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Review for the application of microbial fermentation technology in the study of natural α-glucosidase inhibitors

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Abstract: *Currently, the number of diabetes patients and their corresponding treatment costs have increased year by year. Therefore, it is urgent to develop drugs with low cost, high efficacy and few side effects for the treatment of diabetes. As the first choice drug for type 2 diabetes, α-glucosidase inhibitors (AGIs) is widely used in the clinical treatment of diabetes. However, most of these drugs have been found to potentially cause various side effects. Natural AGIs derived from plants have gained widespread attention due to their mild, long-lasting, few side effects, high efficacy, and low complications. Microbial fermentation has always been one of the important auxiliary methods in the processing of Chinese herbal medicine. With the development of modern biotechnology, it has been widely applied in the discovery and improvement of natural AGIs. This article aims to review the research progresses of microbial fermentation technology in the development of natural AGIs from three aspects, including the types of microbial fermentation in plants, the effects of fermentation on plant AGIs, and the microorganisms used for AGIs fermentation. This article was expected to provide reference for future research and application development of green, efficient, and affordable AGIs drugs.*

Keywords: *Diabetes; Alpha-glucosidase Inhibitors; Microbial fermentation technology; Hypoglycemic plants*

1. Introduction

Diabetes, characterized by hyperglycemia, is a world widely common metabolic disease and generally relates to insulin insufficiency and insulin resistance. At present, diabetes has become the third disease that seriously threatens human health after cancer and cardiovascular and cerebrovascular diseases [1]. It was reported that the number of adults with diabetes globally increased by 630 million from approximately 828 million between 1990 and 2022, correspondingly, the treatment costs of diabetes are also constantly rising [2]. According to the statistics of the 10th version of the global diabetes map released by the International diabetes Alliance, the direct expenditure cost caused by diabetes in 2021 has reached 966 billion dollars, and might rise to 1 trillion dollars by 2030 [2]. Moreover, diabetes will also cause various complications, which will seriously affect human health if there is no effective treatment and long-term control [3]. Therefore, the current research goal is to develop diabetes drugs with low costs, high efficacy and few side effects, to popularize diabetes treatment and improve the quality of life of diabetes patients as much as possible [4, 5].

Alpha-glucosidase inhibitors (AGIs) are regarded as the first - choice drugs for the treatment of type 2 diabetes caused by insulin resistance and impaired insulin secretion [6]. They are intervention drugs, which can directly regulate postprandial blood glucose by inhibiting the activity of α - glucosidase in the small intestine and delaying the digestion and absorption of carbohydrates. However, currently, the commonly used AGI drugs in clinical practice, such as acarbose, voglibose, etc., have some drawbacks. For example, they may cause gastrointestinal side effects like flatulence, diarrhea, and abdominal pain in some patients [3, 7]. This situation has led to the exploration of alternative sources of AGIs, especially those from natural plants. Obtaining natural AGIs from plants, including medicinal and edible plants, Chinese herbs, plant food, etc., have received world widely attentions [8]. A large number of chemical components with natural AGI activity have been isolated from plants, mainly including polysaccharides, flavonoids, phenolic acids, alkaloids, saponins, etc. For example, Gnaphaffine A isolated from the leaves of *Grewia optiva* (Malvaceae) demonstrated a seven-fold stronger inhibition of α-glucosidase activity

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than acarbose [9]. Nine AGIs were isolated from *Rheum tanguticum* waste [10]. Three new alkaloids and one quinolinedione were isolated from *Haplophyllum tuberculatum* as competitive type of in-vitro AGIs [11]. These plant-derived natural AGIs have become a research hotspot due to their advantages such as mild and long - lasting effects, few side effects, multi - target actions, high catalytic activity, and the ability to effectively reduce complications [12].

