Research Progress on the Preparation of Natural α-Glucosidase Inhibitors

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Abstract. Diabetes is one of the major diseases that seriously affect human life and health, especially as it can cause a variety of complications such as cardiovascular diseases, diabetic nephropathy, and neurological diseases, imposing a heavy burden on the quality of life and economy of patients. Alpha-glucosidase inhibitors (AGIs) are important drugs for treating diabetes because they can directly act on α-glucosidase (AG) to decompose carbohydrates in food into glucose, so as to achieve targeted regulation of blood sugar levels. Commonly used clinical drugs, such as acarbose, often have side effects such as gastrointestinal adverse reactions and liver function damage during long-term use. Therefore, there is an urgent need to develop new AGIs with higher efficiency and lower side effects. Researches on natural AGIs have gained global attention in recent years, since they have the advantages of wide availability, relatively more safety and low side effects. Typically, the sources of natural AGIs include extracting from natural plants or generating by microbial fermentation and enzymatic catalysis. This article reviewed the major advancements in both areas in recent years, including the utilization of green solvent extraction techniques and novel screening and separation methods for enhancing the efficiency of extraction and screening of natural AGIs substances, the application of biotechnologies for screening of microorganisms with natural AGIs from both microbial and food sources for expanding the resource pool of natural AGIs.

Keywords: Alpha-glucosidase inhibitors, Diabetes, Novel green solvent extraction technologies, Microbial fermentation, High throughput and computer virtual screening technologies.

1. Introduction

Diabetes is a chronic metabolic disorder characterized by elevated blood sugar levels due to a lack or ineffective use of insulin in the body. In recent years, with the improvement of people's living standards and modern unhealthy lifestyles, the global incidence of diabetes has continued to rise. According to the latest data from the International Diabetes Federation (IDF), the number of diabetes patients worldwide has reached 589 million by 2024 and is projected to exceed 853 million by 2050 [1]. In addition, diabetes can cause a variety of complications, including kidney disease, neurological disease, cardiovascular disease, amputation and blindness, etc. [2].

Maintaining normal blood sugar levels is crucial for controlling the occurrence and development of diabetes-related complications. Alpha-glucosidase (AG) is a collective term for enzymes that catalyze the hydrolysis of α -glucose groups from the non-reducing end of substrates containing α -glucosidic bonds, including sucrase, maltase, isomaltiase, etc. Generally, the carbohydrates in the food would be first hydrolyzed into shorter polysaccharides under the catalysis of amylase in saliva, and then further converted by amylase secreted by the pancreas. At small intestine, α -glucosidase would responsible for hydrolyzing the α-1,4 glycosidic bonds of oligosaccharides and disaccharides and converting them into glucose [3]. A large number of studies have shown that α -glucosidase inhibitors (AGIs) can delay the digestion process of carbohydrates in the diet by limit the catalytic activity of AG, thereby effectively reducing the peak of postprandial blood glucose, adjusting the level of blood glucose in the body, and regulating postprandial hyperglycemia symptoms in patients with type 2 diabetes mellitus. Therefore, AGIs has become an important treatment option for type 2 diabetes and become a hot spot in new drug research and development at present [4].

Currently, the clinically used AGIs major include acarbose, voglipopolol and miglitol. Among them, acarbose, the most widely used, is isolated from *actinomycetes*, voglipopol is isolated from *Streptomyces microbium*, and migliol is derived from 1-deoxynojirimycin, a compound specific to

mulberry plants. In recent years, various adverse effects of these drugs have been reported, such as bloating, diarrhea, nausea, etc., making the investigation of natural AGIs with high efficiency and few side effects of great significance [5]. Due to the rich active ingredients, the main source of natural AGIs is extracted from plants or fermented by special microbes. More and more natural active ingredients, such as polysaccharides, alkaloids, flavonoids, polypeptides, saponins, etc., have shown good inhibitory activity against AG. These plant-based AGIs will become potential resources for the study and treatment of type 2 diabetes [6].

