Application Progress of Biotechnology in the Research of Natural α-Glucosidase Inhibitors

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Abstract. Diabetes is a metabolic disorder disease that seriously threatens human health, meanwhile, owing to its serious complications and long treatment process, diabetes brings huge economic burden to patients. In recent years, investigation of high efficiency, low cost and multi-target α - glucosidase inhibitors (AGIs) has become a hot topic world widely. Attributed to the advantages of rich sources, mild efficacy, less adverse reactions, natural AGIs are popularly applied in the treatment of diabetes and its complications. The rapid development of biotechnologies, including microbial fermentation, enzyme engineering, molecular docking, metabolomics, and synthetic biology, provides novel strategies for the screening, optimization, and mechanism analysis of natural AGIs. In this article, the recent application progresses of biotechnology in the natural AGIs were systematically reviewed. The major contents included AGIs screening and mechanism visualization analysis guided by molecular docking technology, inhibitory activity modification and improvement of AGIs based on complex microbial metabolic networks and enzyme systems, biocatalytic preparation of biological peptides with α-glucosidase inhibitory activity, and the application of synthetic biology and metabolomics in AGI synthesis. This article aims to provide theoretical basis and technical reference for the exploration and application of natural AGIs.

1 Introduction

Diabetes is a metabolic disease, characterized by hyperglycemia resulting from defects in insulin secretion or impaired insulin action, which has become a major global public health issue.

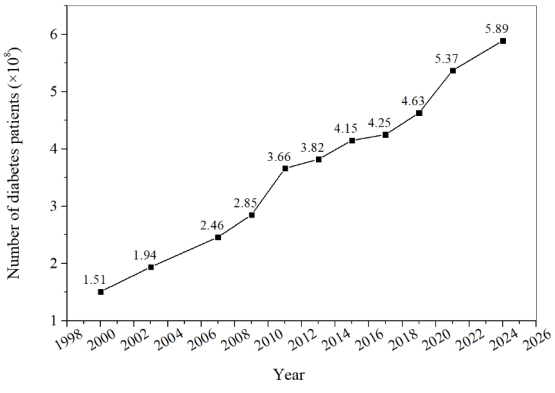

Fig. 1. Estimates and Projections of the global prevalence of diabetes in the 20-79 age group in millions [1]

In recent years, the number of patients with diabetes worldwide has continued to rise. According to the 11th edition of Global Diabetes Map (2024) released the International Diabetes Federation (IDF) , the number of adults aged 20-79 with diabetes worldwide has reached 589 million, projected to exceed 853 million by 2050 (Fig.1) [1]. Diabetes not only disrupts nutrient metabolism but also leads to complications such as cardiovascular disease, retinopathy, and renal dysfunction due to persistent hyperglycemia [2].

Alpha-glucosidase inhibitors (AGIs) are widely used oral hypoglycemic agents in clinical practice. They work by inhibiting α-glucosidase (AG) in the small intestinal brush border, thereby delaying carbohydrate digestion and glucose absorption, effectively controlling postprandial blood glucose levels. However, commonly used AGIs in clinical practice (e.g., acarbose, voglibose) often cause gastrointestinal side effects like bloating and abdominal pain, in some patients with poor tolerability [3]. Long-term uncontrolled hyperglycemia damages cells and tissues, leading to major complications including retinopathy, atherosclerosis, neuropathy, and nephropathy [4]. Therefore, identifying highly effective, low-toxicity AGIs from natural resources has become a current research focus.

Natural AGIs typically originate from plants, microorganisms, and food-derived proteins, offering advantages such as broad availability, structural diversity, minimal side effects, and good biocompatibility [3]. Compared to chemically synthesized drugs, natural AGIs are more readily accepted by the human body and demonstrate superior biocompatibility and safety during long-term use. Furthermore, natural AGIs often exhibit multi-targeted, multi-mechanistic synergistic effects. For instance, certain natural inhibitors not only suppress AG but also possess auxiliary metabolic regulatory functions such as antioxidant and anti-inflammatory properties,

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aiding in the comprehensive management of diabetes and its complications [5].

