Research progress of hypoglycemic active components in plants and their use as α -glucosidase inhibitors

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Abstract: There is a wide range of medicinal and edible plant resources in China. Many of these plants contain flavonoids, alkaloids, polysaccharides, and other hypoglycemic active ingredients, which can reduce blood glucose by inhibiting α-glucosidase activity, promoting the repair of islet β cells, and adjusting insulin signaling pathway. In this paper, the application and research of hypoglycemic active components in plants were reviewed. It provides a new idea for the rational and effective utilization of natural α-glucosidase inhibitors from the medicinal and edible plants.

1. Introduction

Diabetes is one of the most common and fastest growing diseases in the world, and it has become the third serious disease threatening human health after cancer and cardiovascular and cerebrovascular diseases. The International Diabetes Federation (IDF) speculated that about 415 million adults aged from 20 to 79 in the world had diabetes in 2015 and predicted that these number would reach 693 million in 2045[1]. Because of its serious complications and long treatment process, diabetes has unequal medical care expenditure and access to treatment in developed and developing countries, which brings huge economic burden to the general population [2]. There are many reasons for the increasing incidence of diabetes year by year, including population aging, economic development, urbanization. Owing to unhealthy eating habits and sedentary lifestyle, more than 90% of diabetes mellitus belongs to type 2 diabetes mellitus (T2DM)[3]. As the largest developing country in the world, the prevalence rate of diabetes in China increased rapidly from 0.67% in 1980 to 10.4% in 2013[4]. It is estimated that more than 110 million people are suffering from diabetes, which is currently the country with the largest amount of diabetes among all countries. In view of the epidemic stage, the prevalence rate of diabetes may continue to rise, causing a huge burden on the medical insurance system of China [5].

Alpha-glucosidase inhibitor can slow down the hydrolysis of intestinal carbohydrates by inhibiting the glucosidase activity, so as to reduce and delay the increase of postprandial blood sugar. Therefore, it is superior to other hypoglycemic drugs in regulating postprandial blood glucose and can effectively delay the development of pre-diabetes patients to type II diabetes. Presently, α-glucosidase inhibitor has been widely used as a mature clinical drug for treating diabetes. The most commonly used α-glucosidase inhibitors are acarbose, voglibose, miglitol, whereas they have long treatment period, and are expensive in reducing blood glucose in a single treatment. Thus, finding new α-glucosidase inhibitors with high efficiency, multiple targets, safety, and low price has become a research hotspot. This article will start from α-glucosidase inhibitors and their sources, plants with α-glucosidase inhibitory activity and natural active components with α-glucosidase inhibitory activity were reviewed to provide reference for the research of α-glucosidase inhibitors from plants.

2. Alpha -glucosidase inhibitors and their sources

Alpha-glucosidase is a membrane-bound enzyme existing in small intestinal epithelial cells, which can hydrolyze Glucoside bond and produce absorbable monosaccharides such as fructose. Excessive blood glucose will lead to the imbalance of oxidative stress in tissues and cells, resulting in excessive

reactive oxygen species (ROS), which will attack important cell macromolecules and lead to cell damage and death. α-glucosidase inhibitor can reduce postprandial blood glucose of diabetic patients by reversibly inhibiting hydrolysis of oligosaccharides or disaccharides [6]. Therefore, evaluating the antioxidant and α-glucosidase inhibitory activities of natural plant components and screening out effective components with potential for treating diabetes have become common methods for developing hypoglycemic drugs. Alpha -glucosidase inhibitors can slow down intestinal glucose absorption, reduce postprandial blood glucose (PPG) fluctuation and help improve blood glucose control by inhibiting these enzymes.