Conventional organic solvent extraction methods have problems such as high solvent consumption, poor selectivity and heavy environmental burden. However, the content of these active substances in natural plants is usually low and the structure is complex, which put forward higher request for the extraction, purification and screening separation techniques for natural AGIs. Recently, novel green solvents have received extensive attention, such as supercritical fluids, ionic liquids, and deep eutectic solvents (DES), which have been widely applied in the extraction of natural AGIs [7]. Meanwhile, the utilization of high-throughput screening (HTS), specific targeting analysis techniques, immobilization techniques, ultrafiltration techniques, etc., has facilitated the efficient screening and separation of natural AGIs, significantly enhancing the efficiency of AGIs discovery and the depth of mechanism analysis [8]. Bioprocessing is another important way to obtain green AGIs substances. A large number of studies have shown that many microorganisms, such as medicinal fungi, large edible fungi, probiotics, plant endophytes, etc., not only secrete substances with AGIs activity themselves, but also improve the quality and efficiency of natural AGIs substances through biocatalysis by using their powerful metabolic networks and sophisticated enzyme systems [9]. Therefore, this paper focuses on the major progresses in the preparation of natural AGIs in these two aspects in recent years, with the aim of providing theoretical references and new development ideas for the search of potent and safe novel AGIs in natural plants and microorganisms.

2. Novel green solvent used for extracting natural AGIs from plants

In response to the problems of large usage, heavy pollution and poor selectivity of traditional organic solvents, many new green solvents, including supercritical fluids, ionic liquids, deep eutectic solvents (DES), are widely used in the preparation of AGIs active substances in natural plants, especially DES. Deep eutectic solvents usually composed of hydrogen bond acceptors and hydrogen bond donors in a molar ratio, which can promote cell wall deconstruction and release intracellular active components by forming stable complexes with cellulose molecules in the plant cell wall and breaking intermolecular hydrogen bonds [10]. Meanwhile, selective solubilization of different target compounds can be achieved by regulating the types of cationic substituents and anions, result in significantly improving of the extraction efficiency [11]. Moreover, DES has advantages such as low cost, easy preparation, biodegradability and low toxicity. So, DES has been widely used as a solvent in the preparation of plant-derived natural AGIs.

A large number of studies have found that composition and properties have a decisive influence on extraction efficiency in DES extraction systems. Qin et al. [12] found that in DES composed of different types of HBA and HBD, DES (tetraethylammonium:1,2,4-butantriol, Teab:1,2,4-but) had significantly higher extraction rates for TPC and TFC than other solvents. It was mainly attributed to the stronger mobility of DES when 1,2,4-butanediol was used as HBD, which leads to a violent collision between the solvent and the polyphenol, increasing the solubility of the polyphenol and thereby enhancing its extraction efficiency. Moreover, the α -glucosidase inhibition activity of the prepared polyphenol extract was not significantly different from that of acarbose.

Viscosity and acidification are also important properties that affect the extraction efficiency of DES. Typically, a DES system with lower viscosity is conducive to solute diffusion, while moderate acidification can increase the solubility and extraction rate of weakly basic alkaloids by promoting protonation. Among the 11 DES consisting of choline chloride and betaine as HBAs, the betaine-based DES was significantly less efficient in extracting active substances from *Eleutherococcus*

senticosus. This may be due to the increased viscosity hindering the solvent's extraction ability, while DES with choline chloride (ChCl) as HBA and ChCl-lactic acid as HBD showed excellent solubilization ability and thus had higher extraction efficiency [13]. However, Le et al. found that in the extraction of berberine, ChCl had a negative impact on extraction efficiency, possibly because it would compete with berberine to accept hydrogen bonds from carboxylic acids (HBD), thereby reducing the ability of berberine to form carboxylate salts with carboxylic acids. However, the extraction rate of berberine would be enhanced with the addition of water to acetone and reached the highest extraction efficiency in 75% acetone-aqueous solution [14]. In addition, the length of the fatty acid chains that composed of DES also had significant influence the extraction efficiency of alkaline. This is mainly because the salts produced by the reaction of short-chain fatty acids with the target compound tend to dissolve in water, meanwhile, long-chain fatty acids have larger molecular weights and stronger intermolecular forces such as van der Waals forces with the target compound [15].

