

Research Progress of α -glucosidase Inhibitors of Medicinal and Edible Homologous Plants and Their use in the Treatment of Diabetes

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Abstract. Diabetes is one of the common diseases in modern society, which cannot be cured. It has a significant impact on the lives of patients. Type II diabetes patients mainly rely on oral hypoglycemic drugs and insulin injection to maintain blood sugar balance. While traditional hypoglycemic medications such as insulin, biguanides, and sulfonylureas may reduce blood glucose for a brief period of time, it often has some side effects and can lead to body dependence. Therefore, as a safe and economical natural hypoglycemic plant polysaccharide, it has received more and more attention. Natural active ingredients with glucosidase inhibitory activity from plants will become potential resources for research and treatment of type II diabetes. A large number of medicinal and food homologous plants have been identified as an important source of glucosidase inhibitors, and have received widespread attention. This article focuses on homologous medicinal and edible plant species and their application in diabetes treatment, here, we reviewed functional components with glucosidase inhibitory activity in homologous medicinal and edible plants and their state of research. In this paper, we hope to provide a theoretical benchmark for the development of drugs for type II diabetes from natural plants.

Keywords: medicinal and edible homologous plants, diabetes, α -glucosidase inhibitor, Hypoglycemic active ingredients.

1. Introduction

Diabetes is one of the most prevalent and fastest growing diseases worldwide, becoming the third major threat to human health after cancer and diseases of the heart and cerebrovascular system. The 9th edition of the Global Diabetes Map was published by the International Diabetes Federation (IDF) in 2019, which indicated that the worldwide diabetes patients were 463 million currently and will increase to nearly 700 million by 2045 [1]. Diabetes imposes a huge economic burden on the general population due to its serious complications and lengthy treatment process.

Over 90% of patients with diabetes belong to the type II diabetes mellitus group (T2DM). By inhibiting glycosidase activity and retarding the rate of intestinal carbohydrate hydrolysis, α -glucosidase inhibitors are able to reduce and retard the rise in postprandial blood glucose levels. It is thus superior to other glucose-lowering drugs in the regulation of postprandial blood glucose and effectively delays the onset of type II diabetes in prediabetic patients. Currently, α -glucosidase inhibitors are relatively mature clinical medications for the management of diabetes. This article reviews the progress of research on medicinal and edible plants with α -glucosidase inhibitory activity as well as their naturally occurring hypoglycemic components with α -glucosidase inhibitory effects. The purpose of this paper is to provide a reference for expanding and developing new plant-derived α -glucosidase inhibitors.

2. Application status of α -glucosidase inhibitors and their use in the treatment of diabetes

As a widely present natural enzyme, α -glucosidase (α A-glucosidase, E.3.1.20) has wide variety of characteristics. It is a membrane-binding enzyme found in small intestinal epithelial cells, which participates in the digestion and absorption of glucose in the small intestine. Its activity can be

inhibited by α -glucosidase inhibitors, and consequently regulate postprandial blood glucose levels. Therefore, it plays a crucial role in glucose metabolism in humans and can be used as a drug screening model for the treatment of type 2 diabetes. Typically, carbohydrates rich in food are hydrolyzed by a series of α -amylase digestion in the oral or gastrointestinal tract to oligosaccharides. Then, the oligosaccharides were hydrolyzed into monosaccharides such as glucose that can be directly absorbed by small intestinal epithelial cells. Finally, the monosaccharides were transferred to small intestinal epithelial cells by transporters. Alpha-glucosidase inhibitors inhibit postprandial blood glucose by inhibiting activities such as α -amylase and α -glucosidase., weakening the release of glucose from carbohydrates, and delaying glucose absorption (Fig.1) [2]. For this reason, the evaluation of α -glucosidase inhibitory activity of natural plant components has become a common method for screening out active ingredients that have potential for diabetes therapy.