In recent years, rapid advancements in biotechnology, including microbial fermentation, enzyme engineering, molecular docking, metabolomics, and synthetic biology, have provided novel strategies for screening, optimizing, and elucidating the mechanisms of natural AGIs. These technologies not only help improve the screening efficiency of natural AGIs, but also provide strong support for elucidating their molecular mechanisms of action. Furthermore, through the biotransformation of natural products, they significantly enhance inhibitory activity and bioavailability, demonstrating broad application prospects [6]. Virtual screening techniques, such as molecular docking, take the advantages of high efficiency and low cost in AGIs development. By simulating ligand-active site interactions to predict key parameters, such as binding free energy and hydrogen bond formation, these methods enable rapid initial screening of active compounds used as AGIs. Meanwhile, these methods can facilitate visual analysis of mechanisms of action, and provide guidance for structural optimization and the design of novel inhibitors [7-9]. Microbial fermentation technology offers a feasible pathway for the large-scale, green preparation of AGIs. Since, rely on the metabolic networks and diverse enzyme systems, microbial fermentation facilitates the release of AGI compounds from plants, enhances the AG inhibitory activity of active compound through biotransformation, and generates novel substances with AG inhibitory activity [9, 10]. The developments in metabolomics provide powerful tools for systematically deciphering the dynamic changes in AGI compounds and analyzing their biotransformation pathways. For instance, non-targeted metabolomics analysis based on UHPLC-QE-MS enables comprehensive identification of active components in plant extracts and the screening of potential AGIs by combined with multivariate statistical analysis. Transcriptomics analysis can also reveal key genes and metabolic pathways associated with the biosynthesis of AGIs during microbial fermentation [11].

In this paper, recent advances in biotechnology applications for natural AGI development were systematically reviewed, which includes prospective AGI screening guided by molecular docking technology, microbial fermentation biotransformation and dynamic analysis of AGIs based on metabolomics, preparation and catalytic studies for novel bioactive peptides as AGIs, and synthetic biology applications in AGI synthesis. This review aims to provide theoretical foundations and technical pathways for novel natural AGI research and development.

2 AGI screening, design, and mechanism researches based on molecular docking technology

Molecular docking is a structure-based virtual screening method that predicts binding patterns, affinity, and interaction mechanisms by computationally simulating three-dimensional spatial and energy matches between ligands (e.g., small-molecule inhibitors) and receptors (e.g., enzymes) [8]. In recent years, molecular docking has played a significant role in screening natural AGIs. By performed molecular docking studies with Discovery Studio 2.5 software, Xi et al. [12] identified four flavonoids with strong inhibitory potential from 44 flavonoid compounds and proposed ARG1591, ARG1410, and GLU1397 as key active residues for α-glucosidase. Li et al. [13] employed Autodock vina to dock 12 components from *Morus alba*, which identified high-affinity compounds such as 1-deoxynojirimycin and isoquercitrin and suggested Asp69, Asp215, Glu277, and Asp352 as key hydrogen-bonding residues. Yang et al. [14] screened multiple potential inhibitory peptides from walnut protein based on virtual screening and molecular dynamics simulations.

Molecular docking has become a crucial method for elucidating the inhibition mechanisms of AGIs. Extensive molecular docking studies indicate that the active pocket of α-glucosidase primarily consists of a series of conserved amino acid residues, which serve as key sites for noncovalent interactions such as hydrogen bond formation by inhibitors. Take acarbose as an example (Fig.2), The binding site between acarbose and α-glucosidase exhibits optimal spatial complementarity, with hydrogen bonding and van der Waals interactions playing pivotal roles in stabilizing the binding energy. Specifically, eight oxygen atoms on acarbose form eleven hydrogen bonds with residues in α-glucosidase, including Arg281, Asp282, and Asp518. Simultaneously, van der Waals interactions are established between acarbose and residues such as Leu283, Asn524, Arg600, Phe525, Phe649, and Gly615 in α-glucosidase [15].

The visualized three-dimensional map provided by molecular docking makes the differences in binding between different types of inhibitors and key sites of AG catalytic centers clearer. Xu et al. [7] found that amino acid residues Asp542, Asp443, His600, Asp327, and Arg526 in the α-glucosidase molecule were the critical sites for hydrogen bonding between small-molecule monosaccharides and their analogues with the enzyme. They proposed that substituted the O atom on the sugar ring with an N atom would significantly reduce the binding free energy between ligand and receptor, resulting in a more robust interaction. Wang et al. [8] studied *Rhodiola rosea* extracts and found that the contained caffeic acid could form hydrogen bonds with the His-515, Arg-437, Glu-432, and His-348 residues of α-glucosidase. They further pointed out that Arg-437 could be competitively bound by L-malic acid and quercetin, while His-515 would be simultaneously bound by caffeic acid and (+)-epicatechin. This finding was agreed with the results obtained from kinetic analysis that *Rhodiola rosea* extracts exhibited competitive and non-competitive mixed inhibition of AG. In addition, Jiang et al. [16] observed interactions between the diphenyl ethylene compound pinostilbene and residues Val1035 and Asp1056 outside the AG active pocket, structurally confirming its non-competitive inhibitory profile. Molecular docking also provides molecular-level insights into elucidating synergistic interactions among multiple components. For instance, Qin et al. [17] used molecular