DES has been used in the extraction and separation systems of novel AGIs in recent years. Among them, stimulus-responsive DES/H_2O systems can reversibly switch between single-phase and two-phase states depending on experimental conditions (temperature, pH, carbon dioxide, etc.). Therefore, compared with traditional DES/H_2O two-phase systems, these systems facilitate the recycling and reuse of DES and are more in line with green chemistry and sustainable development principles. For example, in a pH-responsive DES/water system, DES itself is inherently acidic, and changes in pH in the extraction system may affect the ionization state of DES, thereby altering their miscibility with water and resulting in pH-responsiveness. Ma et al. [7] reported that when extracted isorhamnetin and 1-DNJ from mulberry leaves at 50% [Hex-A][2-methyl-2,4-pentanediol(2-methyl-2,4-pentanediol, MPD)], at the optimal pH of 3 the distribution ratios of isorhamnetin and 1-DNJ in the [HexA][MPD]: H_2O phases reached 6.69:1 and 1:9, respectively. It meant that the flavonoids represented by isorhamnetin were mainly enriched in the DES phase, and the alkaloids represented by 1-DNJ were enriched in the H_2O phase, thus achieving the in-situ synchronous separation of the two substances. Based on the polarity and acid/base differences of the novel DES composed of citric acid and polypropylene glycol, Yang et al. [16] constructed two two-phase systems to achieve sequential separation of four active substances in tea residue with improved separation selectivity. Firstly, the DES/ ethyl acetate two-phase system was constructed to extract EGCG and ECG, which were more than 95% of the relatively lower polarity, into the ethyl acetate phase. Then, KOH was added to produce an aqueous two-phase system containing polypropylene glycol 400 and potassium citrate, selectively allocating 76% of theanine to the citate-rich phase and 96% of caffeine to the PPG400-rich phase.

3. Novel screening and separation techniques for natural AGIs

After obtaining crude extracts of natural products, how to efficiently and accurately identify components with α -glucosidase inhibitory activity is a key bottleneck in the preparation of natural AGIs. Conventional active ingredient screening methods are mainly based on activity-guided fractionation strategies, which are overall activity-oriented and involve repeated extraction and separation to obtain target monomer compounds. These methods typically have low separation throughput, long cycles, high costs, and are prone to missing trace active ingredients. The introduction of high-throughput screening (HTS), specific targeted analysis techniques, novel immobilization techniques, ultrafiltration techniques, etc. into the efficient screening and separation of natural AGIs has significantly improved the discovery efficiency and mechanism analysis depth of AGIs.

Affinity selection-mass spectrometry method is an emerging HTS method that uses “protein-metabolite” interactions to identify specific ligands of enzymes/receptors. Gao et al. [17] immobilized AG in agarose gels and then thoroughly mixed it with tea samples, as a results 14 polyphenols classified as gallocarylated were screened out by nontargeted metabolite identification analysis. Chen et al. [18] Twenty-eight compounds with AG inhibitory activities were screened from *Polygonum cuspidatum* extract in one go by using a high-throughput bioassay profiling analysis platform which

integrates chromatographic separation, mass spectrometry analysis and activity evaluation modules. This platform significantly increased the throughput and accuracy of AGIs screening by integrated the separation, identification, and activity evaluation.

Magnetic nanoparticle immobilization technology can fix AG on magnetic nano-carriers and then be used for the screening and separation of AGIs from plant extracts. The technology provides reliable technical support for the efficient identification of natural AGIs from complex plant extract and the development of new substances. For example, by immobilized AG with functionalized magnetic nanoparticles Fe_3O_4@SiO_2-NH_2, two potential biflavonoid α -glucosidase inhibitors were successfully screened from the extract of *Selaginella pulvinata* (Hook.et Grev.) Maxim.) [19].

Affinity ultrafiltration technology is another important screening technology for AGIs, especially peptide. It is a selective and effective target-enzyme-directed drug discovery strategy based on affinity binding between the target-enzyme and the corresponding inhibitor, which often combined with HPLC-MS for identifying active compounds from complex matrices [8]. With advantages such as rapidity, effectiveness, high sensitivity and high throughput, it has been used for the rapid screening of AGIs in complex plant extracts. Eight flavonoid AGIs were identified from raspberry leaves by multi-target affinity ultrafiltration combined with HPLC-MS/MS [20]. Several substances with strong inhibitory effects on α -glucosidase and α -amylase were rapidly screened from the aqueous extract of *Mallotus furetianus* Muell Arg, including catechins, epicatechins, rutin, ferulic acid and kaempferin, etc. by combination of affinity ultrafiltration and HPLC ESI qTOF MS/MS [21].

Computer virtual screening techniques such as molecular docking were applied to traditional separation and purification methods, providing a feasible strategy for rapid screening of AGIs in plant extracts. Lu et al. [22] established an effective strategy for rapid screening of potential AGIs from leaves of *Rheum tanguticum* through activity-directed extraction and enrichment optimization, UPLC-QTOF-MS /MS, molecular docking and in vitro validation. The results showed that after been enriched by AB-8 resin, the purity of the flavonoid components was increased by 17 times, and its inhibitory activity against AG was increased by 33.9 times, meanwhile, six potential AGIs were rapidly screened from 36 flavonoid species.

