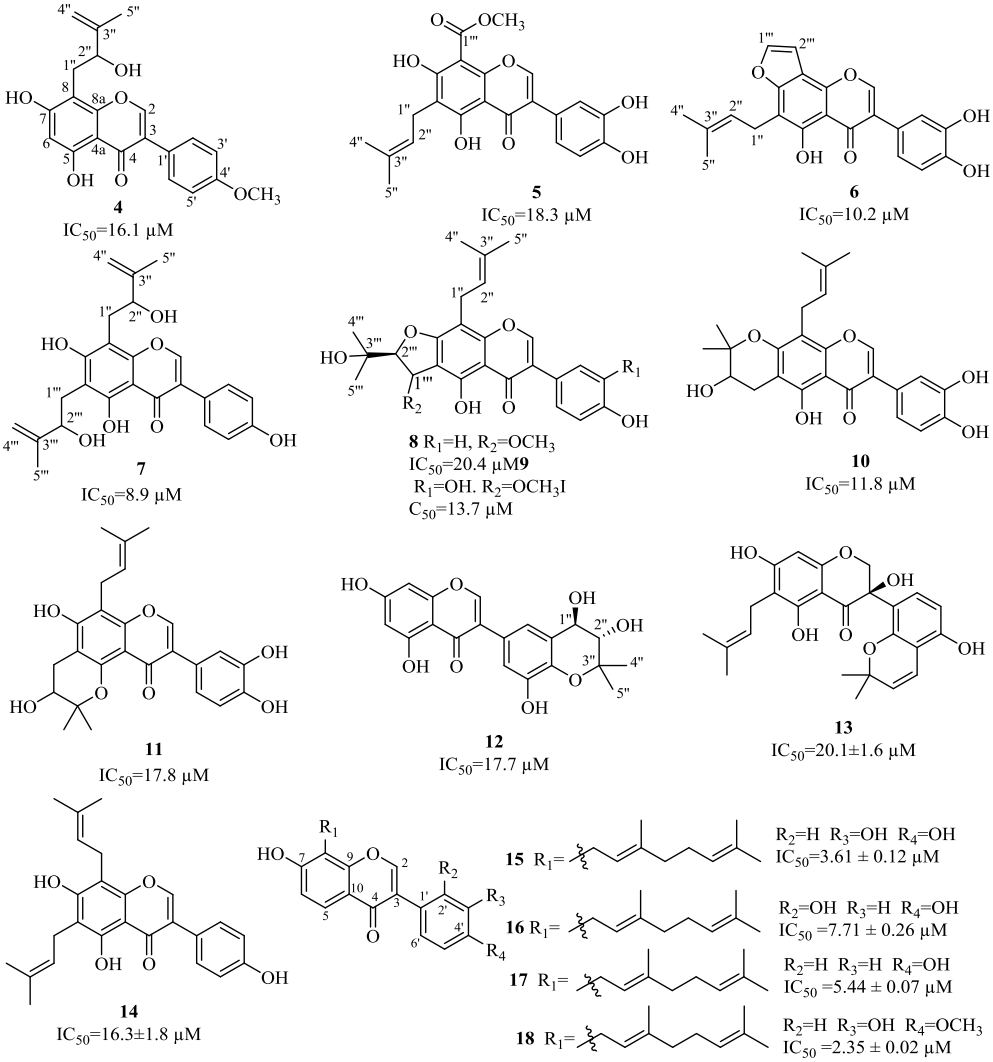


Figure 2. Chemical structures of prenylated isoflavonoid derivatives with strong α-glucosidase inhibition activity isolated from *Masclura tricuspidate, liquorice stems* and *Pueraria lobata* (**4-18**).

Apart from the aforementioned isoflavonoids, Tong et al [68] conducted a study on potential α-glucosidase inhibitors in *Pueraria lobata.* They isolated eight known compounds and two new compounds from the plant and evaluated their hypoglycemic activity. The two new compounds 8-geranyl-7,3',4'-trihydroxy-isoflavone (**15**) and 8-geranyl-7,2',4'-trihydroxy-isoflavone (**16**), along with the known compounds 8-geranyl-7,2′-dihydroxy-isoflavone（**17**）[69] and 8-geranyl-7,3′-dihydroxy-4′-methoxyisoflavone（**18**）[70]（Figure 2）showed excellent inhibitory activity against α-glucosidase when compared to the positive control acarbose ($IC_{50} = 4.1 \pm 0.09 \times 10^{-3}$ μM). The IC_{50} values for the compounds were 3.61 ± 0.12, 7.71 ± 0.26, 5.44 ± 0.07, and 2.35 ± 0.02 μM, respectively. Molecular docking simulations revealed that the geranyl group may be an important functional group contributing to the α-glucosidase inhibition. The results of 3D docking showed that the selected compounds as well as acarbose bound to the enzyme nearly in a same active cavity and formed stable complexes. However, the results of 2D docking suggested that the interaction mechanism of the selected compounds with the enzyme was

different from acarbose. Acarbose showed a binding affinity for α-glucosidase of −7.3 kcal/mol, while the binding affinity values for compounds **15-18** were −8.2、−8.8、−8.1 and −8.0 kcal/mol, respectively, indicating they formed more stable complexes with α-glucosidase than acarbose.

2.1.2 Prenylated flavonoids

Ye et al[67] isolated 86 compounds from *liquorice stems*, glyasperin A (**19**) (Figure 3), showed good inhibition activity against α-glucosidase from mouse with IC_{50} values of 3.2±0.1 μM, respectively, using acarbose (IC_{50} = 166.4 μM) as a positive control. Do et al[71] isolated three new flavonoids and four known compounds from the stem bark of *Melodorum fruticosum* and tested their α-glucosidase inhibitory activity using acarbose as a positive control (IC_{50} = 179 ± 6.02 μM). Among them, the new compounds melodorones A-C (**20**-**22**) and the known chrysin (**23**)[72] (Figure 3), displayed potent inhibitory activity against α-glucosidase from brewer's yeast, with IC_{50} values of 2.59 ± 0.15, 3.33 ± 0.28, 4.00 ± 0.20 and .67 ± 0.25 μM, respectively. The researchers further evaluated the *in-vitro* cytotoxicity of all compounds against three human cancer cell lines (KB, HepG2, and MCF7) using the MTT assay, with rotenone (IC_{50} = 0.31 ± 0.05, 0.33 ± 0.05 and 0.40 ± 0.05 μM) as the positive control, and found that compound **20** exhibited moderate cytotoxicity against all three cancer cell lines with IC_{50} values of 23.5, 19.8 and 23.7 μM. Compound **21** exhibited moderate cytotoxicity against all three cancer cell lines with IC_{50} values of 62.1 ± 4.5, 44.8 ± 4.0 and 73.7 ± 2.8 μM. Compound **22** also had moderate activity against KB and HepG2 cell lines with IC_{50} values of 59.0 and 80.0 μM, respectively. Compound **23** showed certain cytotoxicity against HepG2 and MCF7 cell lines with IC_{50} values of 50.55 and 37.20 μM, respectively. This study suggested that these compounds which exhibited both alpha-glucosidase inhibitory activity and anti-cancer activity, may serve as dual target therapeutic drugs.

2.1.3 Phenols and diphenols

Another flavonoid-type AGIs are phenols and diphenols, Chavasiri et al[73] isolated 17 flavonoid compounds from the stem of *Knema globularia*, including four new Globunones, named Globunone F (**24**), Globunone A (**25**), Globunone B (**26**) and Globunone C (**27**) (Figure 4). They showed extremely potent inhibitory activity against α-glucosidase from commercial yeast *in vitro*, with IC_{50} values of 26.6 ± 1.8, 2.0 ± 0.1, 1.6 ± 0.2 and 1.4 ± 0.1 μM, respectively, compared with the positive control acarbose (IC_{50} = 93.6 ± 0.5 μM). Compounds **25**-**27** had α-glucosidase inhibitory activity with IC_{50} values around 2 μM, and should be hopeful as important lead compounds for the development of anti-hyperglycemic drugs.

Kanokmedhakul et al[74] isolated six new compounds, two previously unreported compounds, and 23 known compounds from *Phyllanthus mirabilis*, and assessed the α-glucosidase inhibitory activity of all compounds. One of the new flavonoid derivatives (−)-taxifolin-3-O-gallate (**28**) (Figure 4), exhibited inhibitory activity against yeast α-glucosidase with an IC_{50} value of 12.40 ± 0.05 μM, as compared to the positive control acarbose (IC_{50} = 71.65 ± 0.66 μM), indicating nearly 6-fold better inhibitory activity than the positive control. Carvrene-containing flavonoid and its derivatives Carvrene-containing flavonoid and its derivatives also consist of flavonoid-type AGIs. Huang et al[75] isolated one new flavonoid derivative with a monoterpenoid substituent and five known compounds from the rhizomes of *Ficus tikoua*, and tested their α-glucosidase inhibitory activities. Among them, the new compound ficusin C (**29**) and the known compound 6-[(1R*,6R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5,7,4'-trihydroxyiso-flavone (**30**)[76] (Figure 5), showed moderate inhibitory activities against α-glucosidase with IC_{50} values of 62.4 ± 6.9 and 32.5 ± 6.7 μM, respectively, using acarbose as a positive control. Furthermore, both compounds exhibited antioxidant activities with EC_{50} values of 49.3 ± 7.8 and 43.3 ± 6.9 μM, respectively, using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay with gallic acid methyl ester as a positive control (EC_{50}=1.8 ± 0.5 μM).

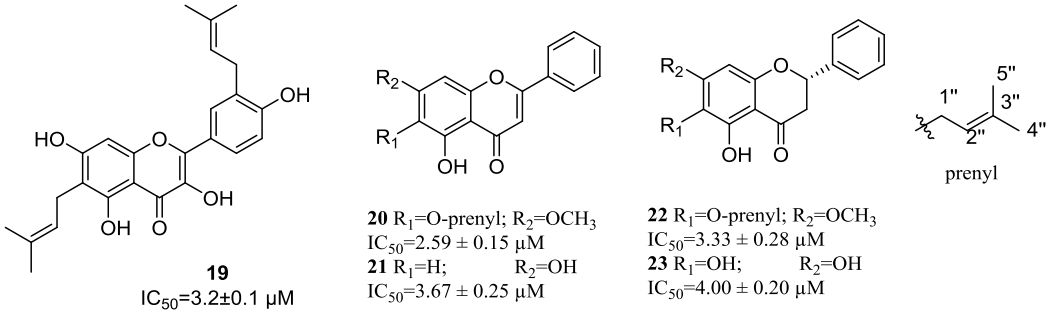
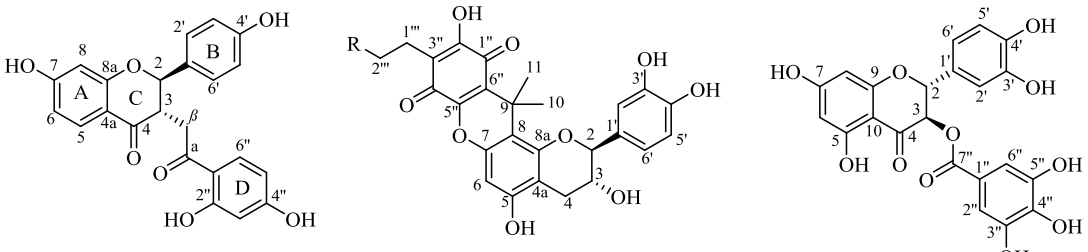


Figure 3. Chemical structures of prenylated flavonoid derivatives with strong α-glucosidase inhibition activity isolated from *liquorice stems* and *Melodorum fruticosum* (**19**-**23**).