2.1 Traditional α -glucosidase inhibitor

At present, α-glucosidase inhibitors (AGI) have been used in the treatment of diabetes. Acarbose, voglibose and miglitol are the most widely used traditional AGI drugs. Compared with other oral hypoglycemic agents, AGI drugs are more effective in postprandial blood glucose. Acarbose has been shown to have an indirect and beneficial effect on islets β. Alpha-glucosidase inhibitors can also increase the level of glucagon-like peptide-1 (GLP-1), which may help to reduce the PPG [7]. These drugs are safe and well tolerated, and hypoglycemic episodes are rare [8]. Yang et al [9] reported that, except in combination with insulin or sulfonylureas, AGIs generally does not increase the risk of hypoglycemia, and excessive use of AGIs is not toxic. However, there was no significant difference in hemoglobin A1C (HbA1c) and Fasting plasma glucose (FPG) between oral hypoglycemic agents [10, 11]. The use of acarbose, is now limited because it is less effective and expensive in reducing blood glucose in a single treatment. Moreover, therapeutic effects of these drugs are sometimes inadequate and have relatively serious side effects, for example they were reported to cause hyperglycemia, weight gain, edema, fractures, lactic acidosis, gastronomic intolerance, and even some adverse hepatic events [12, 13].

2.2 α-glucosidase inhibitors from natural plants

Presently, researchers have done many researches focusing on finding natural plants and active components with α-glucosidase inhibitory activity. Various natural plant active ingredients have shown excellent inhibitory effects on α-glucosidase, such as polysaccharides, saponins, alkaloids, flavonoids, polypeptides, etc. Thus, they become potential resources for treating type II diabetes. Therefore, evaluating the antioxidant and α-glucosidase inhibitory activities of natural plant components and screening out effective components with potentials for treating diabetes have become common methods for developing hypoglycemic drugs [14].

3. Plants with α-glucosidase inhibitory activity and relations with α-glucosidase inhibitor

3.1 Natural medicinal plants

The natural plant resources with α-glucosidase inhibitory activity mainly include medicinal plants, and medicine and food homologous plant. The Chinese herbal medicine includes Rehmannia glutinosa, Anemarrhena asphodeloides, Ganoderma lucidum, Pueraria lobata, Salvia miltiorrhiza, Dendrobium Nobile, Polygonatum sibiricum, Polygonatum odoratum, Acanthopanacis Cortex, Rehmannia glutinosa, etc. Medicine and food homologous plant resources, such as Lycium chinense, Momordica charantia, Folium Mori, Zea mays L, Portulaca oleracea L, Solanum tuberdsm, etc., have become an important source for obtaining α-glucosidase inhibitors and have received extensive attention world widely. Here is a summary of several main natural plant materials with α-glucosidase inhibitory activity.

3.1.1 Momordica charantia

The main active ingredients in Momordica charantia include saponins, protein, alkaloids, steroids, terpenoids, etc., which have the anti-diabetic, anti-viral and anti-tumor effects. Early in 1963, M. charantia was found to be anti-diabetes [15]. The extracts from the pulp, seeds, leaves of M. charantia, even the whole plants, were proved to have hypoglycemic effect [16]. It has been proven that the

methanol extracts and protein extracted from M. charantia fruit and seeds had α-glucosidase inhibitory activity, which could decrease the fasting and postprandial blood glucose levels of diabetic patients significantly [17, 18]. Chaturvedi [19] found that M. charantia reduced carbohydrate digestion and absorption by inhibiting the activities of intestinal maltase, sucrase and pancreatic lipase. Poovitha et al [20] confirmed that the protein extracted from M. charantia could competitively inhibit the activities of α-amylase and α-glucosidase in vitro and significantly reduce the peak blood glucose and AUC of OGTT in T2DM rats. Through comparative clinical experiments, Kim et al [21] found that the glycosylated hemoglobin level of M. charantia group and placebo group remained unchanged after 12 weeks of treatment. However, the average fasting blood glucose level of M. charantia group decreased significantly.