docking simulations to clarify the dual-mechanism of liquiritin (LTG) and acarbose synergistic inhibition of AG through an "allosteric-competitive" mechanism. Specifically, LTG noncovalently binds to enzyme residues, inducing AG unfolding via allosteric effects. Subsequently, acarbose spontaneously binds to the LTG-α-Glu complex via hydrogen bonds as a competitive inhibitor, causing conformational changes that further impede substrate binding to AG.

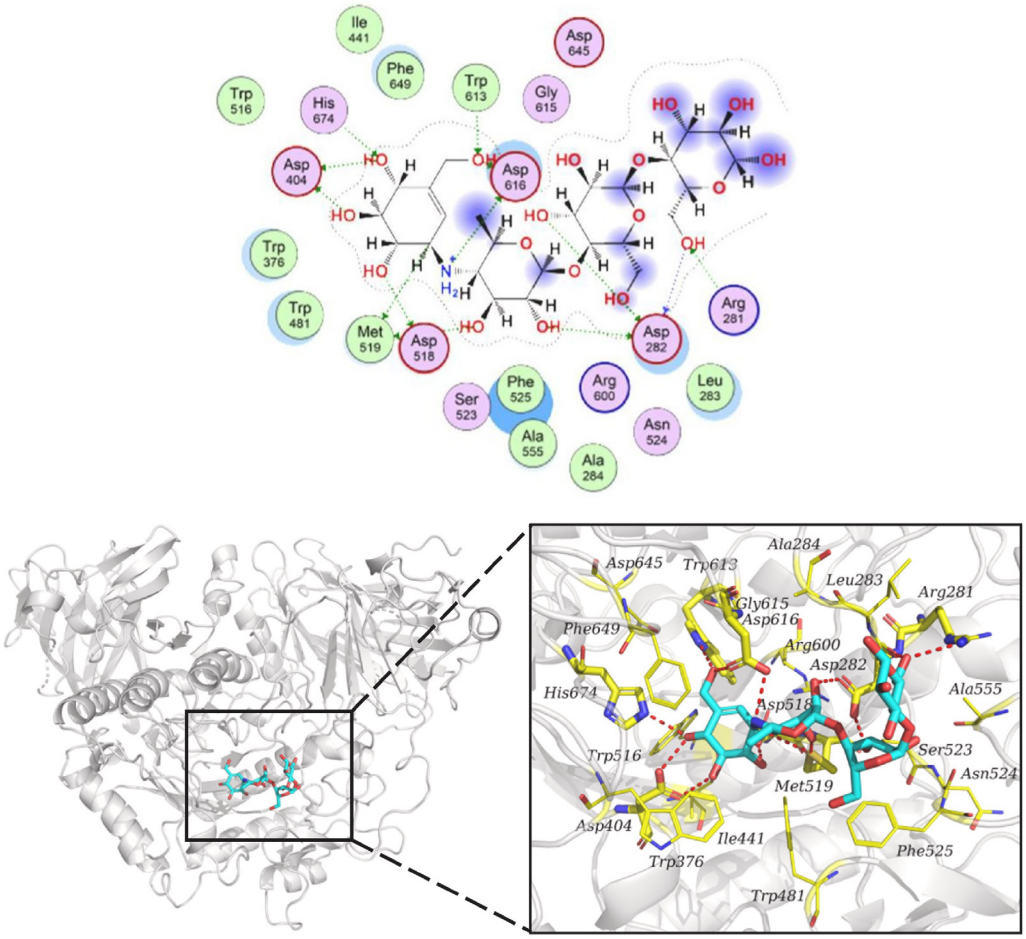

Fig.2 The binding mode of α-Glucosidase and acarbose. A: two-dimensional model, B: three-dimensional model (Green and white represent acarbose and AG respectively, while yellow represents the surface of AG and the residue of AG. The dotted lines indicate the interaction between the two. [15]

