Advances in Biotechnology for α-Glucosidase Inhibitory Research

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Abstract. Alpha-Glucosidase inhibitors (AGIs) are effective agents for managing postprandial hyperglycemia in type 2 diabetes mellitus (T2DM). With the increasing demand for safe and natural hypoglycemic compounds, biotechnology-based approaches have become crucial for the discovery and development of novel AGIs. This article reviews recent research progress of biotechnology in the development of natural AGIs from the following aspects. Firstly, the microbial sources of natural AGIs are constantly expanding, with a large number of AGIs reported from medicinal fungi, edible fungi, probiotics, and endophytic fungi in plants. Meanwhile, studies on using fermentation and enzymatic biotransformation to enhance the content and bioactivity of natural AGIs in medicinal plants have achieved significant progress. In addition, advanced technologies such as metabolomic analysis, synthetic biology, and high-throughput targeted screening have been widely applied in natural AGIs research. The integrated application of these biotechnological approaches facilitates the discovery of potent and safe AGIs, promoting their industrial application and potential value in T2DM management.

Keyword: α-glucosidase inhibitors, diabetes mellitus, microbial fermentation, biosynthesis, bioactive peptides.

1. Introduction

Diabetes mellitus is a global metabolic disorder caused by multiple factors, including genetic predisposition, environmental influences, autoimmune dysfunction, and unhealthy dietary habits. It is primarily characterized by hyperglycemia resulting from insufficient insulin secretion or insulin resistance[1].Over the past decade, the worldwide prevalence of diabetes has continuously increased, and it is projected that the global number of patients with type 2 diabetes mellitus (T2DM) will reach 642 million by 2046[2]. Diabetes is often accompanied by severe acute and chronic complications, such as diabetic ketoacidosis, cardiovascular disease and diabetic nephropathy, which seriously threaten the physical and mental health of patients [3-4].

Based on pathological characteristics of T2DM, current therapeutic drugs can generally be divided into two categories. One category includes drugs that indirectly reduce blood glucose levels, such as metformin and sulfonylureas, which enhance pancreatic β-cell activity and promote insulin secretion. The other category includes drugs that directly reduce postprandial blood glucose levels, mainly α-glucosidase inhibitors (AGIs), which delay the conversion of ingested carbohydrates into glucose and inhibit glucose absorption into the bloodstream. In contrast, AGIs do not directly target pancreatic islet cells or metabolic organs, which is beneficial for alleviating the metabolic burden on insulin to some extent and improving the function of impaired pancreatic β-cells. Therefore, AGIs have become an important strategy for the prevention and treatment of T2DM[5-6].

At present, AGIs such as acarbose and voglibose have been widely used in clinical practice and are regarded as first-line drugs for diabetes treatment. However, these drugs are often associated with gastrointestinal side effects, which limit their broader clinical application[7]. Therefore, the development of natural AGIs with higher safety and fewer side effects has become a major research focus. With the rapid advancement of biotechnology, biotechnological approaches have become an important strategy for obtaining natural AGIs.

On the one hand, an increasing number of biological resources capable of producing natural AGIs have been explored, including various microorganisms and plants. Among these resources ,

microorganisms have gradually become a research hotspot due to their abundant availability, rapid growth, low production cost, and suitability for industrial-scale production. In recent years, numerous natural AGIs have been isolated from secondary metabolites produced by microorganisms such as medicinal fungi, edible fungi, probiotics, and plant endophytes. Some of these compounds even exhibit stronger AGIs activity than clinically used drugs like acarbose. For example,(17R)-4-hydroxy-17-methylincisterol isolated from *Phellinus monticola* 14a[1], a novel bis-γ-butyrolactone from *Grifola frondosa*[8], triterpenoids from *Ganoderma angustisporum*[9], protoasukamycin and its analogs from *Streptomyces sanglieri* GZWMJZ-725[10], and a novel polyketide derivative and pennafuredin from *Penicillium* sp. HK-G2[11] have all shown significant AGI activity. On the other hand, the complex metabolic networks and enzyme systems involved in microbial fermentation processes can facilitate the biotransformation of active substances, resulting in the generation of novel AGIs or AGIs with higher activity. For instance, enzymatic hydrolysis and lactic acid bacteria fermentation can convert bound phenolics into free phenolics by breaking down plant cell walls, consequently enhancing AGIs activity [12, 13].