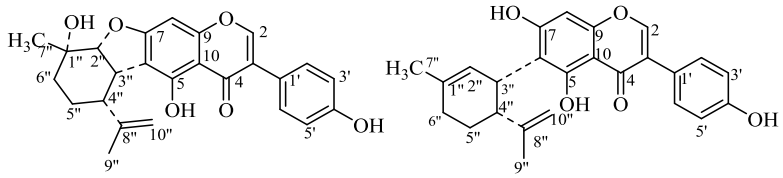


24
IC_{50} =26.6±1.8 μM

25 R= n-C_9H_{19} IC_{50} =2.0±0.1 μM
26 R= n-$C_{11}H_{23}$ IC_{50} =1.6±0.2 μM
27 R= n-$C_{13}H_{27}$ IC_{50} =1.4±0.1 μM

28
IC_{50}=12.40 ± 0.05 μM

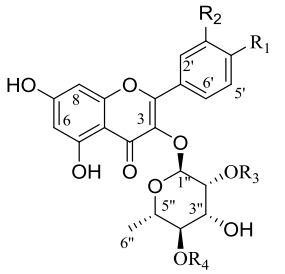
Figure 4. Chemical structures of phenol and diphenol flavonoid derivatives with strong α-glucosidase inhibition activity isolated from *Knema globularia* and *Phyllanthus mirabilis* (**24**-**28**).



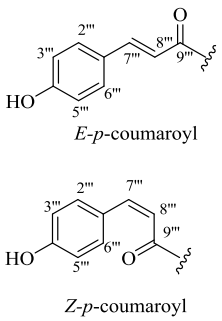
29
IC_{50}=62.4 ± 6.9 μM

30
IC_{50}=32.5 ± 6.7 μM

Figure 5. Chemical structures of flavonoid derivatives containing apigenin from the rhizomes of *Ficus tikoua* with strong α-glucosidase inhibition activity (**29**, **30**).



31 R_1=OCH_3,R_2=OH, R_3=*E-p*-coumaroyl,R_4=*Z-p*-coumaroyl
IC_{50}= 28.2 ± 0.00 μM
32 R_1=OCH_3, R_2=H, R_3=*Z-p*-coumaroyl, R_4=*Z-p*-coumaroyl
IC_{50}=5.9 ± 0.01 μM
33 R_1=OCH_3, R_2=H, R_3=*E-p*-coumaroyl, R_4=*Z-p*-coumaroyl
IC_{50}=6.8 ± 0.00 μM
34 R_1=OCH_3, R_2=H, R_3=*Z-p*-coumaroyl, R_4=*E-p*-coumaroyl
IC_{50}=10.1 ± 0.00 μM
35 R_1=OH,R_2=H, R_3=*E-p*-coumaroyl, R_4=*Z-p*-coumaroyl
IC_{50}=16.1±0.01 μM
36 R_1=OH,R_2=H, R_3=*E-p*-coumaroyl, R_4=*E-p*-coumaroyl
IC_{50}=12.9±0.00 μM
37 R_1=OCH_3, R_2=H, R_3=*E-p*-coumaroyl, R_4=*E-p*-coumaroyl
IC_{50}=26.9±0.01 μM



E-p-coumaroyl

Z-p-coumaroyl

Figure 6. Chemical structures of L-rhamnose flavonoid derivatives with strong α-glucosidase inhibition activity from *Machilus litseifolia* (**31**–**37**).

2.1.4 Flavonoid glycosides

The last flavonoid-type AGIs are flavonoid containing glycosides. Staerk et al[77] isolated 13 *L*-phenolic glycosides from *Machilus litseifolia*, including ten compounds reported for the first time. They conducted α-glucosidase inhibitory activity tests, and the new compounds tamarixetin 3-O-(2″-*E*-*p*-coumaroyl,4″-*Z*-*p*-coumaroyl)-*α*-*L*-rhamnopyranoside (**31**), 4′-O-methyl-2″,4″-di(*Z*)-*p*-coumaroylafzelin (**32**) 4′-O-methyl-(2″-*E*-*p*-coumaroyl-4″-*Z*-*p*-coumaroyl)afzelin (**33**), 4′-O-methyl-(2″-*Z*-*p*-coumaroyl-4″-*E*-*p*-coumaroyl)afzelin (**34**), and known compounds kaempferol 3-O-(2″-*E*-*p*-coumaroyl,4″-*Z*-*p*-coumaroyl)-*α*-*L*-rhamnopyranoside (**35**)[78], kaempferol3-O-(2″,4″-di-*E*-*p*-coumaroyl)-*α*-*L*-rhamnopy-ranoside (**36**)[79] and 4′-O-methyl-2″,4″-di*(E)*-*p*-coumaroylafzelin (**37**)[80] (Figure 6), were tested against the α-glucosidase from *Saccharomyces cerevisiae*, using acarbose (IC_{50} = 266.1 ±0.01 μM) as a positive control. The
compounds showed strong inhibitory activity against the enzyme, with IC_{50} values of 28.2 ± 0.00, 5.9 ± 0.01, 6.8 ± 0.00, 10.1 ± 0.00, 16.1 ± 0.01, 12.9 ± 0.00 and 26.9 ± 0.01 μM, respectively.

2.2 XANTHONES

Kongstad et al[81] isolated one new oxygenated anthraquinone (xanthone) compound and 11 known compounds from an endophytic fungus extracted from *Penicillium species.* All compounds were evaluated for α-glucosidase inhibition activity using acarbose as a positive control (IC_{50} = 969.70 ± 6.62 μM). The structural differences among these compounds were

primarily based on the diverse substituents at the C8 position of the xanthone ring. The new compound, 1,2,3,5,6-pentahydroxy-8-methylxanthone (**38**) and the known compound 1,3,5,6-tetrahydroxy-8-methylxanthone (**39**)[82] (Figure 7), exhibited outstanding α-glucosidase inhibition activities with IC_{50} values of 38.80 ± 1.01 and 33.2 ± 1.01 μM, respectively. Enzyme kinetics studies demonstrated that compound **38** is a mixed-type inhibitor, while compound **39** is a competitive inhibitor.

Laphookhieo et al[83] carried out a bioactivity study on xanrhones isolated from *Garcinia cowa* leaves or inflorescences, and identified five new compounds and seven known compounds, all were screened for α-glucosidase activity using acarbose as a positive control (IC_{50} = 80.0 μM). Among them, the known compound mangostanin (**40**)[84]and the new compounds garciniacowone H (**41**), garciniacowone I (**42**) and garciniacowone J (**43**) (Figure 7) , demonstrated good α- glucosidase inhibitory activity, with IC_{50} values of 11.4, 25.4, 15.4 and 76.2 μM, respectively. Meanwhile, the authors also studied the anti-inflammatory activity of all compounds in LPS-induced RAW264.7 macrophages, among which compounds **40**, **41**, and **43** showed IC_{50} values of 18.6, 7.7 and 5.8 μM in inhibiting NO production, indicating that these natural α-glucosidase inhibitors also possessed anti-inflammatory properties.

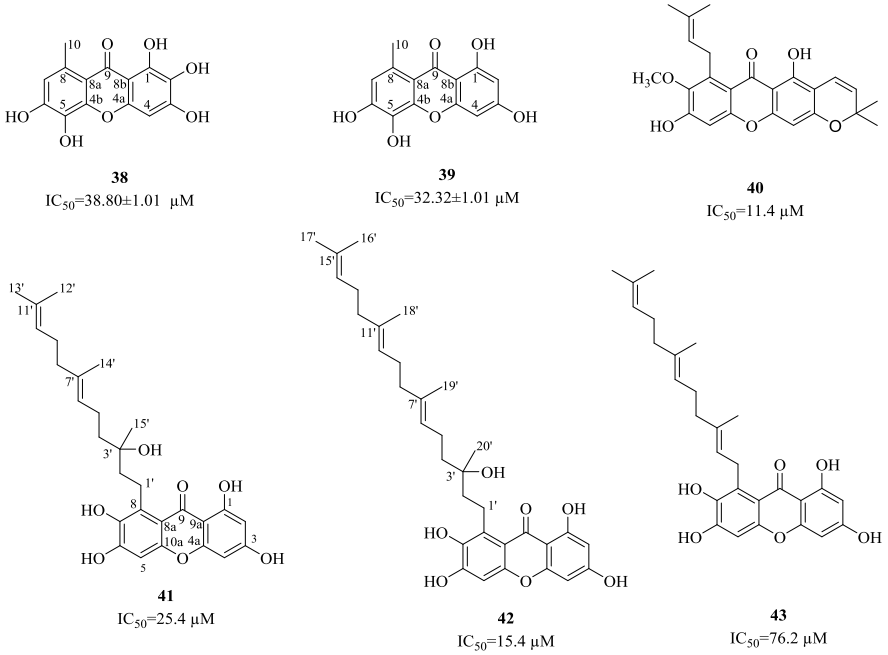


Figure 7. Chemical structures of C-8-substituted xanthones with strong α-glucosidase inhibition activity from *Penicillium species* and *Garcinia cowa* leaves (**38**-**43**).

2.3 ALKALOIDS

2.3.1 Spiro-flavoalkaloids

Some alkaloids known for their unique, attractive structures and various biological activities, were found to contain an important type of AGIs. Bao's group [85] isolated four novel spiro-flavoalkaloids, spiro-flavoalkaloids A – D (**44**-**47**) (Figure 8), from *YingDe* green tea. These compounds displayed excellent inhibitory activity against α-glucosidase derived from brewer's yeast, with IC_{50} values of 3.34, 5.47, 22.50 and 15.38 μM, respectively, using acarbose (IC_{50} = 156.6 ± 1.1 μM) as the positive control. Molecular docking studies revealed that compounds **44** and **45**, which contained a galloyl group, exhibited stronger binding affinities to α-glucosidase than **46** and **47**. Kinetic analysis calculated the binding constants K_i values of compounds **44**-**47** to be 2.23, 1.57, 233.85 and 285.95 μM, respectively. All compounds possessed a spiro-heterocyclic structure, with oxygen and nitrogen atoms in their structures acting as important pharmacophores for antidiabetic drugs[86]. These findings suggest that these compounds have the potential to be developed as therapeutic agents for the treatment of diabetes.

2.3.2 Oxoprotoberberine alkaloids

Laphookhieo and the coauthors[87] conducted the first phytochemical study on *Polyalthia cinnamomea*, from which they isolated two new oxygenated protoberberine alkaloids and 11 known compounds, and evaluated the α-glucosidase inhibitory activity of all compounds. Of these, the two new compounds, (−)-(13*αS*)-polyalthiacinnamine A (**48**) and (−)-(13*αS*)-polyalthiacinnamine B (**49**), and the known compounds, (−)-(13*αS*)-miliusacunine E (**50**) and (−)-(13*αS*)-consanguine B (**51**) (Figure 9), showed satisfactory inhibitory activity against α-glucosidase with IC_{50} values of 59.2, 38.3, 11.3 and 43.2 μM,

respectively, compared to the positive control acarbose (IC_{50} = 83.5 μM). In addition, several compounds were tested for their inhibitory activity on NO production in LPS-induced RAW264.7 macrophages, and compound **51** displayed an IC_{50} value of 24.4 μM, which was better than the positive control indomethacin (IC_{50} = 32.2 μM). NO is generally considered a regulatory molecule of inflammation[88], which is closely related to various diseases such as cancer, diabetes, obesity, and cardiovascular diseases.

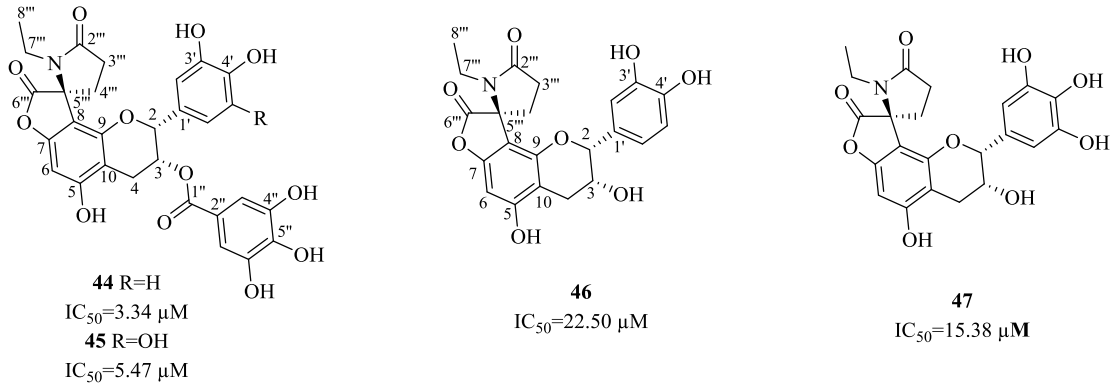


Figure 8. Chemical structures of novel spiro-flavoalkaloid derivatives with potent α-glucosidase inhibition activity from *YingDe green tea* (**44**-**47**).