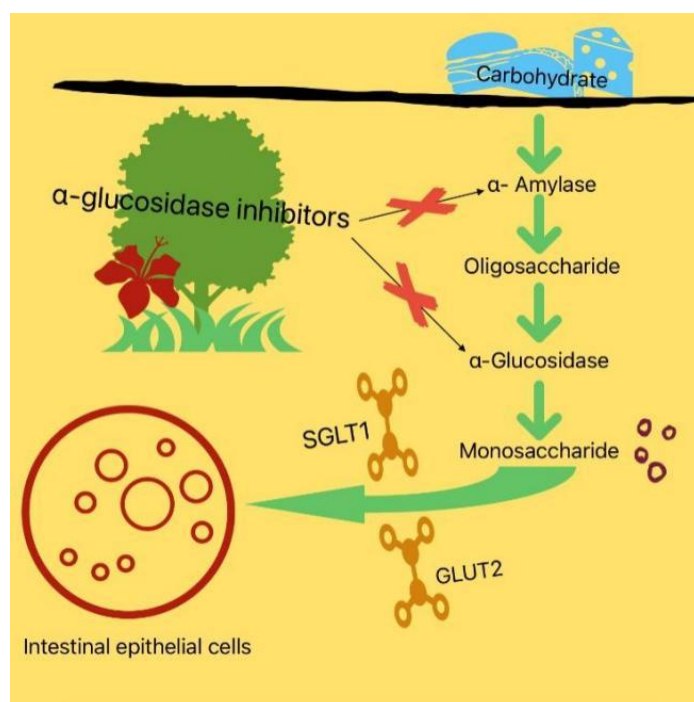


Figure 1. The mechanism of glucosidase and its inhibitor

Acarbose, voglibose and miglitol are the α -glucosidase inhibitors that are most commonly used in clinical practice. However, these medications tend to have side effects such as hypoglycaemia, weight gain, oedema, lactic acidosis, gastrointestinal intolerance and even some adverse events of the liver [3]. These symptoms are mainly caused by the abnormal fermentation of carbohydrates that are not completely digested under the action of the intestinal flora. Therefore, the search for novel high-efficiency, multi-target, safe and inexpensive α -glucosidase inhibitors has become a research hotspot.

3. Medicinal and edible homologous plants with hypoglycemic activity

The active ingredients of natural plants have been shown to have excellent inhibitory properties against α -glucosidase, such as polysaccharides, saponins, alkaloids, flavonoids, peptides and so on. These plant-derived natural active ingredients with α -glucosidase inhibitory activity will be a potential resource for research and treatment of type II diabetes. As the name implies, medicinal and food homologous plants refer to plants with both daily nutritional value and clinical medicinal value, including dietary therapy and medicinal diet in traditional Chinese medicine. These plants are used for both medicine and food, and there is no absolute dividing line between them. At present, a large number of medicinal and food homologous plants have been confirmed to be an important source of α -glucosidase inhibitors, and have received extensive attention from researchers at home and abroad, such as wolfberry fruit, bitter melon, mulberry leaf, goji berry, corn silk, yam, kelp, purslane, purple sweet potato, etc.

Mulberry leaves have been used extensively in the treatment of diabetes since antiquity. Active ingredients, such as flavonoids, polysaccharides and alkaloids, have been shown to have both hypoglycaemic and hypolipidemic effects in mulberry leaves. These active ingredients have been proved to have, and been identified as the main compounds of mulberry leaves to exert hypoglycemic and hypolipidemic effects. Moreover, the unique 1-deoxynojirimycin contained in mulberry leaves is considered as a potent α -glucosidase inhibitors [4]. Cui et al [5] obtain different mulberry leaf polysaccharide components by using fractional alcohol precipitation method. The results showed that the polysaccharide components obtained at low concentrations showed better inhibitory effect on α -glucosidase. Luo et al. [6] reported those two different polysaccharide components isolated and purified from mulberry leaves had efficient inhibitory effects on α -glucosidase activities.

Ji Tao et al. enriched and separated the flavonoids, alkaloids and polysaccharide components in mulberry leaf extract by column chromatography. The results showed that mulberry flavonoids, alkaloids and polysaccharide components all had significant α -glucosidase inhibitory activity, and their inhibition rate increased with the increase of the concentration of each component, and mulberry leaf alkaloids had the strongest inhibitory activity among the three components. They also found synergy between mulberry leaf alkaloids and combinations of mulberry leaf flavonoids or mulberry leaf polysaccharides, confirming the interaction of multiple components of mulberry leaves in regulating blood sugar levels [7].