With the development of bioengineering, metabolic engineering, genetic engineering, and synthetic biology, combined with metabolic network analysis and molecular simulation, microbial fermentation technology has been increasingly applied in the development of natural AGIs. Metabolomics approaches, including widely targeted, targeted, and untargeted metabolomics, enable comprehensive and dynamic profiling of microbial fermentation products. Combined with molecular docking and other computational methods, these approaches allow more efficient screening of AGIs and elucidation of their inhibitory mechanisms, thereby facilitating the discovery of novel and highly active AGIs [14-15]. The identification and analysis of key genes involved in AGI biosynthesis provide the possibility for constructing biosynthetic pathways, making the production of AGIs more efficient, controllable, and environmentally friendly [16-17]. In addition, targeted screening of peptides with high α-glucosidase inhibitory activity from food proteins has also become a current research hotspot [18]. Therefore, this review summarizes recent advances in AGI research from the perspectives of microbial resources and fermentation technologies, dynamic and comprehensive analysis of microbial fermentation metabolic profiles, the application of biosynthesis technologies, and the preparation of bioactive peptides.

2. Natural AGIs derived from microorganisms continue to expand

Microorganisms capable of producing AGIs include medicinal fungi, edible fungi, probiotics, and plant endophytes. Studies have shown that secondary metabolites produced by plant endophytes possess diverse and complex chemical structures as well as significant antidiabetic activity, indicating promising potential for screening natural AGIs [19]. For example Li et al. isolated three novel compounds from *Streptomyces sanglieri* GZWMJZ-725, an endophytic actinomycete of *Houttuynia cordata Thunb*, including one protoasukamycin and two protoasukamycin analogs, all of which exhibited higher α-glucosidase inhibitory activity than acarbose [10]. Compound (17R)-4-hydroxy-17-methylincisterol, isolated from the secondary metabolites of *Phellinus monticola* 14a, was found to bind stably to the active site of α-glucosidase. It forms a complex with the active pocket of the enzyme through hydrogen bonding and hydrophobic interactions, thereby exerting inhibitory activity [1]. In terms of edible fungi, more than twenty compounds have been isolated and identified from *Grifola frondosa*, among which several pyrrole alkaloids and ergosterols exhibited significant α-glucosidase inhibitory activity[20]. These compounds exert hypoglycemic effects by delaying carbohydrate digestion and absorption, thus serving as natural antidiabetic agents. Furthermore, during the preparation of polysaccharides from *G.frondosa*, grifolamine A, a novel bis-γ-butyrolactone compound, was identified, which showed strong in vitro inhibitory activity against α-glucosidase [8].

On the other hand, microorganisms possess complex metabolic networks and diverse enzyme systems.During fermentation, microorganisms secrete various enzymes, including amylases, proteases,β-glucosidases,tannases,and cellulases. These enzymes hydrolyze and biotransform

bioactive compounds covalently bound to plant cell walls. This has the advantages of enhancing the solubility of active substances, modifying the structure of active components, and generating novel bioactive compounds[13]. Therefore, exploring new AGIs from microbial fermentation metabolites has become a research hotspot [21]. For instance, solid-stated fermentation of mulberry leaves with *Aspergillus cristatus* could enhance the total flavonoid content by approximately three fold [12]. Pan et al.[22] identified eight phenolic compounds with strong AGI activity from lactic acid bacteria-fermented pecan kernels, including methyl ellagic acid glucoside, methyl ellagic acid, and dimethyl ellagic acid glycosides. These compounds exhibited low binding energy with α-glucosidase and could form hydrogen bonds with amino acid residues in the catalytic active site, thereby inhibiting enzyme activity. Moreover, Ruan et al.[15] reported that fermentation of lychee pulp by *Lactiplantibacillus plantarum* NCU0011259 could significantly enrich compounds with high antioxidant and AGI inhibitory activity, such as p-coumaric acid, ferulic acid, and tiliroside. They proposed that deglycosylation is the primary pathway to increase AG inhibitory activity, since it hydrolyzes the glycosidic bonds and releases aglycones with stronger lipophilicity and tighter binding affinity to α-glucosidase, thereby improving inhibitory effects. The high content of bound phenolics and glycosylated compounds in passion fruit peel limits its AG inhibitory activity. Tang et al. [23] found that the fermentation with β-glucosidase-producing *Lactobacillus* could achieve target hydrolysis of bound phenolics and significantly increase beneficial polyphenol content. With computer-aided screening, 38 phenolic compounds, including phenolic acids, flavonoids, and flavonols, were identified as potential dual inhibitors of α-glucosidase and α-amylase.