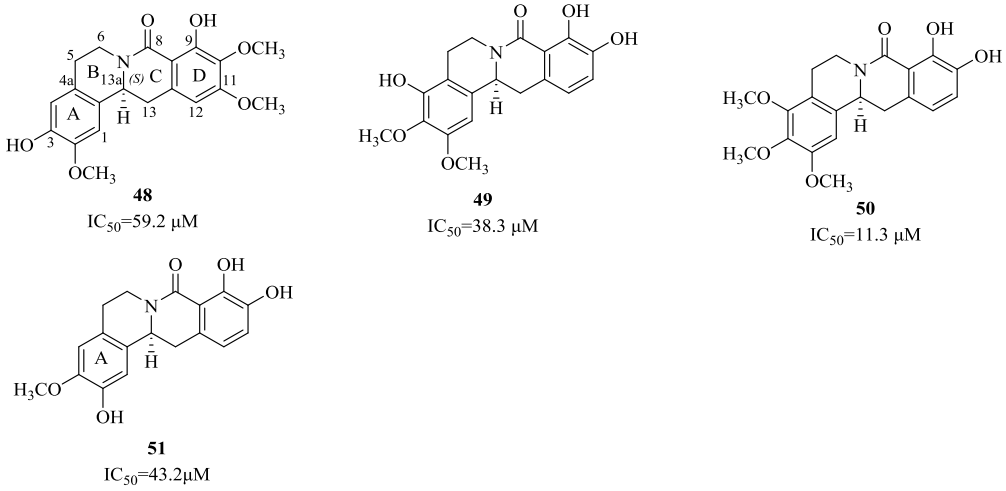


Figure 9. Chemical structures of oxoproberberine alkaloid derivatives with strong α-glucosidase inhibition activity isolated from *Polyalthia cinnamomea* (**48**–**51**).

2.4 BENZOPYRANONES/BENZOFURANONES

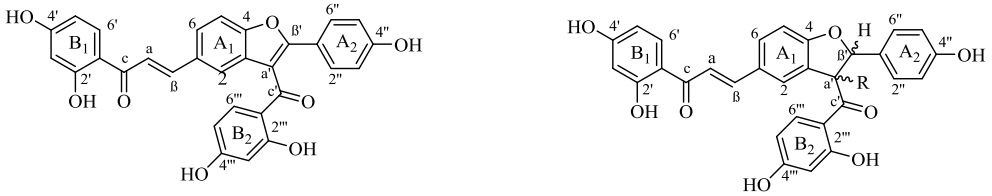
2.4.1 m-Dihydroxypropiophenone/benzophenones

Recently, Chavasiri et al[73] isolated two new furanone compounds dehydrolophirone C (**52**) and lophirone P (**53**), three known compounds lophirone C (**54**)[89], calodenins A (**55**) and calodenins B (**56**)[90] from the stem of *Knema globularia* (Figure 10). These compounds showed extremely strong inhibitory activity against α-glucosidase from *Saccharomyces cerevisiae in vitro*, with IC_{50} values of 3.2 ± 0.2, 5.6 ± 0.9, 2.3 ± 0.2, 2.5 ± 0.5, 0.4 ± 0.1 and 1.3 ± 0.1 μM, respectively, compared to the positive control acarbose (IC_{50} = 93.6 ± 0.5 μM). These results indicated that these compounds hold promise to be therapeutic antihyperglycemic drugs. Kinetic analysis of compound **55** revealed that it is a non-competitive inhibitor with a K_i value of 3.4 μM.

2.4.2 Ormeloxifenes

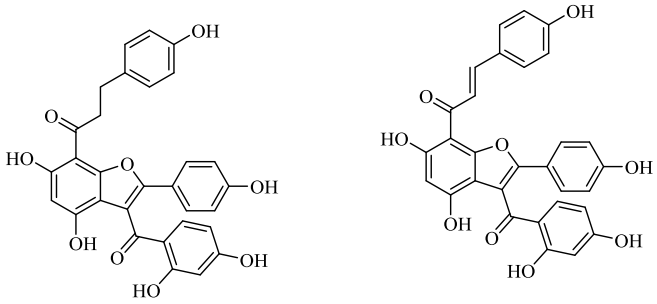
Benzopyran compounds are very common chemical structures in AGIs, Staerk's group [91] isolated 13 new and four known compounds from *Rhododendron capitatum*. Among these new compounds, capitachromenic acid C **(57)**, capitachromenic acid

I (**58**) and capitachromenic acid J (**59**) (Figure 11), showed moderate to good inhibitory activity against α-glucosidase from baker's yeast, with IC_{50} values of 93.5 ± 2.3, 21.2 ± 1.4 and 18.6 ± 0.7 μM. respectively, using acarbose as a positive control (IC_{50} = 796.2 ± 73.2 μM). The authors also reported the PTP1B inhibitory activity of these compounds, which is another promising target for type II diabetes treatment, using RK-682 as a positive control (IC_{50} = 6.9 ± 0.2). The IC_{50} values of these compounds were 36.3 ± 14.6, 10.3 ± 0.4 and 6.0 ± 0.6 μM, respectively. PTP1B acts as a negative regulator in the insulin signaling pathway by dephosphorylating activated insulin receptors and insulin receptor substrates[92]. Therefore, the inhibition of PTP1B prolongs the effect of insulin, thereby contributing to glucose homeostasis. These findings provide the first-hand evidences to support the potential therapeutic use of *Rhododendron capitatum* towards type II diabetes treatment (T2D) in the future.



52
IC_{50} =3.2±0.2 μM

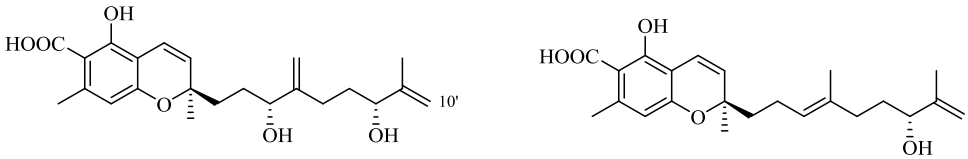
53 R=OH, *a'R,β'R* IC_{50} =5.6±0.9 μM
54 R=H, a'*S,β'S* IC_{50} =2.3±0.2 μM



55
IC_{50} =0.4±0.1 μM

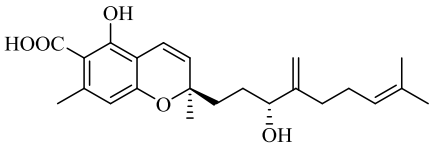
56
IC_{50} =1.3±0.1 μM

Figure 10. Chemical structures of *m*-dihydroxyacetophenone/benzophenone derivatives with α-glucosidase inhibition activity isolated from *Knema globularia* stems (**52-56**).



57
IC_{50}= 93.5±2.3 μM

58
IC_{50}= 21.2±1.4 μM



59
IC_{50}=18.6±0.7 μM

Figure 11. Chemical structures of benzofuran ring derivatives with α-glucosidase inhibition activity from *Rhododendron capitatum* seeds (**57-59**).

2.5 TERPENES

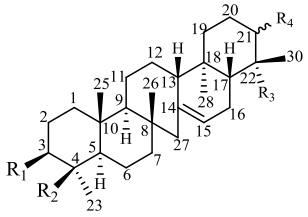
2.5.1 Serrated lycopine triterpenoids

Terpenes are ubiquitous compounds in nature, Wei group [93] from China identified seven undescribed serrulatane triterpenoids and 11 known analogues from *Lycopodium cernuum L*, including five new compounds 3*β*,(21*β*-dihydroxyserra-14-en-24-oic acid-3*β*-(5′-hydroxybenzoate) (**60**), (3*β*,21*β*,24-trihydroxyserrat-14-en-3*β*-(5′-hydroxybenzoate) (**61**), 3*β*,14*α*,21*β*-

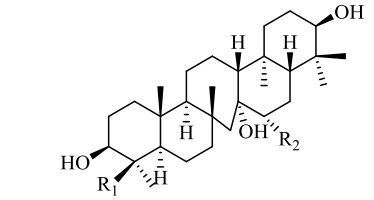
tetrahydroxyserratane-15*α*-(4′-methoxy-5′-hydroxybenzoate)−24-methyl ester (**62**), 3*β*,14*α*,21*β*-tetrahydroxyserratane-15*α*-(4′-methoxy-5′-hydroxybenzoate) (**63**) and 3*β*-hydroxy-21*β*-acetate-16-oxoserrat-14-en-24-oic acid (**64**) (Figure 12), which exhibited strong inhibitory activities against α-glucosidase from brewer's yeast, with IC_{50} values of 23.22 ± 0.64、25.36 ± 0.67、28.10 ± 0.81、30.49 ± 0.65 and 49.20 ± 1.33 μM , respectively, with positive control acarbose (IC_{50} = 409.5 ± 4.2 μM). The highest inhibition rate reached 99% at a concentration of 100 μM, and the overall inhibition rate was 10 to 20 times higher than that of acarbose. Some of the compounds can be potential candidates for the treatment of diabetes. The researchers also conducted structure-activity relationship studies on their inhibitory activities and chemical structures and found that the $\Delta^{14,15}$ group played a crucial role in the inhibition of these serratins. The combination of the 5-hydroxybenzoate ester at C-3, the β-hydroxy at C-21, and the carboxylic acid group at C-24 were necessary to improve the inhibition of α-glucosidase. The presence of 4′-methoxy-5′-hydroxybenzoate ester at C-15 was beneficial for inhibiting the antibacterial activity of selaginellane triterpenoids without the double bonds between C14 and C15.

2.5.2 Kaurene-type diterpenoid enantiomers

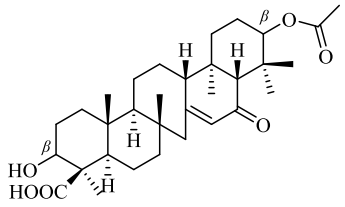
Different from the structures of the serrated lycopine triterpenoids, Kaurene-type diterpenoid enantiomers can also be found in AGIs. Hong et al[94] identified 11 new and two known diterpenoid enantiomers of the cafestol type from *Coffea Cultivar S288*, among which the new compounds Cafeane Acid A (**65**), abeo-20(10→9)-16 *a* -Hydroxy-l7-acetoxy-5(10)-ent-kauren-19-oic Acid (**66**), 20-Nor-cofaryloside III (**67**), Dehydrotricalysiolide C (**68**), Dehydrotricalysiolide E (**69**) and Adenostemmoic Acid H (**70**) (Figure 13), exhibited moderate to good α-glucosidase inhibitory activities against the enzyme derived from brewer's yeast, with positive control acarbose (IC_{50} = 60.71 ± 16.45 μM); IC_{50} values were 22.04 ± 0.05, 18.76 ± 1.46, 26.84 ± 0.99, 4.88 ± 0.03, 12.35 ± 0.91 and 12.64 ± 0.59 μM, respectively, among which compounds **67**-**69** exhibited fair inhibitory activity characterized by the double bond between C-15 and C-16, and compound **66** exhibited moderate inhibitory activity due to the rearranged diterpenes in the C/D ring system. Molecular dynamics experiments revealed that compound **67** formed a strong hydrogen bond with amino acid residue ARG315 of α-glucosidase, which explained its moderate α-glucosidase inhibitory activity.



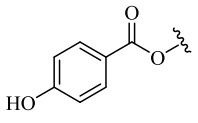
60 R_1=4-hydroxybenzoate, R_2=COOH, R_3=CH_3, R_4=*β*OH
IC_{50}=23.22 ± 0.64 μM
61 R_1=4-hydroxybenzoate, R_2=CH_2OH,R_3=CH_3,R_4=*β*OH
IC_{50}=25.36 ± 0.67 μM



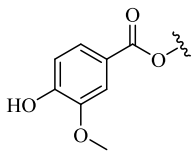
62 R_1=$COOCH_3$, R_2=4'-methoxy-5'-hydroxybenzoate
IC_{50}=28.10 ± 0.81 μM
63 R_1=CH_3, R_2=4'-methoxy-5'-hydroxybenzoate
IC_{50}=30.49 ± 0.65 μM



64
IC_{50}=49.20 ± 1.33 μM



4-hydroxybenzoate



4'-methoxy-5'-hydroxybenzoate

Figure 12. Chemical structures of serrated lycopine triterpenoid derivatives with α-glucosidase inhibition activity isolated from *Lycopodium cernuum L* (**60**-**64**).