Microbial fermentation has always been one of the important auxiliary means for preparing medicinal materials. With the development of modern biotechnology, it has been widely used in the discovery and improvement of natural AGIs [13]. On one hand, an increasing number of microorganisms capable of secreting AGIs have been discovered. On the other hand, researches on enrichment and modification of substances with hypoglycemic activity using beneficial microorganisms become more and more popular. Numerous studies have been conducted to prove that under the action of microorganisms, a series of biotransformations such as oxidation, polymerization, and coupling can occur to various natural hypoglycemic active substances in plants [14, 15]. These transformations can not only increase the content of active substances but also enhance their inhibitory activity against α-glucosidase, even more generate new components with inhibition activity of α-glucosidase. This article mainly reviews the research progress in the application of microbial fermentation technology in the development of natural α - glucosidase inhibitors, including the microbial fermentation types for plants, the effects of fermentation on AGIs in plants, and the microbes used for the AGIs fermentation. The aim of this paper was to provide a comprehensive understanding of this field and offer references for future research and drug development.

2. Microbial fermentation types for plants

The application of microbial fermentation technology in plant resources, especially in traditional Chinese medicine, has a history of thousands of years. Microbial fermentation technology, including liquid fermentation and solid-state fermentation, has played a key role in improving and enhancing the quality of Chinese herbal resources and promoting resource utilization [16].

Solid-state fermentation represents a traditional yet pivotal fermentation method that employs natural or inert substances as substrates, facilitating the metabolic activities of either single or mixed microbial strains in the absence of free water. With the advancement of scientific and technological innovations, modern solid-state fermentation techniques for Chinese herbal medicines have achieved significant achievements, including the transition from open to closed fermentation systems, from empirical to controlled fermentation processes, from shallow tray static fermentation to mechanized fermentation, and from single-strain to mixed-strain fermentation. Especially, the bidirectional solid-state fermentation technology using Chinese herbal medicine as the substrate achieves dual purposes of fermentation, that is, the herbal substrate provides essential nutrients for microbial growth, while microbial metabolism promotes biotransformation and enhances the pharmacological effects of active compounds in herbs [17, 18]. Moreover, these advancements enable the integration of upstream fermentation processes with downstream product separation, thereby promoting the synergism and integration of traditional Chinese medicine fermentation processes, and achieving the maximization of the utilization and value of traditional Chinese medicine resources [15]. Currently, solid-state fermentation has been widely applied in the researches that aimed at enhancing the content and efficacy of AGIs in medicinal and edible plants. Xiao et al. reported that in the soybeans (*Glycine max L.*) after been solid-state fermented with the probiotic *Eurotium cristatum*, there was a substantial reduction in the levels of undesirable compounds, accompanied by a significant increase in the concentrations of desirable flavors such as pentanal-D, methylpropanal, 2-propanol, and propyl acetate. Meanwhile, the α-glucosidase inhibitory activity of the fermented soybeans was enhanced by 22.4% [19]. Magro et al. employed *Aspergillus oryzae* and *Aspergillus niger* for the solid-state fermentation of lentils. The extract derived from *A. niger*-fermented lentils demonstrated the capacity to inhibit up to 90% of α-glucosidase activity, while the extract obtained from *A. oryzae*-fermented lentils exhibited an α-amylase inhibition rate exceeding 75% [20].

Liquid fermentation has emerged as a novel approach for microbial processing of α-glucosidase inhibitors from plants, owing to its advantages in industrial scalability and highly automated control systems. For instance, Ye et al. demonstrated that liquid fermentation with yeast enhanced the α-glucosidase inhibition rate of the fermentation broth by 1.5-fold compared to pre-optimized conditions [21]. Hong et al. utilized *Zygosaccharomyces rouxii* to ferment *Cynanchum auriculatum* Royle ex Wight beverages, which not only significantly increased the key flavor metabolites but also modified the distribution of polyphenols, leading to substantial changes in gallic acid, kaempferol, and gossypol levels. Consequently, both antioxidant capacity and α-glucosidase inhibitory activities were significantly

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enhanced in the fermented products [22]. Wang et al. investigated the fermentation of *Monascus purpureus* to enhance the flavonoid content in mulberry leaves, which demonstrated that both solid-state fermentation and submerged fermentation could significantly increase flavonoid levels, thereby improving the anti-diabetic properties of mulberry leaves. Additionally, submerged fermentation was found to enhance the flavonoid bioavailability during simulated in vitro digestion [18].