As early as 1963, bitter *gourd* was found to have anti-diabetic effects [8]. Many studies have shown that the main active ingredients in bitter gourd, including saponins, proteins, alkaloids, steroids and terpenoids, have significant anti-diabetic effects. The extracts and proteins obtained from the fruit and seed of bitter *gourd* have α -glucosidase inhibitory activities. Bitter melon pulp extracts have the potential to significantly reduce fasting and postprandial blood glucose levels in patients with diabetes [9]. Chaturvedi [10] found that bitter melon reduced carbohydrate digestion and absorption by inhibiting intestinal maltase, sucrase and lipase activity in the pancreas. Poovitha et al. [9] confirmed that bitter gourd extracts were able to competitively inhibit α -amylase and α -glucosidase activities, in the meantime they had equivalent levels of hypoglycemia with acarbose.

Corn silk have long been used as oral antidiabetic drugs in the Chinese. Its main hypoglycemic components are alkaloids, flavonoids, phenols, saponins, tannins and phytosterols. Sabiu et al. [11] found that maize silk extract was able to reduce postprandial blood glucose through competitive inhibition of various α -glucosidase and α -amylase localized to the small intestine. Through in vitro experiments, Chen et al [12] found that polysaccharides from maize silk have a significant inhibitory effect on α -glucosidase activity.

Wolfberry fruit leaves are usually considered as dietary supplement in China. In wolfberry fruit, polysaccharides were the main functional active ingredients, which have the capacity to regulate certain metabolic pathways or processes in the human body [13]. Perilla leaf extracts, including polysaccharides, flavonoids and phenolic acids, have inhibitory effects on different origin α -glucosidases. It was reported that perilla leaf extracts could reduce glucose transport by inhibiting maltase and sucrase. Li Xianghui carried out a preliminary study on the hypoglycaemic effect and the related mechanism of the perilla leaf extract. This showed that the perilla leaf extract had an inhibitory effect on α -glucosidase from a variety of sources and belonged to the type of competitive inhibition. Moreover, perilla leaf extract had a good inhibitory effect on maltase and sucrase, and had a certain inhibitory effect on glucose transport [14].

4. Polysaccharides as α -glucosidase inhibitors

Polysaccharides are widely distributed in almost all plants, and are one of the major functional active ingredients in plants. It has been widely applied in the fields of medicine and functional foods due to a variety of biological activities such as lowering blood lipids, lowering blood glucose, antioxidant activity and enhancing immunity. The hypoglycemic properties of many polysaccharide components originated from medicinal and food homologous plants has been confirmed. For example,

Chen et al. [15] found that the polysaccharide from pumpkin and puerarin have a clear effect on mice with Type II diabetes mellitus, especially their combination having even greater synergistic hypoglycemic effects. Liu et al. [16] found that polysaccharides in mulberry leaves were able to reduce free fatty acid and inflammatory mediator levels in diabetic rats, reduce damage caused by oxidative stress, improve mitochondrial function of pancreatic β -cells. Wolfberry fruit polysaccharides have the potential to significantly reduce postprandial blood glucose levels in diabetic mice, improve glucose tolerance in diabetic mice and enhance β -cell reactivity. Masci et al. [17] Preclinical in vitro and in vivo studies reveal that Wolfberry fruit polysaccharides can act at different levels. They enhance the proliferation and secretion of insulin from pancreatic β -cells, or the metabolism of glucose by hepatocytes and adipocytes.

Medicinal and food homologous plant polysaccharides have significant inhibitory effect on α -glucosidase. It is possible that the strong inhibitory activity of maize silk polysaccharide against α -glucosidase may be related to its low relative molecular mass. Kinetic analysis demonstrated that the inhibitory effect of the maize silk polysaccharide against α -glucosidase was irreversible and competed [18]. Zhao et al. [19] reported that black tea polysaccharides had clear inhibitory effects on both the α -amylase enzymes and the α -glucosidase enzymes of tea. Meanwhile, the selenized polysaccharides of black tea was significantly enhanced and exhibited competitively reversible inhibition on both enzymes. Tian et al [20] pointed out that the inhibition rate of 24 mg *Lycium barbarum* polysaccharide on α -glucosidase was as high as 88%. In addition, guava polysaccharides were reported to be a sort of potential α -glucosidase inhibitor and may be used in the treatment of type II diabetes [21].