In summary, on the one hand, microorganisms are important sources for screening natural AGIs, on the other hand, biotransformation during the microbial fermentation process represents a key strategy for obtaining novel and highly efficient AGIs.

3. Obtain novel AGIs from microbial fermentation metabolic profiles

Due to the complex and diverse composition of microbial fermentation broths compared with plant extracts, various analytical tools and techniques have been widely used to comprehensively and dynamically analyze the metabolic profiles of microbial fermentation metabolites. Moreover, combined with molecular docking analysis, AGIs substances can be screened accurately and quickly, thus facilitating the discovery of novel and highly active AGIs.

Widely targeted metabolomics is a high-throughput analytical approach capable of simultaneously detecting hundreds or thousands of metabolites. This technique enables comprehensive characterization of metabolic changes during microbial biotransformation. Zhao et al.[24] conducted a UPLC-MS/MS-based widely targeted metabolomic analysis to investigate the dynamic changes in metabolites of quinoa fermented by mixed lactic acid bacteria (*Lactobacillus casei*, *Lactobacillus plantarum*, and *Ruminococcus*). The results indicated that fermentation increased the concentrations of quercetin, kaempferol, and hesperidin in quinoa by 14.63, 48.31, and 21.39 times, respectively, compared to unfermented samples. And five new flavonoid metabolites were detected in the fermentation broth, including three isoflavones, one flavonol, and one unidentified flavonoid. All these results confirmed that fermentation can convert low-activity, bound glycoside compounds into highly active, free aglycones or phenolic compounds, thereby enhancing their α-glucosidase inhibitory activity. Meanwhile, fermentation could also cause significant accumulation of phenolic acids (such as dihydroferulic acid) and amino acids (such as γ-Aminobutyric acid), which may help alleviate insulin resistance and regulate hepatic glucose metabolism.

Untargeted metabolomics analysis showed that solid-state fermentation of mulberry leaves by *Grifola frondosa* could upregulate 29 metabolites, among which key components such as Loureirin D and ferulic acid derivatives effectively enhanced the α - glucosidase inhibitory activity of mulberry leaf extracts [12]. With the help of UPLC-Q-TOF/MS-based untargeted metabolomics, Ruan et al. [15] found that LAB fermentation could target key metabolic pathways such as phenylpropanoid biosynthesis and regulate the production of more accessible precursor substances, such as

phenylalanine and tyrosine, thereby reshaping the metabolic pathways in lychee pulp. They confirmed that tyrosine is a precursor for the biosynthesis of chlorogenic acid in lychee pulp, and that lactic acid bacteria fermentation regulated this precursor-product relationship. Using UPLC-QQQ-MS/MS-based widely targeted metabolomics to analyze metabolites of mulberry leaves under solid-state fermentation by a mixed microbial strain (including *Lactiplantibacillus plantarum*, *Saccharomyces cerevisiae*, *Trichoderma harzianum*, and *Bacillus subtilis*), 441 differential metabolites were identified, of which 165 were significantly upregulated and 276 were significantly downregulated during fermentation. These differential metabolites, mainly phenolic acids and flavonoids, influenced the antioxidant and α-glucosidase inhibitory activities of the fermentation products[25].

These findings underscore the importance of biological analysis techniques in exploring the complex reaction mechanisms of microbial fermentation, identifying and verifying reaction products, and have become essential methods for obtaining novel and highly active AGIs through microbial fermentation.

4. The application of biosynthesis technologies in AGIs

Compared with traditional chemical synthesis, biosynthesis technologies offer advantages such as lower cost, environmental friendliness, and strong controllability, and have been widely applied in the development of AGIs. Plant tissue culture is an important biosynthetic approach that can replace conventional cultivation to obtain required cells or metabolites, thus becoming an important method for obtaining AGIs with inhibitory activity. Liu et al. developed a suspension culture system of *Carthamus tinctorius cells*, and found that *C. tinctorius* cells-derived CGAs had good α-glucosidase inhibitory activity, especially diacyl- and triacyl-CGAs[26]. Mehmood et al.[27] reported that ultrasonic stimulation significantly affected the enzyme activities and gene expression involved in the biosynthesis of 1-deoxynojirimycin (1-DNJ) and phenolic compounds, ultimately leading to 200.10%, 266.66%, and 211.32% increases in 1-DNJ, TPC, and TFC in mulberry leaves.