3.1.2 Mulberry leaf

Mulberry leaf is classified as medicine and food homologous plant which has been widely used in diabetes treatment since ancient times [22]. Modern medical analysis shows that the active ingredients of mulberry leaf are mainly flavonoids, polysaccharides, alkaloids, etc., which have obvious α-glucosidase inhibitory activity and can reduce blood sugar and blood lipid [23]. In the development of type 2 diabetes mellitus, the decrease of islet β cell quality can lead to the damage of insulin secretion. However, Patlada et al [24] found that the intake of mulberry leaves maintained the function of pancreatic islet β cells in diabetic mice. In addition, edible mulberry leaves not only can significantly reduce cell death by decreasing endoplasmic reticulum stress in pancreas, but also can significantly increase the proliferation of β cells in pancreas and the expression of homeobox 1 mRNA in pancreas and duodenum. It is concluded that eating mulberry leaves can partially maintain insulin level and pancreatic β cells by inhibiting endoplasmic reticulum stress in mice with type 2 diabetes. Ji [25] also reported that the ethanol extract of mulberry leaves can obviously induce autophagy of islet cells in vivo and in vitro. By inducing autophagy of type 2 diabetes mediated by AMPK/mTOR, the ethanol extract of mulberry leaves would thereby protect islet cells from damage and death.

3.1.3 Corn silk

Corn silk is the dry style and stigma of Zea mays in Gramineae, which mainly contains active ingredients such as polysaccharide, saponin, volatile oil, alkaloid and phytosterols. For a long time, corn silk was used as an oral antidiabetic drug in China [26]. Sabiu [27] found that corn stigma extract had strong and moderate inhibitory effects on α-amylase and α-glucosidase, respectively, in a concentration-dependent manner. Phytochemical analysis showed that alkaloids, flavonoids, phenols, saponins, tannins and phytosterols are the possible inhibitory components of corn silk. Zhao [28] found that the polysaccharide extract, flavone extract and sterol extract of corn stigma all can slow down the absorption of glucose in intestinal tract and reduce postprandial hyperglycemia by competitively inhibiting various α-glucosidases and α-amylases located in small intestine. Meanwhile, with the increase of extract concentration, the inhibitory activity of enzymes was also increased. Chen et al [29] reported that the polysaccharides of corn silk contained free carboxylic groups that inhibited the activity of α-amylase.

3.1.4 Lycium barbarum

Lycium barbarum leaves are considered as a dietary supplement, and the functional active ingredients are biomolecules, which mainly exist in composition of phytochemicals in foods. L. barbarum have the ability to regulate one or more metabolic processes or pathways in human organisms, thus contributing to health promotion [30]. A large number of studies have shown that polysaccharide as the main active component of L. barbarum, can significantly reduce the postprandial blood glucose level of diabetic mice, improve the glucose tolerance of diabetic mice, and improve the reactivity of β -cells. It is found that L. barbarum polysaccharide can reduce blood sugar by protecting islet β cells and increasing insulin sensitivity [31]. L. barbarum polysaccharide also have α-glucosidase inhibitory activity. Tian [32] pointed out that the α-glucosidase inhibitory rate of L. barbarum polysaccharide was higher than 88%.

3.1.5 Psidium guajava

Psidium guajava is a tropical plant distributed in southern China, South Asia and Mexico. It is a traditional hypoglycemic drug and functional food, which has been used as an auxiliary drug for diabetes treatment for hundreds of years [33]. Many researches have shown the anti-diabetes effect of guava polysaccharide (GP), which can effectively reduce fasting blood glucose, serum insulin level and steady-state insulin resistance model in type 2 diabetic rats. In addition, it can improve oral glucose tolerance and increase insulin sensitivity in T2 DM rats. Histopathological observation shows that GP can alleviate the damage of islet cells. Meanwhile, GP also shown obvious α-glucosidase inhibition in vitro [34, 35].

3.1.6 Polyporaceae fungi

Many fungi have lower toxicity than sulfonylureas, biguanides and other chemicals, and are also the main source of natural medicinal products. According to different targets, the active ingredients for treating type II diabetes have become the research focus of scholars. Many reported polyporaceae fungi, such as Inonotus obliquus, Phellinus igniarius, Grifola frondosa, Poria cocos, etc., have good hypoglycemic function, and have great application potential in treating diabetes, especially type II diabetes.