3. Effects of fermentation on the AGI in plants

Microbial fermentation plays a crucial role in processing dual-purpose plants for both food and medicinal applications. Its effects on AGI-related substances in plants is manifest through multifunctional mechanisms, such as preserving active ingredients, modulating pharmacological activities, enhancing therapeutic potency, mitigating toxicity, and broadening clinical applications through improved safety profiles.

Diverse enzyme system secreted by microorganisms, such as cellulase, ligninase, pectinase, etc., play an important role in the bioconversion of AGIs in plants. These enzymes can catalyze and degrade the cell walls of plants, improve the membrane permeability, and facilitate the release of bioactive constituents from herbal matrices [23]. Zhao et al. discovered that the fermentation of *Aspergillus cristatus* could significantly increase the polyphenol content in mulberry leaves. It was owing to the secreted hydrolytic enzymes of *A. cristatus*, including β-glucosidase, α-amylase, cellulase and protease, which could effectively hydrolyze the hemicellulose in the cell wall, thus disrupting the combination between hemicellulose and polyphenol substances, and releasing soluble free phenols. Therefore, the fermented mulberry leaves had higher scavenging activity against ABTS radicals and higher inhibitory activity against α-glucosidase [14]. Ren found that fermentation of *Aspergillus niger* could significantly improve the bioaccessibility of polyphenols and antioxidant activity of naked oats in the gastrointestinal tract, meanwhile, under the action of colonic microbiota, polyphenolic substances that bounded to polysaccharides and proteins in the naked oats cell wall would be released, leading to an increase in total phenolic content and antioxidant activity [24].

It is particularly important that during the fermentation process, the metabolic effects of microorganisms and the various secreted enzyme systems can carry out biotransformation or decomposition of the natural active ingredients in plants, thus achieve the purposes of enhancing the content and efficacy of bioactive substances, and generating new components. The non-targeted metabolomic analysis of the synthesis pathways of flavonoids and phenylpropanoids during *A. cristatus* fermentation of mulberry leaves indicated that the contents of p-coumaroyl quinic acid, ferulic acid, etc. were slightly decreased owing to the oxidation of polyphenol oxidases (such as laccase and tyrosinase), etc. secreted by *A. cristatus*. At the same time, oxidative products such as dihydromyricetin could undergo redox reactions or further modifications to generate new structural forms, consequently increasing the content of flavonoid compounds and enhancing the antidiabetic activities of fermented products [14]. Zheng et al. reported that after been fermented by *Aspergillus oryzae*, the contents of total phenols and total flavonoids in the pomelo peel were obviously enhanced, the redox capacity and the inhibitory abilities against α-amylase and α-glucosidase were improved significantly. They suggested that purpurin, apigenin, genistein, and paxilline were the major compounds that enhanced the inhibitory activities of the fermented pomelo peel extract against α-amylase and α-glucosidase [25].

4. Microbes used for the fermentation

Microorganisms used for plant fermentation mainly include edible fungi, endophytic bacteria, medicinal fungi, probiotics, etc.

Edible fungi are important sources for obtaining natural AGIs, which are also widely used for plant fermentation to improve its α-glucosidase inhibitory activity [26]. To improve nutritional components and enhance biological activity of soybean, Cai et al. employed *Auricularia auricula* for the fermentation of soybeans, which demonstrated that the levels of polysaccharides, total phenolics, and total flavonoids all increased obviously. Additionally, the fermentation facilitated the conversion of isoflavone glycosides into aglycones and significantly enhanced the α-glucosidase inhibitory activity of the fermented soybeans [27]. In the work of Wang et al. eight edible fungi were utilized for the solid-state fermentation of *Dendrobium officinale* leaves (DOL), among which *Aspergillus oryzae* showed relatively higher inhibitory effects on α-glucosidase and α-amylase. In the fermented DOL, the contents of total phenolics, free phenolics, bound phenolics, quercetin, and rhoifolin were all increased, and new generated bioactive compounds such as luteolin, gallic acid, and kaempferol were detected [18].