5. Alkaloids as α -glucosidase inhibitors

Alkaloids are a broad class of natural products that have a complex structure and significant pharmacological activity, including anti-tumour, anti-viral, antibacterial, anti-inflammatory, hypoglycaemic etc. Because alkaloid is structurally similar to sugar, it is likely to replace the position of sugar and bound to α -glucosidase. Moreover, the binding of alkaloid with α -glucosidase will be strengthened owing to the presence of nitrogen. The development of modern pharmacological research has led to the continued exploration of alkaloids with α -glycosidase inhibitory activities, and their hypoglycemic mechanisms have also been the subject of intense investigation [22].

Polyhydroxy alkaloids in mulberry leaves are the major antidiabetic constituents, which have the inhibitory effect on the absorption of sugars in the small intestine and can reduce postprandial blood glucose, represented mainly by 1-deoxynojirimycin (DNJ). Yue et al. found that 5, 6, 7-trihydroxyflavone glycosides and 1-DNJ have been shown to have a synergistic inhibitory effect on the α -glucosidase activity of mice, which could provide a theoretical basis for designing dietary supplements containing mulberry leaf material [23]. Cong et al. found that the inhibition rate on α -glucosidase of different mulberry leaf extracts was sorted from high to low is protein mulberry, protein mulberry and fruit mulberry. The inhibition rate of protein mulberry extracts against α -glucosidase was 86.0%. The α -glucosidase inhibition rate of mulberry leaf extract originated from the Province Qin of China was as high as 89.0% and the inhibition type was reversible non-competitive inhibition. [24]

The alkaloid extract of *Ramulus mori* (SZ-A) has been shown to have disaccharidase-inhibiting activity, which is made up of 1-deoxynojirimycin (1-DNJ), fagopyrin (FAG), and 1, 4-dideoxy-1, 4-imino-D-arabinitol (DAB). The increase in SZ-A content in the extract was accompanied by a gradual increase in α -glucosidase inhibitory activity. When the SZ-A content reached 50%, the α -glucosidase inhibitor activity increased by a factor of more than 200 compared to the crude extract. The SZ-A has highly selective inhibitory effect on small intestinal glycosidase activity, and gastrointestinal side effects could be reduced by 50% compared with acarbose. In 2020, the first approved innovator drug of Chinese traditional medicine in China with the name "*Ramulus mori* Total Alkaloid Tablets" was applied for the treatment of T2DM. Was the only natural drug effective in the area of DM treatment[25]. Song [26] et al. found that alkaloids in bamboo leaf pepper were able to effectively

inhibit α -glucosidase activity, and that the intensity of inhibition was concentration-dependent. At the same time, the type of inhibition was typical noncompetitive inhibition, which could be combined with enzymes and substrate complexes to accomplish the goal of reducing α -glucosidase activity.

6. Flavonoids as α -glucosidase inhibitors

Flavonoids are natural strong antioxidants, which can be used as effective supplements for the prevention of diabetes and effectively reduce complications through the regulation of glucose metabolism, blood lipids, hepatic enzyme activity, protein kinase inhibitory activity, and so on [27]. Members of the flavonoid family contain thousands of compounds and can be divided into numerous subclasses on the basis of chemical structure, such as flavonoids, isoflavones, flavonols, flavanols and anthocyanins. Several studies have demonstrated that flavonoids can inhibit α -glucosidase activity and ameliorate insulin resistance in cells. Jia, et al. [28] compared and studied 27 kinds of dietary flavonoids, which indicated that all of them can be used as α -glucosidase inhibitors and insulin sensitizers. One of these, apigenin-7-O-glucoside, may be the most effective α -glucosidase inhibitor and insulin sensitizer in this regard. The total flavonoid content of *Ampelopsis Grossedentata* and its derivatives has a good effect on the inhibitory and hypoglycaemic activity of α -glucosidase [29].

Wei et al. found that both the crude extract and the isolated components of Henan propolis and the homologous cottonwood gum had good inhibitory activity of α -glucosidase in vitro, and had stronger inhibitory activity compared to the commercially available α -glucosidase inhibitor acarbose [30]. Wang et al. used the ethanol reflux extraction method to optimize the best process of banana flavonoids and the enzyme activity experiment of banana flower ethanol extract was carried out by α -glucosidase. The researchers found that the rate of inhibition of α -glucosidase activity of banana flower ethanol extract was as high as 88.56%, which was greater than that of the acarbose positive control (56.45%), indicating that the banana flower ethanol extract had a strong inhibitory activity against α -glucosidase [31].