3.1.7 Inonotus obliquus

Inonotus obliquus, also known as Chaga mushroom, is a rare medicinal mushroom and a potential source of new AGIs because they have extensive pharmacological effects in the process of preventing and controlling diabetes. In nature, I. obliquus mainly inhabits the trunk of birch, forming an irregular sclerotic nodule [36]. Since the 16th century, I. obliquus have been used to treat gastrointestinal cancer, cardiovascular disease and diabetes in Russia, Poland and most Baltic countries. I. obliquus contains many active ingredients [37], such as polysaccharides, aromatic substances, folic acid derivatives, polyphenols, steroids and triterpenoids. Modern pharmacological studies have also proved that I. obliquus extract has hypoglycemic, anti-tumor, anti-oxidation, anti-mutation, anti-virus, anti-inflammatory, anti-fungal and anti-complementary efficiencies [38]. Wang et al [39] found that gastrointestinal digestion in vitro has an impact on physical and chemical properties and biological activities of I. obliquus polysaccharides. After digestion, the inhibitory activity of I. obliquus polysaccharide on α-amylase and α-glucosidase increased significantly. Huang etc. [40] reported that the lanosterol, inooidiol and trametenolicacid obtained from I. obliquus fruiting body and triterpenoids isolated from mycelium all have certain inhibitory effects on α-glucosidase and α-amylase. Li et al[41].found that the cytoplasm and sclerotium of I.obliquus have certain inhibitory effects on α-amylase and α-glucosidase, which will be helpful to expand the application prospect of Inonotus obliquus in diabetes treatment.

At present, I. obliquus resources are scarce and wild resources are increasingly exhausted. The existing resources can no longer meet a large number of clinical needs. However, the medicinal mycoplasm-Inonotus obliquus mycoplasm can be obtained by bidirectional solid fermentation with I. obliquus as fermentation strain and Chinese medicine residue as fermentation substrate under specific conditions, thus improves the therapeutic effect of I. Obliquus on diabetes.

3.1.8 Phellinus igniarius

Phellinus igniarius, also known as Phellinus linteus, is very popular in eastern countries and has been used as food and medicine traditionally. It belongs to Phellinus spp. of Basidiomycotina, Polyporaceae, and mainly parasitizes the trunk, stumps or fallen trees of broad-leaved trees such as mulberry, willow, poplar, oak and hawthorn. P. igniarius contains various active compounds including polysaccharide, fatty acid, ergosterol, flavone, larch tannic acid, coumarin, aromatic acid, mushrooms, and various amino acids [42]. Therefore, P. igniariu is considered as a famous functional plant for preventing and treating various diseases, such as gastrointestinal diseases, lymphatic diseases, and cancer [43]. Liu et al [44]using high-fat diet (HFD)-induced and low-dose streptozotocin (STZ)-induced type 2 diabetes rats as models to evaluate the hypoglycemic and hypolipidemic effects of P.

linteus mycelial extract (PLE). They found that PLE can reduce the hepatic glucose production by inhibiting the expression of key hepatic gluconeogenesis enzymes (FBPase, G6Pase) and the degradation of hepatic glycogen. Huang et al. [45] studied the inhibitory activities of several P. linteus extracts on α-glucosidase, among which ethanol extracts showed strong inhibitory activities with IC50 ranging from 9.25 to 332.55 μg/mL. The isolated Hispidin, Hisplon and Inotyrone all showed strong inhibitory effect on α-glucosidase activity.

3.1.9 Grifola frondos

Grifola frondosa, which belongs to Basidiomycetes, is a kind of edible and medicinal fungi mainly used to treat dysuria, edema, beriberi, and ascites due to cirrhosis, diabetes, hypertension and obesity [46]. G. frondosa has inhibitory effect on digestive enzymes related to type 2 diabetes. Su et al. [47] analyzed the chemical composition and inhibition kinetics of G. frondosa bioactive components, which indicated that the n-hexane extract of G. frondosa showed strong anti-α-glucosidase activity.