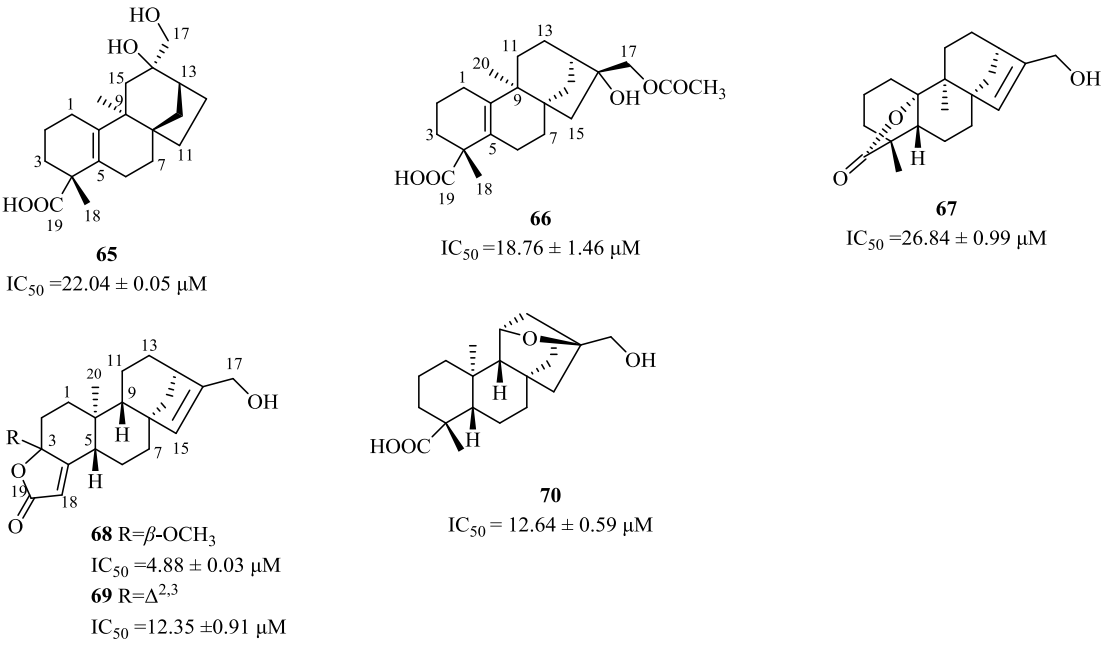


Figure 13. Chemical structures of Kaurane-type diterpene enantiomeric derivatives with α-glucosidase inhibitory activity identified from *Cofiea Cultivar S288* (**65**-**70**).

2.5.3 Clerodane-type furan diterpenoids

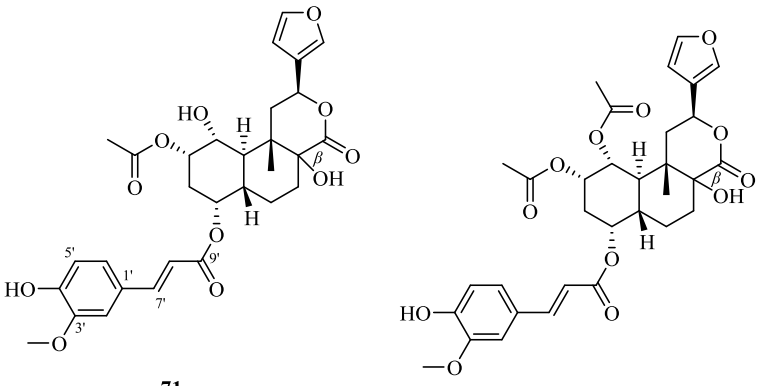
Clerodane-type furan diterpenoids are another type of terpenes in AGIs, Zhang et al[95] have isolated 10 new clerodane furan diterpenoids from the ethanol extract of *Tinospora sinensis*, among which tinosinoid I (**71**) and tinosinoid J (**72**) have shown good inhibition activity against
α-glucosidase from brewer's yeast (Figure 14), with positive control of acarbose (IC_{50} = 840.0 ± 35.0 μM), the IC_{50} values are 46.0 ± 0.6 and 29.7 ± 3.3 μM, respectively. Enzyme kinetic studies revealed that compound **72** was a non-competitive α-glucosidase inhibitor with a K_i value of 157.7 μM. Besides, the abovementioned compounds were also tested for their anti-proliferative effects against HeLa and HCT116 tumor cells, but unfortunately, none of the compounds displayed cytotoxicity against these cells. Moreover, molecular docking experiments have indicated that the ferufoyl group was the key moiety for the α-glucosidase inhibition activities of these compounds.

2.5.4 Iridoids

Unlike the structures of other terpenes, iridoids are very unusual structures in terpene-type AGIs. Piacente and the coauthors [96] isolated 28 compounds from the methanol extract of *Scabiosa atropurpurea*, including three iridoid compounds reported for the first time. The α-glucosidase inhibitory activity of all the compounds was tested. The three new compounds secologanin-methyl-hemiacetal (**73**), atropurpurin A (**74**), and atropurpurin B (**75**) (Figure 15), exhibited inhibitory activity against α-glucosidase derived from brewer's yeast when compared to the positive control acarbose (IC_{50} = 175.00 ± 3.50 μM). The IC_{50} values for the compounds were 49.95 ± 1.08, 86.96 ± 3.50, and 92.59 ± 3.52 μM, respectively.

2.5.5 Serrulatane diterpenoid

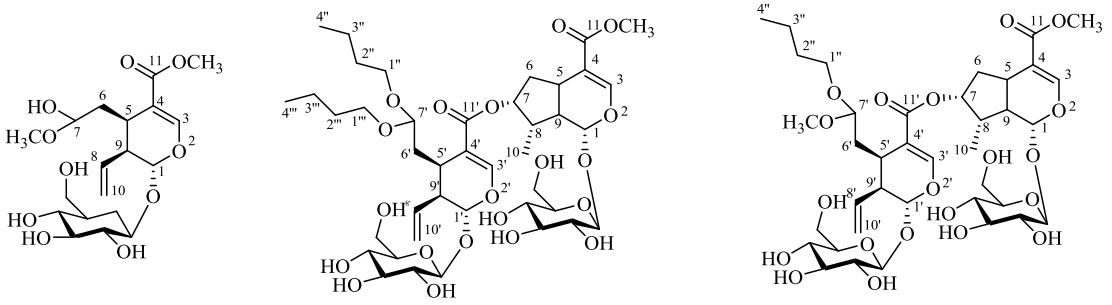
Recently, Staerk's group[97] isolated 28 compounds from *Eremophila phyllopoda subsp. Phyllopoda*, out of which 21 compounds were reported for the first time. Both the α-glucosidase inhibitory activity and PTP1B inhibitory activity of all the compounds were evaluated. Among them, two new compounds, eremophyllane H (**76**) and eremophyllane T (**77**) (Figure 16), which belong to another type of terpenes, i.e. serrulatane diterpenoids, exhibited strong α-glucosidase inhibitory activity, compared to the positive control acarbose (IC_{50} = 583.6 ± 11.2 μM). The IC_{50} values for compounds **76** and **77** were 28.4 ± 1.4 and 64.2 ± 8.0 μM, respectively. Moreover, compound **76** is the only serrulatane diterpenoid compound among all the compounds with a hydroxyl group at the C-18 position, indicating that the hydroxyl group at the C-18 position may be associated with increased α-glucosidase inhibitory activity. In addition, compound **77** showed moderate inhibitory activity against PTP1B, using RK-682 (14.4 ± 1.0 μM) as the positive control, with an IC_{50} value of 16.6 ± 0.8 μM.



71
IC_{50}=46.0±0.6 μM

72
IC_{50}=29.7±3.3 μM

Figure14. Chemical structures of Clerodane-type furan diterpenoid derivatives with α-glucosidase inhibitory activity isolated from *Tinospora sinensis* (**71, 72**).

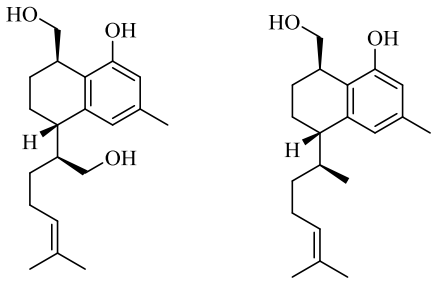


73
I_{C50}= 49.95 ± 1.08 μM

74
IC_{50} =86.96 ± 3.50 μM

75
IC_{50} = 92.59 ± 3.52 μM

Figure 15. Chemical structures of iridoid derivatives with moderate α-glucosidase inhibitory activity isolated from *Scabiosa atropurpurea*(**73-75**).



76
IC_{50}=28.4 ± 1.4 μM

77
IC_{50}=64.2 ± 8.0 μM

Figure 16. Chemical structures of serrulatane diterpenoid derivatives with α-glucosidase inhibitory activity isolated from *Eremophila phyllopoda subsp. Phyllopoda* (76, 77)

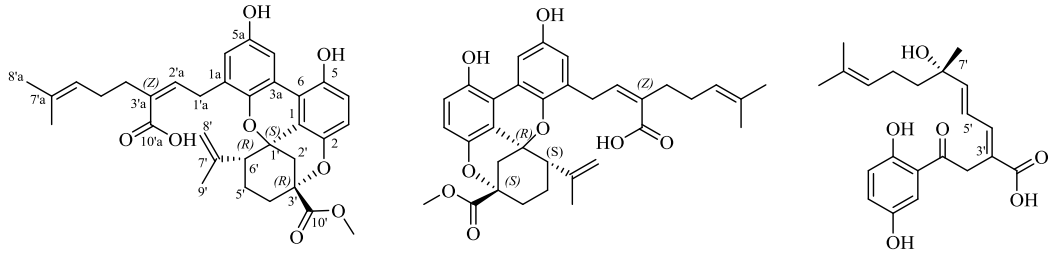
2.5.6 Meroterpenoids

Meroterpenoids also belong to the terpene-type AGIs. Peng and the coauthors reported [98] the isolation of three new meroterpenoid compounds and three known compounds from *Ganoderma cochlear*. The α-glucosidase inhibitory activity of all the compounds was evaluated. The results showed that the new enantiomeric compounds (+) and (−)-Cochlearin J (**78**), and (+)-Cochlearin K (**79**) (Figure 17), with positive controls of ursolic acid (IC_{50} = 49.6 ± 2.21 μM) and acarbose (IC_{50} = 350 ± 31.2 μM), exerted potent inhibitory effects against α-glucosidase. Their IC_{50} values were 24.18 ± 1.98, 26.49 ± 3.20, and 29.68 ± 2.73 μM, respectively, compared to the positive control, ursolic acid (IC_{50} = 49.65 ± 2.21 μM). Molecular docking experiments revealed that the docking energy of (+)-**78**, (−)-**79**, and **79** was -10.2, -10.6, and -8.9 kcal/mol, respectively. Additionally, **79** exhibited a different binding mode with α-glucosidase, which resulted in its distinct inhibitory activity.

2.5.7 Tirucallane-type triterpenoids

Zhang's group et al [99] recently isolated eight tirucallane-type triterpenoid compounds from *Melia toosendan Sieb. et Zucc*, including four new compounds. The inhibitory activity of all the compounds against α-glucosidase was evaluated using acarbose as the positive control (IC_{50} = 326.9 ± 4.5 μM). Among them, the new compound (3S,5R,9R,10R,13S,14S,17S,20R,22R,23S,24S)-Lanost-7-ene-3,23,24-triol-22,25-epoxy (**80**) and the known compound cinamodiol (**81**) [100] (Figure 18), exhibited weak inhibitory activity against α-glucosidase derived from *Saccharomyces cerevisiae*, with the IC_{50} values of 120.3 ± 5.8 and 104.9 ± 7.1 μM.