Chang et al [32] established a method for the simultaneous determination of HPLC of seven flavonoids including mulberry A, cryptochlorogenic acid, rutin, isoquercetin, viola vervetin, quercetin and kaempferol, and found that the total content of seven flavonoids in mulberry leaves from different origins was positively correlated with its α -glycosidase inhibitory activity.

7. Polyphenolic compounds as α -glucosidase inhibitors

Polyphenols are common natural bioactive substances in plants and have attracted huge attentions in reducing the risk of obesity and diabetes of humans. Stewart and McDougall found that polyphenol-rich berry extracts could inhibit α -glucosidase and α -amylase activity in vitro, which would help prevent and manage diabetes and obesity [33]. Polyphenols from tea are considered as potential drugs for the prevention and control of type II diabetes as they have been shown to have significant inhibitory effects on both amylase and glucosidase activity [34]. Tong et al. studied the inhibitory effect of aqueous extract of black tea under cooking treatment on alpha amylase and alpha glucosidase, and found that torrefaction treatment was an effective means of improving β -amylase and β -glucosidase inhibition [35]. Polyphenolic compounds found in natural grains such as buckwheat, quinoa, and sorghum can effectively retard the glycaemic response caused by bread. It might be owing to the interaction between polyphenols and starch, for example reducing the number of enzyme site bindings, the inhibition of polyphenols on the activity of amylases [36,37]. Recently, purple perilla showed great potential for preventing and treating diabetes. Purple perilla seed phenolics and rosmarinic acid extracts from purple perilla leaves can both effectively inhibit the activities of α -glucosidase and aldose reductase in order to achieve the goal of effective hypoglycaemia. can achieve a hypoglycaemic effect by inhibiting α -glucosidase activity.

8. Saponin as α -glucosidase inhibitors

Saponins are glycosides composed of saponin ligands and sugars, uronic acids, or other organic acids. Saponins are a more complex class of compounds present in the plants, which are composed of saponins and glycosyls. Since the hydroxyl structure of saponins may be the active site of a certain enzyme, it has good physiological activity. Studies have confirmed that saponins are the main material basis for inhibiting α -glucosidase activity in bitter melon. These enzymes can efficiently inhibit the activities of α -glucosidase and aldose reductase, as well as activate the activities of hexokinase and glucose-6-phosphate dehydrogenase, thereby effectively controlling glucose metabolism to inhibit glucose synthesis and promote glucose breakdown. Liu et al[38] isolated 7 saponins from *Momordica charantia*, including momorcharaside A, momordicoside A, karaviloside XI, momordicoside F2, momordicoside K, (23E)-3 β , 7 β , 25-trihydroxycucubita-5, 23-dien-19-al, and Kuguacin N, their IC₅₀ value of α -glucosidase varied from 1.55 to 4.96 mg·mL⁻¹. Jin et al[39] developed a kind of sustained-release *Momordica charantia* saponins alginate chitosan microspheres, which can significantly reduce postprandial blood glucose in normal mice and mice with type 2 diabetes. At the same time, saponins are significantly positively correlated with the rate of inhibition and α -glucosidase content. Many studies have found that the saponins isolated from quinoa also have strong inhibitory effect on α -glucosidase [40]. For example, Dong et al [41]. revealed through kinetic studies that quinoa bran total saponin extract has mixed competitive inhibition effect on glucosidase.

9. Conclusion

Diabetes is gaining global attention due to its high incidence and diabetes has rapidly become one of the most common and costly chronic diseases. Alpha-glucosidase is known to be the major target enzyme for prevention and therapy of type II diabetes. However, most of the current antidiabetic drugs in clinical use have many adverse effects. In recent years, there has been much interest in extracting α -glucosidase inhibitors with excellent activity and fewer side effects from natural plants. Medicinal and edible plants and their active ingredients have been confirmed to have good α -glucosidase inhibition effect, and corresponding drugs have been developed and applied in the clinical treatment and prevention of diabetes. However, α -glucosidase inhibitors from natural plants still have problems such as low content, low extraction efficiency, high separation and purification costs, and lack of efficacy researches. Thus, the clinical application of natural inhibitors of plant α -glucosidase still faces great challenges in large-scale production as well as pharmacological and pharmacodynamic investigations. Further research should be conducted in the future on mining and rapid screening of naturally occurring α -glucosidase inhibitors, enrichment and modification of inhibitors via microbial fermentation, and the development of novel extraction, separation, purification and concentration approaches.

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