Probiotics can be used not only as functional food or supplement to improve blood sugar control of diabetes patients, but also as adjunctive therapy of traditional diabetes treatment to improve its therapeutic efficacy [28]. Using probiotics as the core strain for plant fermentation can significantly enhance the α-glucosidase inhibitory activity of active substances in the plants. For example, the content of theabrownin in mulberry leaf tea would be enhanced by fermented with *Eurotium cristatum*, thereby improving its α-glucosidase inhibitory capacity [29]. Zhao et al. demonstrated that *Aspergillus cristatus* could enhances the content of total flavonoids in mulberry leaves significantly, particularly lourerin D and arachidoside. It was associated with the secretion of carbohydrate hydrolase by *A. cristatus* during the fermentation process [14].

Medicinal fungi, including *Ganoderma lucidum*, *Phellinus igniarius*, and *Grifola frondosa*, are capable of secreting substances with α-glucosidase inhibitory activity. Yu et al. reported that the EtOAc extract from *P. igniarius* culture medium exhibited significant α-glucosidase inhibitory activity. Four anti-diabetic styrylpyrones isolated from the culture broth and they had higer or comparable α-glucosidase inhibition activities to that of positive control drugs, but lower cytotoxicity [30]. By UHPLC-Q-Exactive Orbitrap MS targeted analysis, Zhen et al. identified 45 compounds, including phenolic, flavonoid, and terpenoid, from the extracts of *Phellinus linteus*. These compounds, particularly polyphenols, showed significant α-glucosidase inhibitory activity [31]. Chen et al. successfully isolated a novel bis-γ-butyrolactone compound, grifolamine A (1), from *G.frondosa* polysaccharides, which had potent inhibitory activity against α-glucosidase [32]. Zhang et al. reported that after been fermented by *G. lucidum*, the polysaccharides, total phenols, flavonoids, and triterpenes in Tartary buckwheat was increased by 122.19%, 113.70%, 203.74%, and 123.27%, respectively. They found that there were 445 metabolites exhibited substantial differential expression. Particularly, the concentration of hesperidin, xanthotoxin, and quercetin 3-O-malonylglucoside was increased by 240.21-fold, 136.94-fold, and 100.77-fold, respectively. The differences in these metabolites were the reason why fermented buckwheat has higher inhibitory activities on α-amylase and α-glucosidase compared to unfermented buckwheat [33].

5. Conclusion

In view of the rapid increase in the number of diabetes patients and treatment costs in recent years, the development of low-cost, efficient, less side effects of diabetes drugs has become a research hotspot. Considering that α - glucosidase inhibitors (AGIs) can not only reduce fasting blood glucose, but also reduce postprandial blood glucose, they are considered as the first choice for the treatment of diabetes, especially type II diabetes. In order to overcome the serious side effects of commonly used AGI drugs in clinical practice, natural AGIs have received widespread attention. Microbial fermentation technology, especially solid-state fermentation technology, plays an important role in increasing the content and improving the efficacy of active substances in plant resources. More and more microorganisms, including edible fungi, endophytic fungi, medicinal fungi, probiotics, etc., are being used in the fermentation of hypoglycemic plants. Under the growth and metabolism of microbes and biotransformation of enzyme systems secreted by these microorganisms, the content and dissolution rate of active substances in these plants are increased, as well as their α-glucosidase inhibitory activities. Therefore, the hypoglycemic effect of these plants was significantly improved.

However, there are still many problems need to be resolved in the preparation of AGIs derived from the fermented plants. In the future, further research should be focused on the following areas, exploring microorganisms that are safe for consumption and have high fermentation efficiency, establishing suitable separation and purification technologies to address the increased complexity of AGIs components caused by the coexistence of microbial metabolites, conducting comprehensive and in-depth safety assessment of AGIs substances obtained from the fermented plants, etc.

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