Apart from the above two types of steroids, phytosterol-type steroids are also one important type of triterpenoids. Van et al[101]isolated two new compounds and four known stigmasterol-type steroidal saponins from the leaves of *Vernonia amygdalina*. Using acarbose (IC_{50} = 127.53 ± 1.73 μM) as the positive control, they tested the α-glucosidase inhibition of these compounds. Two new compounds, vernonioside K (**82**) and vernonioside L (**83**) (Figure 18), displayed significant inhibition against α-glucosidase having IC_{50} values of 78.56 ± 7.28 and 14.74 ± 1.57 μM, respectively. These compounds were also found to have no inhibitory effect on xanthine oxidase activity, making them potential candidates as natural antidiabetic agents.

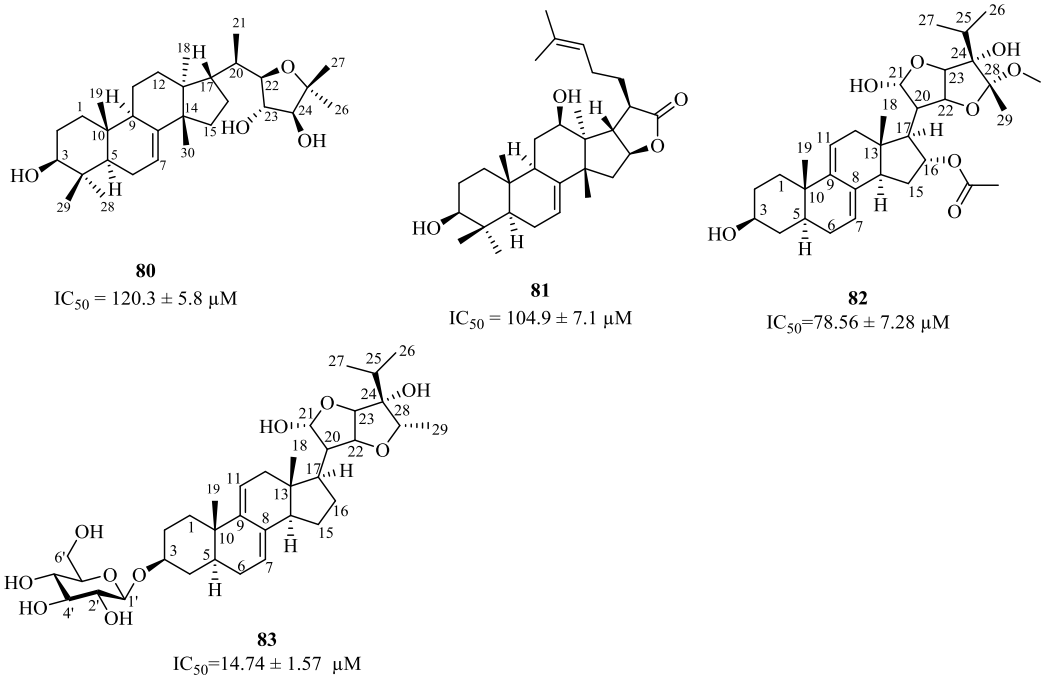


(+)-78
IC_{50} = 24.18 ± 1.98 μM

(-)-78
IC_{50} =26.49 ± 3.20 μM

79
IC_{50} = 29.68 ± 2.73 μM

Figure 17. Chemical structures of meroterpenoid derivatives with α-glucosidase inhibitory activity isolated from *Ganoderma cochlear* ((+,−)-**78**, **79**).



80
IC_{50} = 120.3 ± 5.8 μM

81
IC_{50} = 104.9 ± 7.1 μM

82
IC_{50}=78.56 ± 7.28 μM

83
IC_{50}=14.74 ± 1.57 μM

Figure 18. Chemical structures of tirucallane-type triterpenoid derivatives with moderate α-glucosidase inhibitory activity isolated from *Melia toosendan Sieb. et Zucc* and *Vernonia amygdalina* leaves (**80**-**83**).

2.6 SAPONINS

2.6.1 Oleananes

Saponins are ubiquitously present in plants, which attract much attention from the scientific community due to their significant biological activities, they are one type of important AGIs. Kiem et al[102] more recently reported the isolation of five new dammarane-type saponin derivatives and three known compounds from *Camellia petelotii*. All compounds were tested for their α-glucosidase inhibitory activity using acarbose (IC_{50} = 200.4 ± 10.5 μM) as the positive control. Among the new compounds, campetelosides A (**84**) its 28-acetate and campetelosides B (**85**) (Figure 19), exhibited good α-glucosidase inhibitory activity with IC_{50} values of 166.7 ± 6.0 and 45.9 ± 2.6 μM, respectively. The sulfonato group in the sugar moiety and a highly oxygenated oleanane framework could be explained for the α-glucosidase inhibition. The presence of sulfonato and acyl groups greatly increase the number of hydrogen bond acceptors, which could make these compounds more favorable to bind at the active pocket of the enzyme.

2.6.2 D-Glucose

Abdel-Sattar and the coauthors[103] reported the isolation of four new saponin derivatives with D-glucose modified from the dichloromethane extract of *Caralluma hexagona*, *viz:*12*β*-O-benzoyl 3*β*,8*β*,12*β*,14*β*,20-pentahydroxy-(20*S*)-pregn-5-ene-3-O-*β*-D-glucopyranosyl-(1→4)-O-*β*-D-digitaloside (**86**), 3*β*,8*β*,14*β*,20-tetrahydroxy-(20*S*)-pregn-5-ene-3-O-*β*-D-glucopyranosyl-(1→4)-O-*β*-D-digitaloside-20-O-3-isoval-*β*-D-glucopyrano-side (**87**), 3*β*,8*β*,14*β*,20-tetrahydroxy-(20*R*)-pregn-5-ene-3-O-*β*-D-glucopyranosyl-(1→4)-O-*β*-D-digitalo-side-20-O-3-isoval-4-benzoyl-*β*-D-glucopyranoside (**88**) and （ 3*β*,8*β*,14*β*,20-tetrahydroxy-(20*R*)-pregn-5-ene-3-O-*β*-D-glucopyranosyl-(1→4)-O-*β*-D-digitaloside-20-O-3,4-di-benzoyl-*β*-D-glucopyranoside (**89**) (Figure 20). They showed very weak inhibitory activity against α-glucosidase from *Saccharomyces cerevisiae*, with IC_{50} values of 0.92 ± 0.02 and 0.67 ± 0.01 mM for compounds **86** and **87** respectively, and 0.74 ± 0.02 mM for a mixture of compounds **88** and **89**, compared to the positive control acarbose (IC_{50} = 0.81 ± 0.86 mM). Additionally, they exhibited moderate inhibitory activity against rat lipase *in vitro*, with IC_{50} values ranging from 5.17 ± 0.04 to 43.53 ± 2.02% at a concentration of 100 μM, using orlistat (IC_{50} = 7.41 ± 2.26 μM) as the positive control. This is because obesity is usually considered as an important factor leading to type II diabetes[104], and the glycosidic groups in the above compounds are believed to have a protective effect against the metabolic syndrome by inhibiting fat hydrolysis enzymes and reducing oxidative stress. Furthermore, they also tested the anti-glycation activity in a BSA-fructose model, and the IC_{50} values of compounds **86**, and a mixture of **88** and **89** were 502.36 ± 70.88 and 452.67 ± 74.33 μM, respectively. Advanced glycation end products (AGEs) are a key result of long-term hyperglycemia[105], and inhibiting glycosidases and lipase, as well as reducing oxidative stress and AGEs formation, is beneficial for the metabolic syndrome. Therefore, *Caralluma hexagona* may be a potential candidate for treatment of the metabolic syndrome.

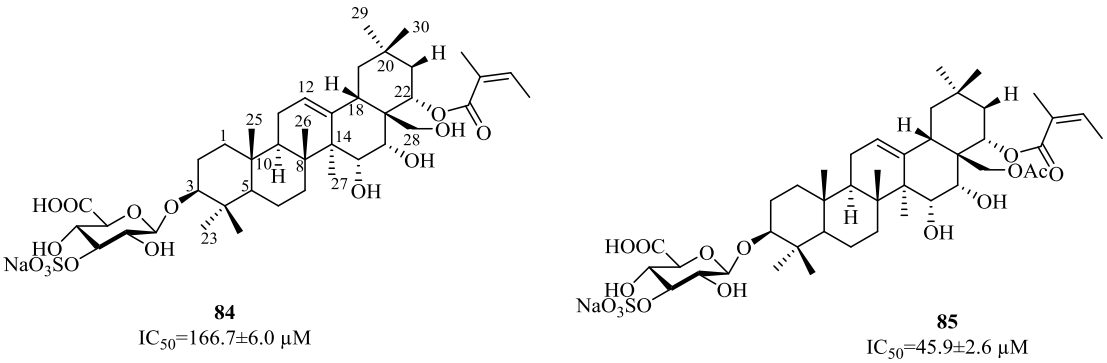


Figure 19. Chemical structures of oleanane-type saponin derivatives with better α-glucosidase inhibitory activity from *Camellia petelotii* (**84**, **85**).

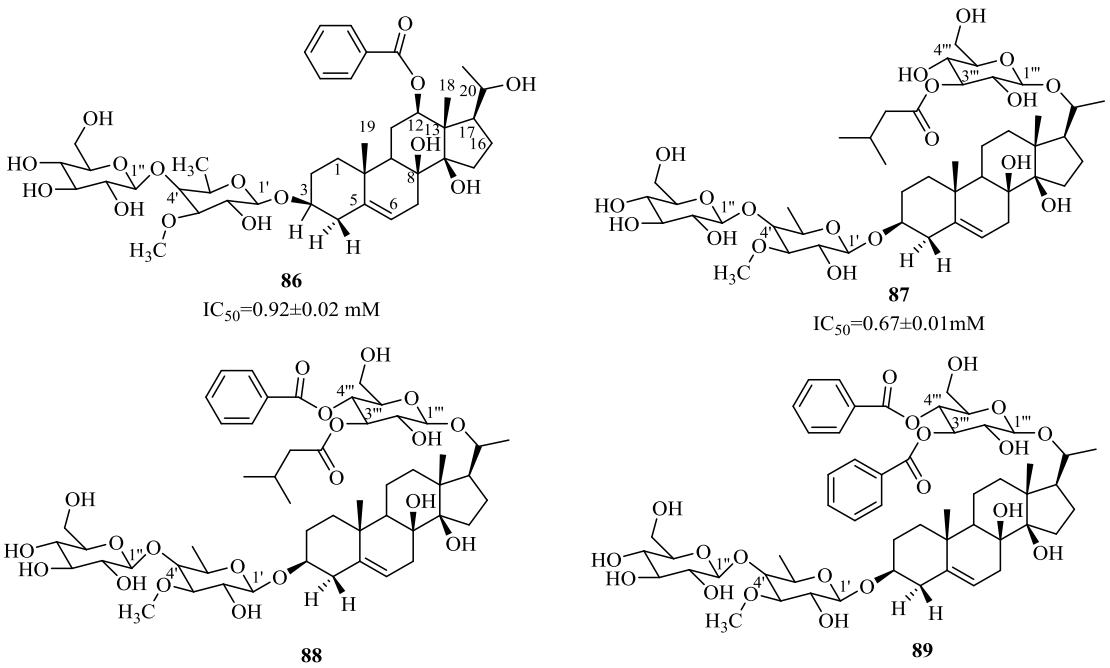


Figure 20. Chemical structures of D-glucosaponin derivatives with better α-glucosidase inhibitory activity from *Caralluma hexagona* (**86**-**89**).

2.7 PHENOLS/ALCOHOLS

2.7.1 Glucosides

Phenols are also one significant type of AGIs, which broadly exist in plants. In recent years, Chen et al[106] isolated 2 unknown phenolic glycosides and 4 known analogues from *Trollius chinensis*. Among them, a new compound, trochinenol B (**90**) and a known compound, 1'-O-*β*-D-(3,4-dihydroxyphenyl)-ethyl-6'-O-vanilloyl-glucopyr-anoside (**91**)[107] (Figure 21), exhibited potent inhibition of α-glucosidase with 50.3 ± 0.05% and 95.7 ± 0.55% inhibition rates at a concentration of 50 μM, respectively. Enzymatic kinetic studies demonstrated that both compounds were typical non-competitive inhibitors, and exerted the inhibition effects in a dose-dependent manner, with IC_{50} values of 25.96 μM and 3.14 μM, respectively. Kinetic results showed that compound **90** was a typical non-competitive inhibitor, while compound **91** was an uncompetitive inhibitor of α-glucosidase, which holds promise in the development of potential antidiabetic drugs. Further molecular docking experiments revealed that compound **90** primarily interacts with α-glucosidase *via* hydrogen bonding, while the hydrogen bonding between compound **91** and α-glucosidase may enhance the stability of the complex.