4. Natural active components with α-glucosidase inhibitory activity in plants

4.1 Polysaccharide

Polysaccharide is a kind of compounds compose of many identical or different monosaccharides linked by α or β-glycosidic bonds. Polysaccharide is ubiquitous in plants, including starch, cellulose, polysaccharide, pectin, etc. Because of the wide sources of plant polysaccharides, the molecular composition and molecular weight of different kinds of plant polysaccharides are different. Polysaccharide is one of the main functional active ingredients of various plants since it has many biological activities such as reducing blood lipid, lowering blood sugar, resisting oxidation and enhancing immunity, hence it has a wide application prospect in the fields of medicine and functional food.

The role of polysaccharides from various plants in the treatment of diabetes has been deeply investigated. The increased insulin may be related to the hypoglycemic characteristics of polysaccharides, since it can reduce β cell damage and accelerate glucose metabolism in liver of experimental diabetic animals [48]. Edible fungi have certain potential in anti-diabetic phytotherapy. They are rich in natural compounds, such as polysaccharides, which have been considered to have the effect of reducing hyperlipidemia since ancient times. A polysaccharide component PP80 and a low molecular weight water soluble polysaccharide (PPW-1) isolated from P. igniarius fruiting body can inhibit α-glucosidase and improve glucose consumption in the insulin resistance cell model. Moreover, the α-glucosidase inhibition of PPW-1 was significantly higher than that of PP80 and acarbose [49].

Acacia polysaccharides can significantly increase the content of active glucagon-like peptide-1 (GLP-1) in the ileum and colon, thereby significantly reducing hyperglycemia in diabetic rats [50]. Liu et al[51] found that mulberry leaf polysaccharides can reduce the levels of free fatty acids and inflammatory mediators in diabetic rats, weaken the oxidative stress damage, improve the mitochondrial function of pancreatic islet cells and protect pancreatic β cells. Corn silk polysaccharide has a strong inhibitory activity on α-glucosidase, which may be related to its relatively small molecular weight. Moreover, the inhibitory effect was found irreversible and competitive [52].

The selenized polysaccharides (PRSP) obtained from black tea polysaccharides (RCP) has a significantly higher inhibitory effect on α-amylase and α-glucosidase than the purified RCP (PRCP) and shown competitively reversible inhibition effect on both enzymes [53].

4.2 Alkaloids

Alkaloids are a kind of natural products with complex structure and remarkable pharmacological activities, which have anti-tumor, anti-virus, anti-bacterial, anti-inflammatory, and hypoglycemic effects. With the deepening of modern pharmacological research, alkaloids with α-glycosidase inhibitory activity are constantly being explored, and their hypoglycemic mechanism has also been deeply studied [54].

Polyhydroxy alkaloids in mulberry leaves are one of the main anti-diabetic active ingredients. Besides, it has the effect of inhibiting the absorption of sugar in the small intestine and reducing blood sugar after eating, especially 1-deoxynojirimycin (DNJ). DNJ is a piperidine alkaloid and is considered to be one of the most effective α-glycosidase inhibitors [55]. Moreover, the synergistic effect of flavonoid and DNJ on the inhibitory activity of α-glucosidase was found. For example, Yue et al [56] reported the synergistic inhibitory effect of 5, 6, 7-trihydroxyflavone aglycone and 1-DNJ on α-glucosidase in mice. Song [57] found that alkaloids contained in Zanthoxylum armatum have a good inhibitory effect on α-glucosidase, and the inhibitory intensity is dependent on the concentration. The inhibitory type is typical non-competitive inhibition, which can reduce the activity of α-glucosidase by combining with enzyme and substrate complex. Zheng [58] constructed the three-dimensional structure of α-glucosidase in Saccharomyces cerevisiae using homologous modeling, and analyzed the inhibition mechanism phellodendrine on α-glucosidase activity using molecular docking technology. It was found that phellodendrine was a reversible anti-competitive inhibitor of α-glucosidase. The hydrogen bonding, hydrophobic interaction and π -anion interaction were the main forces between phellodendrine and α-glucosidase molecules. In the alkaloid extracts of Coptis, palmatine and berberine had obviously inhibitory effect on α-glucosidase, and the IC50 of palmatine and berberine on α-glucosidase were 1.24 mg/mL and 2.02 mg/mL respectively [59]. Matrine is a bitter compound extracted from Sophora flavescens. Matrine can significantly improve the glucose metabolism and increase the secretion of insulin and GLP-1 in diabetic mice. Therefore, it is expected to become a potential drug in treating diabetes [60].