In addition to plant-based biosynthesis, constructing microbial synthesis metabolic pathways for AGIs have also attracted considerable attention from researchers worldwide. Especially for 1-DNJ, due to its potent AG inhibitory activity, the construction of its biosynthetic pathway has always been a research focus. Researchers have found that the biosynthetic pathways of DNJ differ significantly between plants and microorganisms, with different enzymes and genes involved in its biosynthesis. For microorganisms, Lorraine [28] first revealed the core mechanism of DNJ biosynthesis in *Bacillus amyloliquefaciens*, indicating that gabT1, yktc1, and gutB1 were involved in the core process of DNJ synthesis, encoding putative transaminase, phosphatase, and zinc-dependent dehydrogenase, respectively. For plants, Xin et al.[29] found that mulberry seed extracts could induce the production of DNJ during fermentation with *Streptomyces lavendulae*, and speculated four pathways involved in DNJ biosynthesis, namely starch and sucrose metabolism, pentose phosphate pathway, glycolysis/gluconeogenesis, and alanine, aspartate, and glutamate metabolism pathway, as well as six key genes associated with DNJ biosynthesis.

In conclusion, biosynthesis will gradually replace traditional extraction methods as an important new technique for the production of AGIs due to its controllability, high production efficiency, and environmental safety.

5. Preparation and catalytic mechanisms of biopeptides

Food-derived α-glucosidase inhibitory peptides (AGIPs) have attracted considerable attention due to their high bioavailability, significant therapeutic effects in T2DM, and lower side effects compared with traditional AGIs. Their functional characteristics are influenced by amino acid composition, sequence, peptide chain length, spatial configuration, and preparation methods [30]. Enzymatic hydrolysis and microbial fermentation are the major preparation methods for AGIPs. By hydrolyzing peanut meal with commercial proteases, Zhou et al.[31] found that peanut peptide with molecular weights ranging from 500 Da to 3 kDa exhibited the best AG inhibitory activity. They significantly reduced postprandial and fasting blood glucose levels and insulin resistance in diabetic mice, while minimizing liver damage. The molecular docking analysis indicated that these peptide sequences enhanced their inhibitory activities through hydrogen bonds, hydrophobic interactions, and the formation of salt bridges with α-glucosidase. They interacted strongly with catalytic residues of AG, disrupting the enzyme-substrate binding, and bound with allosteric residues of AG, inducing non-competitive conformational changes, thereby reducing AG catalytic efficiency. By hydrolyzing *Cyperus esculentus* meal protein with alkaline protease and trypsin, Bian et al. [32] screened eight possible AGIPs from 443 known peptide sequences, and then synthesized three novel AGIPs: AAGF, QPTM, and QGSM. They pointed out that the synthesized AGIPs exhibited different inhibition mechanisms but all exerted inhibitory effects through hydrogen bonding, as well as hydrophobic and electrostatic interactions.

Although preparation of AGIPs through enzymatic hydrolysis has the advantages of high activity and environmental friendliness, its industrial application is limited by the low availability and high cost of food-grade enzymes. The preparation of AGIPs through microbial fermentation has attracted increasing attention worldwide due to the low cost and ease of production. For example, Han et al. prepared Pyropia hypoglycemic active peptide (PBP) by fermentation with *Bacillus subtilis*. Molecular docking studies showed that the peptides APPVDID, GPPDSPY, PPSSPP, and SPPPPA obtained from PBP all showed highly efficient inhibition of α-glucosidase activity, even higher than acarbose. In addition, these PBPs could also promote insulin secretion, improve insulin sensitivity, extend the duration of action, and alleviate inflammatory reactions [33].

In summary, bioactive peptides have advantages such as safe and readily available of raw materials, milder and more efficient preparation processes, and good prospects for industrial application. Furthermore, biopeptides can effectively alleviate diabetes-related symptoms and potentially improve the internal environment of the human body.

6. Conclusion and Outlook

Natural AGIs, characterized by high safety, low side effects, and abundant natural sources, have become an important research direction for the alleviation and treatment of diabetes and the development of functional foods. This review summarizes the research progress on the development of α-glucosidase inhibitors (AGIs) using biotechnology. Green technologies such as microbial fermentation, biosynthesis, and enzyme-assisted production can not only enhance the yield and activity of AGIs but also effectively address the problem of chemical synthesis pollution and low yield from natural raw materials. Meanwhile, combining metabolomic analysis and molecular simulation enables efficient screening and mechanism elucidation of natural AGIs, accelerating the development of novel hypoglycemic substances.

In the future, with the development of multi-omics technologies and synthetic biology, research on natural AGIs will be further deepened, and its industrial application will be promoted. In conclusion, biotechnology will provide more sustainable solutions for AGIs in the prevention and treatment of T2DM.

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