Glycosyl phenols are novel AGIs, and Chen et al [108] also isolated three new compounds, viburosides A-C (**92**-**94**) (Figure 21) from another plant *Viburnum luzonicum Rolfe* leaves. The inhibitory activity against both α-glucosidase and α-amylase was tested. Acarbose was used as a positive control with IC_{50} values of 17.30 ± 0.86 and 28.73 ± 1.14 μM for α-glucosidase and α-amylase, respectively. The IC_{50} values against α-glucosidase were 15.57 ± 0.49, 15.69 ± 0.73, and 10.31 ± 0.26 μM for compounds **92**, **93** and **94**, respectively. The IC_{50} values against α-amylase were 17.52 ± 0.78, 12.29 ± 0.43, and 18.11 ± 0.96 μM for compounds **92**, **93** and **94**, respectively. Enzyme kinetic studies were conducted on compounds **93** and **94**, and the results showed that compound **93** inhibited α-amylase activity in a competitive manner, while compound **94** exhibited competitive inhibition on α-glucosidase, and in molecular docking analysis, the configuration seemed to have significant influence on their a-amylase and α-glucosidase inhibitory activities, suggesting that compounds **93** or **94** with the *threo* form could exert more potent inhibition on α-amylase or α-glucosidase than compound **92**.

Similar with the structures of compounds **92**-**94**, a new compound (7*R*,8*S*)-guaiacylglycerol 9-O-β-D-glucopyran-oside (**95**) (Figure 21) was isolated from *Viburnum cylindricum* leaves by Zhao's group in this year[109]. Using acarbose as a positive control (IC_{50} = 18.84 μM), the new compound showed strong inhibitory activity against α-glucosidase with an IC_{50} value of 10.73 μM.

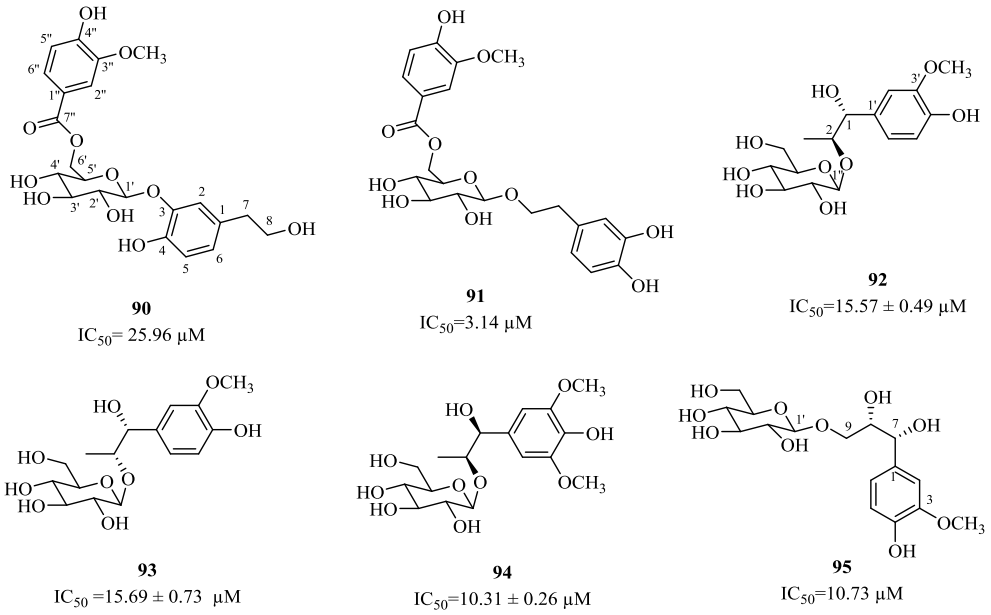
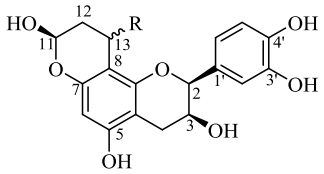


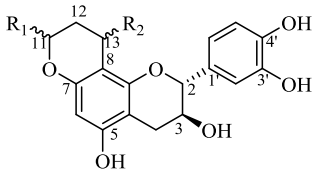
Figure 21. Chemical structures of phenolic glycoside derivatives with α-glucosidase inhibitory activity isolated from *Trollius chinensis, Viburnum luzonicum Rolfe* leaves *and Viburnum cylindricum* (**90**-**95**).

2.7.2 Flavanols and Fatty Alcohols

Aside from the above phenol-type AGIs, flavanols and fatty alcohols consist of one significant type of AGIs. Geng et al[110] reported the isolation of 19 new hybrid compounds of flavanols and fatty alcohols, tsaokoflavanols A~S (**96~114**) (Figure 22), from *Amomum tsao-ko*. Using acarbose as a positive control (IC_{50} = 180.0 ± 1.7 μM), the α-glucosidase inhibitory activity of all compounds was tested, and they all displayed strong inhibition, with IC_{50} values of 9.0 ± 0.6, 7.7 ± 0.8, 35.8 ± 9.3, 18.9 ± 1.7, 20.0 ± 0.6, 5.6 ± 2.1, 35.6 ± 3.0, 13.3 ± 6.4, 10.4 ± 1.2, 26.8 ± 0.1, 5.2 ± 1.0, 37.5 ± 4.3, 58.0 ± 0.3, 43.8 ± 3.9, 108.5 ± 9.2, 15.1 ± 2.4, 37.7 ± 6.2, 6.3 ± 0.7 and 35.2 ± 4.0 μM, which were 3-35 times stronger than the positive control, acarbose. Using suramin sodiumc (IC_{50} = 200.5 ± 1.9 μM) as a positive control, the inhibitory activity of all compounds against PTP1B was also tested, and all compounds except **99**, **102**, **104**, **109**, **111** and **113** showed good inhibition against PTP1B. The respective IC_{50} values were 238.2 ± 1.0, 114.9 ± 0.1, 155.9 ± 1.8, 356.1 ± 0.1, 56.4 ± 5.0, 151.7 ± 0.1, 75.1 ± 2.4, 80.4 ± 3.2, 73.0 ± 0.5, 101.0 ± 4.3, 134.7 ± 21.3, 359.4 ± 14.9 and 69.8 ± 1.8 μM. In addition, using suramin sodiumc (IC_{50} = 411.4 ± 1.4 μM) as a positive control, the inhibitory activity of all compounds against T-cell protein tyrosine phosphatase (TCPTP) [which has important therapeutic applications in diseases such as cancer and inflammation] was tested as well, and compounds **101**, **107**, **108** and **114** were found to exert good suppression effects against TCPTP with IC_{50} values of 359.2 ± 5.8, 306.5 ± 4.0, 238.7 ± 5.3 and 209.3 ± 0.5 μM, respectively. Enzyme kinetics studies showed that compounds **96**, **97**, **101** and **106** were mixed-type inhibitors of α-glucosidase and PTP1B with K_i values of 13.0, 11.7, 2.9 and 5.3 μM for α-glucosidase and 142.3, 88.9, 39.2 and 40.8 μM for PTP1B, respectively. Docking simulations proved the importance of hemiacetal hydroxy linkage, the orientation of 3,4-dihydroxyphenyl, and the length of alkyl chain in binding with α-glucosidase and PTP1B. It is well recognized that protein tyrosine phosphatase 1B (PTP1B) plays a key role in negatively regulating insulin action by dephosphorylation of activated insulin receptors and downstream substrate proteins, and thus, PTP1B inhibitors are fascinating candidates for developing antidiabetic agents[111]. However, the clinical use of PTP1B inhibitors is severely impeded by their poor membrane permeability and weak selectivity against TCPTP, the most similar protein to PTP1B [112], therefore, compounds from *Amomum tsao-ko* with α-glucosidase and/or PTP1B inhibitory effects will provide valuable clues in searching for new antidiabetic candidates in nature.



96 R=*α*-pentyl (C_5H_{11})
IC_{50} =9.0 ± 0.6 μM
97 R=*α*-heptyl (C_7H_{15})
IC_{50} =7.7 ± 0.8 μM
98 R=*β*-heptyl (C_7H_{15})
IC_{50} =35.8 ± 9.3 μM
99 R=*α-(E)*-7-hydroxyhept-5-en-1-yl ($C_7H_{12}OH$) IC_{50} =18.9 ± 1.7 μM
100 R=*α-(E)*-7-acetoxyhept-5-en-1-yl ($C_7H_{12}OAc$) IC_{50} =20.0 ± 0.6 μM
101 R=*α*-nonyl (C_9H_{19})
IC_{50} =5.6 ± 2.1 μM



102 R_1=*α*-OH, R_2=*α*-pentyl (C_5H_{11}) IC_{50} =35.6 ± 3.0 μM
103 R_1=*α*-OH, R_2=*β*-pentyl (C_5H_{11}) IC_{50} =13.3 ± 6.4 μM
104 R_1=*β*-OH, R_2=*β*-pentyl (C_5H_{11}) IC_{50} =10.4 ± 1.2 μM
105 R_1=*α*-OH, R_2=*α*-heptyl (C_7H_{15}) IC_{50} =26.8 ± 0.1 μM
106 R_1=*α*-OH, R_2=*β*-heptyl (C_7H_{15}) IC_{50} =5.2 ± 1.0 μM
107 R_1=*β*-OH, R_2=*β*-heptyl (C_7H_{15}) IC_{50} =37.5 ± 4.3 μM
108 R_1=*β*-OH, R_2=*α*-heptyl (C_7H_{15}) IC_{50} =58.0 ± 0.3 μM
109 R_1=*α*-OH, R_2=*β-(E)*-7-hydroxyhept-5-en-1-yl($C_7H_{12}OH$) IC_{50} = 43.8 ± 3.9μM
110 R_1=*β*-OH, R_2=*α-(E)*-7-hydroxyhept-5-en-1-yl($C_7H_{12}OH$) IC_{50} = 108.5 ± 9.2 μM
111 R_1=*α*-OH, R_2=*β-(E)*-7-acetoxyhept-5-en-1-yl($C_7H_{12}OAc$) IC_{50} = 15.1 ± 2.4 μM
112 R_1=*β*-OH, R_2=*α-(E)*-7-acetoxyhept-5-en-1-yl($C_7H_{12}OAc$) IC_{50} = 37.7 ± 6.2 μM
113 R_1=*α*-OH, R_2=*β*-nonyl (C_9H_{19}) IC_{50} = 6.3 ± 0.7 μM
114 R_1=*β*-OH, R_2=*α*-nonyl (C_9H_{19}) IC_{50}=35.2 ± 4.0 μM

Figure 22. Chemical structures of flavanol-fatty alcohol derivatives with α-glucosidase inhibitory activity from *Amomum tsao-ko* (**96-114**).