4.3 flavonoid

Flavonoids refer to a large class of compounds containing a benzo-γ-pyrane structure with two phenyl rings and one heterocyclic ring, which is known for numerous biological activities and low toxicity. The flavonoid family contains thousands of compounds, which can be further divided into many subclasses according to their chemical structures, including flavonoids, isoflavones, flavonols, flavanols and anthocyanins [61]. Many studies have shown that flavonoids can inhibit α-glucosidase and improve insulin resistance of cells [62]. It was also found that flavonoids can effectively reduce diabetes complications by regulating glucose metabolism. Numerous studies have shown that dietary flavonoids could inhibit α-glucosidase and improve cell insulin resistance, insulin receptor (IR), protein tyrosine phosphatases (PTPs), peroxisome proliferator-activated receptor γ (PPAR-γ), and adenosine monophosphate-activated protein kinase (AMPK) are the main targets of the insulin-sensitization effects of flavonoids [63]. Dietary flavonoids as secondary metabolites of plants are widely found in daily consumed vegetables and fruits, and they have various health promoting effects. By compared 27 kinds of dietary flavonoids, it was shown that apigenin-7-O-glucoside may be the most effective α-glucosidase inhibitor and insulin sensitizer [64]. Ampelopsis grossedentata flavonoids and their derivatives have good effects on α-glucosidase inhibition and hypoglycemic activity [65].

4.4 Polyphenol compounds

Polyphenols are natural bioactive substances widely distribute in plant raw materials and have increasingly focused in reducing the risk of obesity and diabetes in recent years. Studies have shown that eating fruits and vegetables is related to disease prevention, which was mainly emphasizing the potential of using natural compounds to treat obesity and diabetes [66].

Several polyphenols in common fruits, such as anthocyanins, procyanidins, flavonoids, flavonols, flavan-3-ols, flavonoids and phenolic acids, have been reported [67], as well as their antioxidant activities. Stewart and McDougall [68] found that berry extract rich in polyphenols can inhibit the activities of α-glucosidase and α-amylase in vitro, which might benefit for preventing and curing diabetes and obesity. Many studies have confirmed that tea polyphenols have obvious inhibitory effects on amylase and glucosidase activities [69]. More importantly, tea polyphenols are considered as potential drugs for preventing and controlling type 2 diabetes mellitus [70].Tong et al [71] investigated the inhibitory efficiency of water extracts from natural black tea and water extracts from

baked black tea on α-amylase and α-glucosidase activities. It was found that baking treatment would increase the content of tea polyphenols with low polarity and thereby effectively improve the inhibitory efficiency. Several natural grains that containing polyphenol compounds, such as buckwheat, quinoa and sorghum, can effectively delay the blood sugar reaction caused by flour wrappers [72]. It can be attributed to the following possible mechanisms. Firstly, polyphenols can interact with starch to decrease the binding sites of enzyme. Secondly, polyphenols have the ability to inhibit the activity of starch digestive enzymes [73, 74].

5. Problems and prospects

The high incidence of diabetes has attracted worldwide attention and quickly become one of the most common and costly chronic diseases. Alpha -glucosidase inhibitory are considered as the preferred choice for preventing and treating of type 2 diabetes. However, most of the current α-glucosidase inhibitors drugs used in clinic have various side effects. Extracting α-glucosidase inhibitors with better activity and less side effects from natural plants is a hot topic in recent years. Active ingredients such as polysaccharides, flavonoids, polyphenols, and alkaloids in natural plants are potential resource library for finding good α-glucosidase inhibitors. However, the problems such as low content and the high extraction and separation cost of active ingredients put forward higher requirements and challenges for the clinical application of natural α-glucosidase inhibitors from plants. In the future, the research on natural α-glucosidase inhibitors should not only focus on the exploring of more diverse plant active ingredients with α-glucosidase inhibitory activity, but also on decreasing the production cost of natural α-glucosidase inhibitors.

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