In summary, the application of high-throughput screening and computational simulation methods has broadened the sources of natural AGIs, shortened the screening cycle, and provided important technical support for the precise development of natural AGIs based on molecular-level mechanism of action.

4. Investigation on microorganisms secreting AGIs and their fermentation

Microorganisms and their fermentation processes are also important sources for obtaining natural AGIs. On the one hand, many microorganisms have been found to secrete substances with AGI activity. On the other hand, some microorganisms can also convert the active ingredients in plants into new and more active AGIs through their powerful metabolic networks and rich enzyme systems.

The microbial sources of natural AGIs are mainly medicinal fungi, edible fungi and probiotics, etc. From medicinal fungus *Grifola frondosa*, bis-γ-butyrolactone grifolamine A, a γ-butyrolactone dimer firstly isolated in nature, showed a strong inhibitory effect on α -glucosidase in vitro, stronger than the three isolated monomers γ-butyrolactone and even stronger than the positive control acarbose. Molecular docking studies indicated that it could locate in the active pocket of AG via van der Waals forces, alkyl interactions, etc. and alter the microenvironment structure of AG [23]. Two new styrylpyrone dimers with multiple phenolic hydroxyl groups and aromatic rings were identified from the culture broth of *Phellinus igniarius SY489*. They can effectively form hydrogen bonds, Pi-Pi T-shaped interactions and other forces with the amino acid residues of AG, resulting in a low binding energy of AG to substrate [24]. Xiao et al. [25] isolated more than 20 compounds from *Cordyceps* fruiting bodies, among which ergosterol compound, alkaloid compounds, and aliphatic derivatives showed strong inhibitory effects on AG than acarbose, especially a aliphatic derivative (5-hydroxy-octadeca-(*6E*, *8Z*)-dienoic acid) showed the most significant inhibitory effect. Edible fungi are

another major source of AGIs. Hericenone D, hericene A and D in the fruiting body of *H. erinaceus* and erinacerins Q-T in mycelium of *H. erinaceus* all have AG inhibitory activity, which can reduce carbohydrate absorption and thus reduce blood sugar. Additionally, erinacerin C-L, isolated from the solid culture of *H. Erinaceus*, also has AG inhibitory activity [26].

Microbial fermentation can also improve the inhibitory activity of active substances in natural plant substrate through the complex enzyme system and powerful metabolic network of microorganisms. Therefore, many microorganisms with low nutritional requirements for fermentation and strong ability to degrade plant substrates are widely used in the preparation of novel and highly active AGIs in hypoglycemic plants. After been solid-state fermented by *Monascus purpureus*, the content of daidzein, genistein and genistein in soybean residue could be reduced by 21.29 times, 6.99 times and 22.71 times, respectively. Kim et al. [27] found that AG inhibitory activity of the fermented soybean residue was 16.54 times higher than that in the unfermented soybean residue, which could be attributed to the β -glucosides produced during solid-state fermentation converting isoflavone glycosides into aglycone. On the other hand, with the development of metabolite analysis methods, dynamic analysis of the fermentation process provides new ideas for finding novel AGIs from fermentation metabolites. Untargeted metabolomics studies revealed the metabolite differences between *Ganoderma lucidum* fermented Tartary buckwheat and non-fermented Tartary buckwheat, which indicated that fermentation could enhance the concentrations of hesperidin, xanthotoxol and quercetin 3-O-malonylglucoside by 240.21 times, 136.94 times and 100.77 times, respectively [28]. By studied with extensive targeted metabolomics, Zhao et al. find that mixed lactic acid bacteria fermentation had significant effects on the metabolic characteristics of quinoa, resulting in an obvious increase in the content of flavonoids, phenolic acids, and amino acid derivatives. In particular, the fermentation not only enhanced the flavonoids concentration by more than 40 times, but also catalyzed the new flavonoid metabolites generation, including three isoflavones, one flavonol, and one unclassified flavonoid [29].

5. Conclusion

The technology for obtaining natural α -glucosidase inhibitors is moving towards being green, efficient and precise. New extraction solvents such as DESs and ILs and auxiliary extraction techniques such as UAE and SAE have significantly improved extraction efficiency and selectivity; The application of high-throughput screening platforms, affinity mass spectrometry, immobilized enzyme fishing and other techniques has accelerated the discovery and identification of active ingredients; Microbial fermentation and biotransformation provide new approaches for the large-scale production of natural AGIs.

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