2.8 ESTERS

2.8.1 Cyclopentene-*γ*-lactones

Liu et al[113] mutagenized the marine fungus *Aspergillus terreus ML-44* using diethyl sulfate (DES) to obtain a new mutant strain ASM-1, and conducted bioactivity studies on this mutant strain. Six aspulvinone derivatives were isolated from the culture medium, and all compounds were tested for α-glucosidase inhibitory activity, with acarbose as a positive control (IC_{50} = 17.2 ± 1.8 μM), including three new compounds aspulvinones V (**115**), aspulvinones W (**116**), aspulvinones X (**117**), and three known compounds aspulvinone H (**118**)[114], aspulvinone J-CR (**119**)[115], and aspulvinone R (**120**)[116] (Figure 23). All presented inhibitory activity against α-glucosidase from brewer's yeast with IC_{50} values of 2.2 ± 0.4 μM, 32.0 ± 5.8, 38.6 ± 5.2, 4.6 ± 1.3, 44.3 ± 8.9 and 10.8 ± 2.3 μM, respectively. Enzyme kinetics studies were carried out on compounds **115** and **118**, indicating that both compounds were mixed-type inhibitors. The inhibition constants K_i were 6.60 and 6.58 μM, respectively, and the mixed-type IC_{50} values were 2.2 and 4.6 μM. The K_i values of these two compounds were both smaller than their K_{IS} values, which were 3.15 and 4.70 μM and 8.23 and 6.62 μM, respectively. This indicated that these two compounds had higher affinity for the enzyme than for the substrate. In addition, the compound **118** with the best inhibitory activity was studied in female C57 BL/6J mice. After oral administration of sucrose [2 g/kg body weight (BW)], the blood glucose level rapidly increased from 5.00 ± 0.07 μM to a maximum of 14.24 ± 0.45 μM within 30 minutes, followed by a recovery to the pre-treatment level at 120 minutes in the presence of acarbose (50 mg/kg BW) as a positive control. Compared to the negative control group, compound **118** significantly suppressed the blood glucose rise at 30 and 60 minutes and led to a 13.2% decrease of the AUC at a dose of 25 mg/kg BW comparable to that of acarbose (11.8% decrease) at a dose of 50 mg/kg BW. Based on experiment, it was confirmed that compound **118** could alleviate postprandial hyperglycemia by inhibiting intestinal α-glucosidase, indicating that compound **118** also exerted excellent *in-vivo* antidiabetic effect in the C57BL/6J mice. In addition, molecular docking simulations showed that the straight chain isoprene group in the compound was a key factor which affected α-glucosidase inhibitory activity, while the configuration of the $\Delta^{4,5}$ double bond had no clear effect on the inhibitory activity against α-glucosidase.

2.8.2 Prenyl Derivatives

Lee and the coauthors[117] reported the isolation of another ester-type AGIs from *Hericium erinaceus*, including four new compounds and 6 known compounds and measured the α-glucosidase inhibitory activity of all compounds. Among them, the new compound, erinacenol D (**121**), and the known compounds hericene A (**122**), hericene D (**123**)[118] and hericenone D (**124**)[119] (Figure 24), displayed strong inhibitory activity against α-glucosidase from brewer's yeast, compared to the positive control acarbose (IC_{50} = 71.2 μM), with IC_{50} values of 19.6, 6.7, 3.9 and 15.5 μM, respectively. Molecular docking experiments further revealed that compound **121** formed hydrogen bonds with Gln353, Arg 442, Asp307, and Asp69, with lengths of 2.25, 1.83, 1.98, and 2.13 Å. Hydrogen bonds were formed between compound **124** with Gln353, Asp307, Tyr158, and Glu411, with lengths of 1.89, 2.42, 2.59 and 2.51 Å. These results indicated that these compounds could be inserted into the active site of the

enzyme and bind tightly to the catalytic amino acid residues, which could contribute to the α-glucosidase inhibition. Thus, it was suggested that *Hericium erinaceus* could be used as an adjuvant therapy for diabetes.

2.8.3 Ellagic acid esters

Liu's group[120] extracted and isolated five hydrolysable tannins derivatives which constitute another ester-type AGIs from the *n*-butanol extract of the *Potentilla kleiniana Wight et Arn*, and evaluated their α-glucosidase inhibitory activity. 2 novel compounds 3,3′- di- O- methylellagic acid- 4′- O- *β*- D- glucopyranoside (**125**) and 3,3′- di- O- methylellagic acid (**126**) (Figure 25), exhibited moderate inhibitory activity against α-glucosidase from brewer's yeast, with IC_{50} values of 44.63 ± 2.50 and 20.73 ± 2.56 μM, respectively, compared to positive control acarbose (IC_{50} = 332.12 ± 5.52 μM).

2.8.4 Gallic acid gluconates

Gallates ubiquitously exist in nature, thus gallic acid gluconates are also important ester-type AGIs. Kanokmedhakul et al[74] isolated two newly isolated gallate compounds from *Phyllanthus mirabilis Müll.Arg* and evaluated their α-glucosidase inhibitory activity. The new benzylmethyl glucoside derivatives phyllantenocoside-O-gallate (**127**) and epi-phyllantenocoside-O-gallate (**128**) (Figure 26), exhibited moderate inhibitory activity against α-glucosidase from yeast with IC_{50} values of 148.51 ± 0.35 and 102.88 ± 0.47 μM, respectively, using acarbose (IC_{50} = 71.65 ± 0.66 μM) as a positive control. The cytotoxicity of two compounds was also tested using the MTT method against human epidermoid carcinoma (KB), human cervical carcinoma (HeLa), human lung carcinoma (A549), human hepatocellular carcinoma (HepG2), and African green monkey kidney (Vero); however, they exhibited no cytotoxicity against any of the tested cancer cells at concentrations >100 μM.

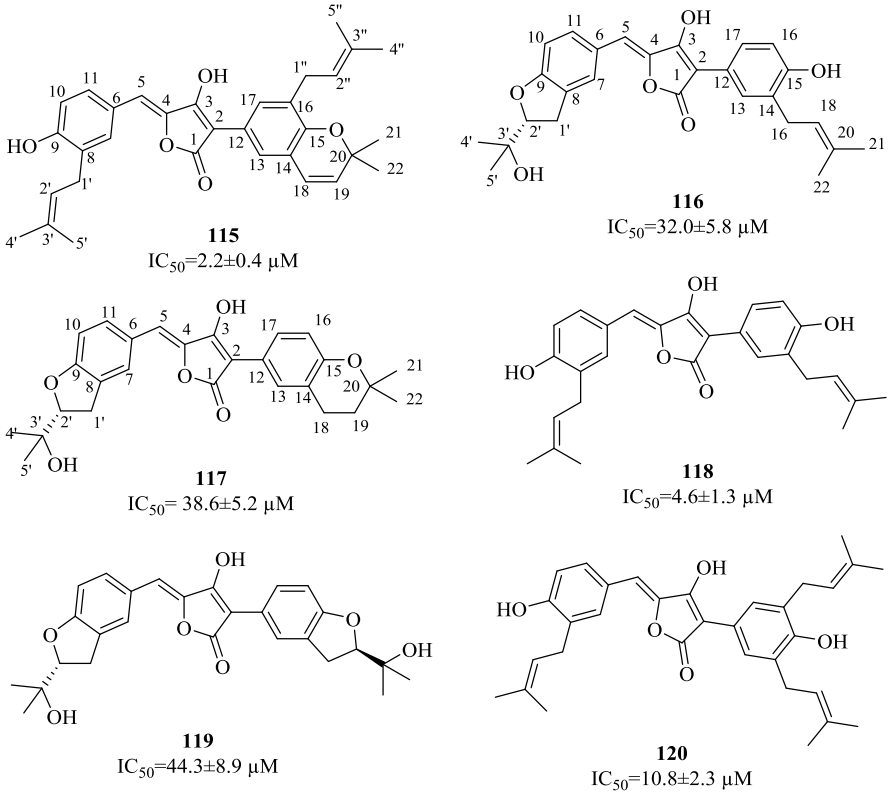
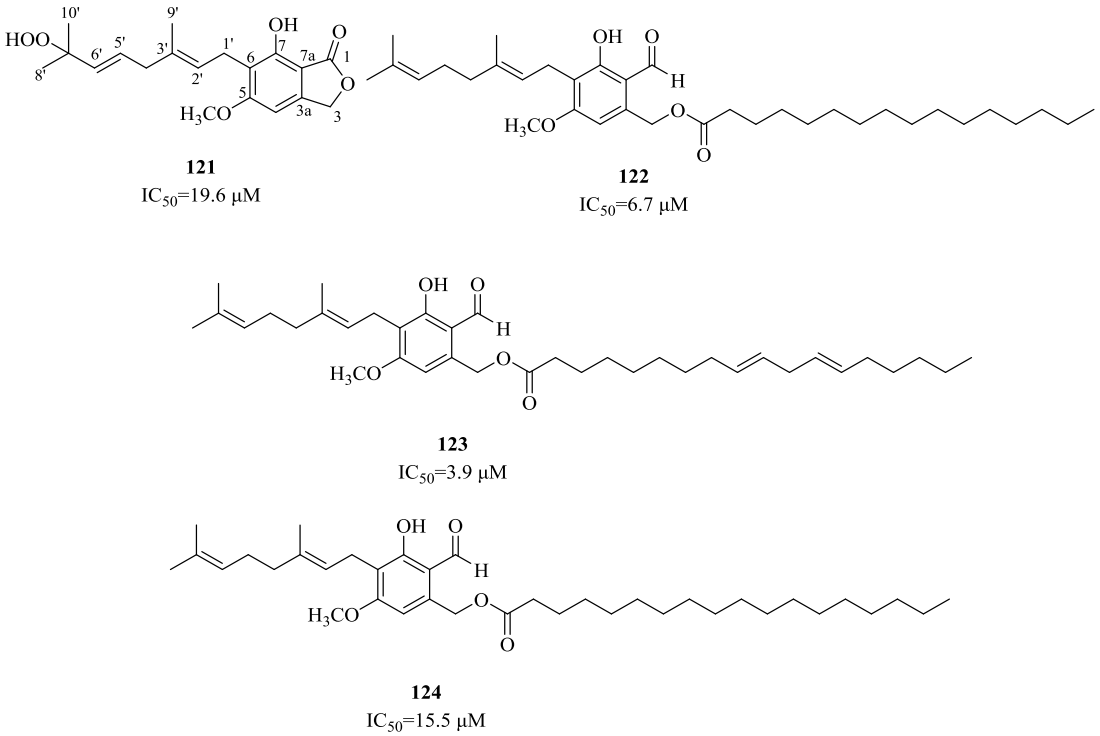


Figure 23. Chemical structures of cyclopentene-*γ*-lactone derivatives with α-glucosidase inhibitory activity isolated from *Aspergillus terreus ML-44* mutant strain *ASM-1* (**115-120**).



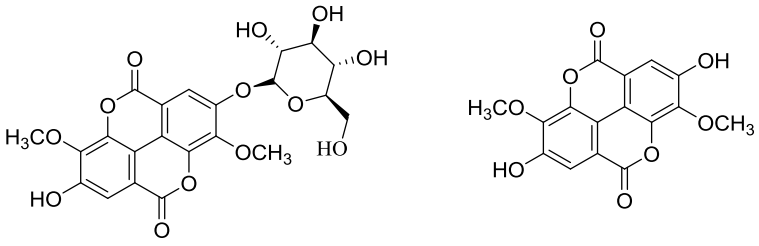
121
IC_{50}=19.6 μM

122
IC_{50}=6.7 μM

123
IC_{50}=3.9 μM

124
IC_{50}=15.5 μM

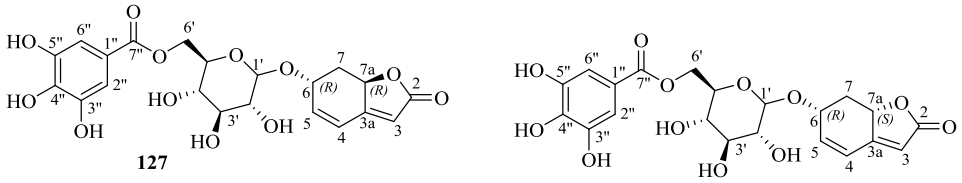
Figure 24. Chemical structures of prenyl ester derivatives with good α-glucosidase inhibitory activity isolated from *Hericium erinaceus* (**121**–**124**).



125
IC_{50}=44.63 ± 2.50 μM

126
IC_{50}=20.73 ± 2.56 μM

Figure 25. Chemical structures of ellagic acid derivatives with α-glucosidase inhibitory activity isolated from *Potentilla kleiniana Wight et Arn*(**125**, **126**).



127
IC_{50}=148.51 ± 0.35 μM

128
IC_{50}=102.88 ± 0.47 μM

Figure 26. Chemical structures of gallic acid gluconate derivatives with α-glucosidase inhibitory activity from *Phyllanthus mirabilis Müll.Arg* (**127**, **128**).

2.8.5 Depsidones

Quite different from aforementioned structures of ester-type AGIs, depsidones have novel chemical structures. Sichaem's group[121] conducted a biological activity study on the lichen *Parmotrema cristiferum (Taylor)* Hale, where they isolated two depsidones compounds and assessed their inhibitory activity against α-glucosidase. The two compounds cristifone A (**129**) and cristifone B (**130**) (Figure 27), showed potent inhibitory activity against α-glucosidase with IC_{50} values of 21.5 and 18.4 μM, respectively. Enzyme inhibition kinetics analysis was performed on compound **130**, revealing that it is a non-competitive

inhibitor with a K_i value of 20.7 ± 1.8 μM and a K'_I value of 20.9 ± 1.7 μM. These results can provide insight into the development and utilization of this lichen in the intervention of diabetes.

Another group, i.e. Duong's group[122], also isolated a new depsidone and three known compounds from the same lichen *Parmotrema cristiferum*. They evaluated the inhibitory activity of all compounds against α-glucosidase, The new compounds, parmoferone A (**131**) and parmosidone K (**132**) [123] (Figure 27), demonstrated strong inhibitory activity against α-glucosidase with IC_{50} values of 18.1 ± 0.6 and 6.1 ± 0.2 μM, respectively, using acarbose as a positive control (IC_{50} = 360 ± 3.1 μM). Compound **132** was further selected to examine the mechanism of its α-glucosidase inhibition, and the enzyme inhibition kinetics revealed that it acted as a non-competitive inhibitor. The K_i value of compound **132** was determined as 23.1 μM.

2.8.6 Phenoxy gallates

Phenoxy gallates are another class of ester-type AGIs, which are structurally close to the above gallic acid gluconates, with a phenoxy group substituting glucose. Kanokmedhakul et al[74] reported the isolation of six unknown compounds, two newly identified compounds, and 23 known compounds from *Phyllanthus mirabilis Müll.Arg* and evaluated their α-glucosidase inhibitory activity of all compounds. Two new tyramine derivatives, phyllatyramine A (**133**) and phyllatyramine B (**134**) (Figure 28), showed inhibitory activity against α-glucosidase from yeast with IC_{50} values of 152.16 ± 4.92 and 21.09 ± 0.69 μM, respectively, with acarbose (IC_{50} = 71.65 ± 0.66 μM) as a positive control. Besides, the cytotoxicity of all compounds were also evaluated using the MTT method against human epidermoid carcinoma (KB), human cervical carcinoma (HeLa), human lung carcinoma (A549), human hepatocellular carcinoma (HepG2), and African green monkey kidney (Vero) cells, with Doxorubicin (IC_{50} values of 0.11 ± 0.01, 0.0728 ± 0.0069, 0.295 ± 0.017, 0.295 ± 0.01,and 1.06 ± 0.1 μM) as a positive control. Compound **133** showed moderate cytotoxicity against KB cells with an IC_{50} value of 89.26 ± 7.68 μM, while compound **134** exhibited good cytotoxicity against KB and HeLa cell lines with IC_{50} values of 54.42 ± 2.56 and 59.80 ± 3.79 μM, respectively.

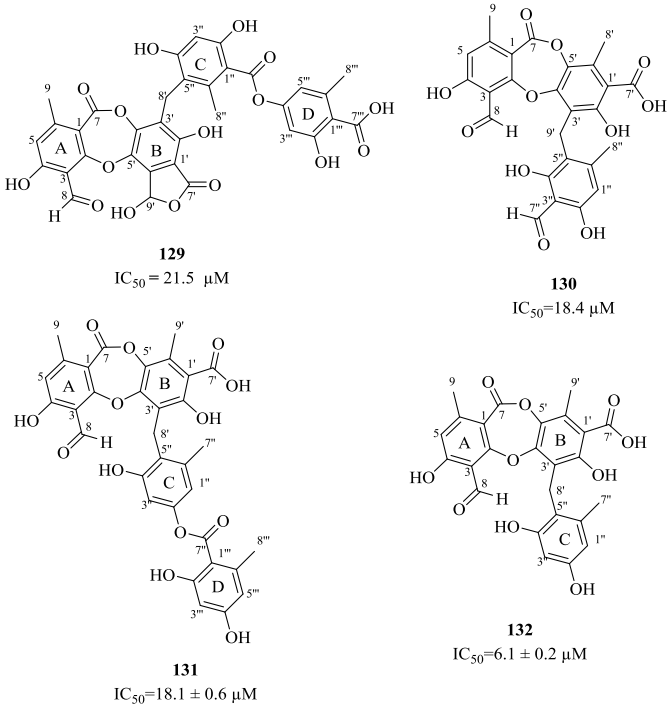


Figure 27. Chemical structures of Depsidones derivatives with α-glucosidase inhibitory activity from lichen *Parmotrema cristiferum (Taylor)* Hale and lichen *Parmotrema cristiferum* (**129**-**132**).

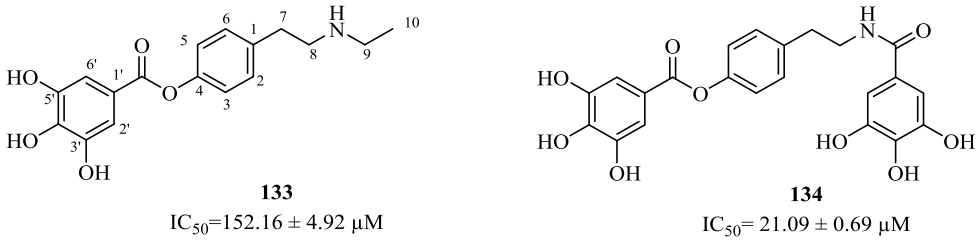


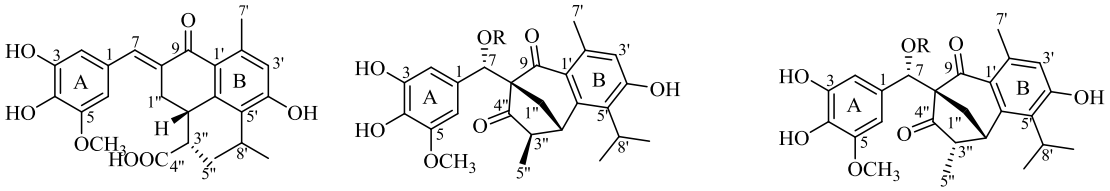
Figure 28. Chemical structures of phenoxyl gallates with α-glucosidase inhibitory activity from *Phyllanthus mirabilis Müll.Arg* (**133**-**134**).

2.9 CHALCONES

Chavasiri et al[124] isolated six new isoprenylated chalcone derivatives from *Mansonia gagei* and evaluated their inhibitory activities against α-glucosidase and DPPH. Compounds gagone A-E (**135**-**139**) (Figure 29) exhibited strong α-glucosidase inhibitory activity with IC_{50} values of 33.4 ± 3.7, 17.5 ± 0.8, 27.4 ± 1.6, 3.6 ± 0.4 and 4.3 ± 0.04 μM, respectively, with acarbose as the positive control (IC_{50} = 93.6 ± 0.5 μM). Except for compound **138**, all the tested compounds showed potent antioxidant activities with IC_{50} values ranging from 12.8 ± 0.2 to 20.1 ± 0.4 μM, using ascorbic acid as the positive control (IC_{50} = 30.2 ± 0.5 μM). Thus, these compounds can act as anti-α-glucosidase and antioxidant dual inhibitors.

2.10 OTHERS

Liang's group [125] isolated two cyclo-peptides which were composed of eight amino acids from *Stachys geobombycis C. Y. Wu.* The α-glucosidase inhibitory activity of this two compounds was evaluated using acarbose (IC_{50} = 178.73 μM) as a positive control. The two compounds cyclogeobomptide A (**140**) and cyclogeobomptide B (**141**) (Figure 30), exhibited significant inhibition against α-glucosidase with IC_{50} values of 26.00 and 19.16 μM, respectively. Furthermore, enzyme kinetic studies revealed that compounds **140** and **141** exerted competitive reversible inhibition on the enzyme. Molecular docking simulations were performed to investigate the binding of acarbose and the two compounds with α-glucosidase protein. It was visualized that the amino acid residues of α-glucosidase interacted with acarbose, **141** and **142**, respectively, and showed that they can bind to α-glucosidase. These findings indicated that all compounds may have the potential to be developed as novel anti-hyperglycemic drugs.

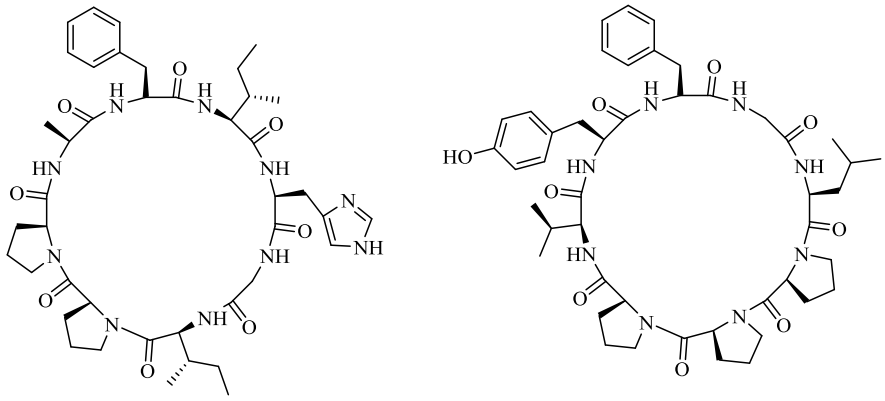


135 IC_{50}=33.4±3.7 μM

136 R=H IC_{50}=17.5±0.8 μM
138 R=OCH_3 IC_{50}=3.6 ± 0.4 μM

137 R=H IC_{50}=27.4 ± 1.6 μM
139 R=OCH_3 IC_{50}=4.3 ± 0.04 μM

Figure 29. Chemical structures of prenylated chalcone derivatives with α-glucosidase inhibitory activity from *Mansonia gagei* (**133**–**137**).



140 IC_{50}=26.00 μM

141 IC_{50}=19.16 μM

Figure 30. Chemical structures of other compounds with α-glucosidase inhibitory activity from *Phyllanthus mirabilis Müll.Arg and Stachys geobombycis C. Y. Wu* (**138**–**141**).

3 CONCLUSION AND PROSPECTS

Due to the diverse biological activities of α-glucosidase inhibitors, such as anti-hyperglycemic, anti-tumor, treating obesity, antiviral etc., α-glucosidase inhibitors have drawn substantial attention from researchers. These α-glucosidase inhibitors are mainly derived from natural plants and microorganisms. In this study, a total of 139 compounds with strong α-glucosidase inhibitory activity were summarized from 33 selected plants or microorganisms, and all compounds were classified based on their structures, including flavonoids, xanthones, alkaloids, benzopyranones/benzofuranones, terpenes, saponins,

phenols/alcohols, esters, chalcones, and others. The IC_{50} values of α-glucosidase inhibitory activity of these compounds were mostly below 50 μM, better than the positive control acarbose, with many even below 5 μM, such as compounds **15**, **18**, **19-23**, **25-27**, **44**, **52**, **54-56**, **68**, **91**, **115**, **118**, **123**, **138** and **139**, exhibiting excellent α-glucosidase inhibitory activity. The compound with the best α-glucosidase inhibitory activity was compound **55** (IC_{50} = 0.4±0.1 μM), and compound **118** also showed a significant *in-vivo* antidiabetic effect in mice. Therefore, these compounds can be used as important lead chemical structures for the development of AGI-type hypoglycemic drugs. In addition, some compounds also showed moderate anti-cancer activity, such as compounds **20** and **21** exhibiting certain cytotoxicity against KB, HepG2, and MCF7, while compounds **22**, **133**, **134** showed weak cytotoxicity against KB, and compounds **29**, **30**, **135-137** and **139** displayed not only α-glucosidase inhibitory activity, but also antioxidant activity; compounds **40**, **41**, **43** and **51** exhibited anti-inflammatory activity. Therefore, natural α-glucosidase inhibitors are expected to become a pivotal source for the development of drugs for the treatment of various diseases. In the future, more structurally novel, unique, and diverse natural α-glucosidase inhibitors will be isolated and identified, and more in-depth animal experiments will be conducted to study the molecular mechanisms of inhibitory activity and establish potential drug targets, which will be the focuses of future research.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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