Molecular docking provides precise targets for structure-based inhibitor optimization, aiding in the design of compounds with enhanced α-glucosidase inhibitory activity. For instance, the monomeric peptide FNSL isolated from mung bean protein hydrolysates exhibits potent inhibition of AG [15]. Molecular docking combined with molecular dynamics simulations revealed that the activity of FNSL owing to the interactions with amino acid residues such as Asp616, Leu678, and Phe649, driven by hydrogen bonds, salt bridges, and van der Waals forces. Subsequently, based on the basic sequence of the small-molecule mung bean peptide, two tetrapeptide molecules, FFFM and YYFM, with higher inhibitory activity of AG were designed. These molecules could enter the active pocket of AG to form stable bonds [15]. Liu et al. [6] predicted the inhibition mechanism of a substance with AG inhibitory activity from secondary metabolites of *Phellinus monticola* through molecular docking simulations, which indicated that the active moieties of this substance are the carbonyl group and aliphatic side chain. It binds to the THR-310 residue of AG via hydrogen bonding, and could also interact with multiple other residues of the protein through hydrophobic interactions. This enables the active site of the enzyme to bind stably and exert inhibitory effects. In summary, molecular docking technology is evolving from single "binding energy prediction" to "multi-scale mechanism simulation." It can not only deeply integrate enzyme kinetic data, achieve "visualization" of inhibition types and synergistic effects at the atomic level, but also guide the design and development of new and efficient AGIs more prospectively [9].

3 Enhancing inhibition efficiency of AGIs through microbial fermentation

Many bioactive compounds in plants, particularly polyphenols, exist as complexes with cell wall polysaccharides and proteins via ester bonds and hydrogen bonds. This results in low extraction efficiency and bioavailability for these active components.

Microbial fermentation possesses complex metabolic networks and diverse enzyme systems. The active compounds bound to the cell wall undergo glycosidic bond hydrolysis under the catalysis of enzymes, and are released from cell wall. Then these compounds would be further converted into various modified products through intricate metabolic pathways, further enhancing the biological efficacy of these compounds [18].

Currently, diverse microorganisms are obtained significant attention in natural AGI researches. Lactic acid bacteria, as probiotics, can produce multiple enzymes, such as β-glucosidase, amylase, and cellulase, which facilitate the release of bounded bioactive compounds from cell wall and further convert them into more readily absorbable free forms [19]. Li et al conducted dynamic evolution analysis of all components during quinoa fermentation via widely targeted metabolomics and molecular simulation. The results showed that the metabolic profile of quinoa changed significantly during the fermentation process, with a significant increase in flavonoids, phenolic acids, and amino acid derivatives in the fermented quinoa extract, along with emergence of five new flavonoid metabolites. It was also indicated that the fermented quinoa polyphenol extracts could significantly inhibit AG activity [2]. Flavonoids in mulberry leaves undergo "glycoside-aglycone" conversion when fermented by *Monascus* spp., primarily attributed to the synergistic effect of secreted hydrolytic enzymes such as glycosidases and cellulases. Targeted metabolomics analysis revealed that the aglycone contents of kaempferol and quercetin in fermented mulberry leaves increased by 6.59-fold and 4.36-fold, respectively. This resulted in a 93.3% enhancement of AG inhibitory activity in fermented mulberry leaves and a significant improvement in the bioavailability of their flavonoid compounds [20]. Yeast fermentation has also been extensively applied in the research of natural AGIs. *Zygosaccharomyces rouxii* fermentation would significantly change the polyphenol distribution of *Cynanchum auriculatum* Royle ex Wight beverages (CAB), increasing total phenolic and total flavonoid contents by 11.50% and 60.30%, respectively, meanwhile markedly enhancing α-glucosidase inhibitory activity [21]. Additionally, medicinal fungus *Ganoderma lucidum* is frequently employed in studies aiming to enhance the content of bioactive compounds in Chinese herbal medicines through two-way solid-state fermentation [22].

Research on microbial enzyme systems and metabolic networks provides more precise fermentation strategies for regulating natural AGIs through microbial fermentation. For instance, Tang et al. [10] selected β-glucosidase-producing *Lactobacillus* to ferment passion fruit peel (PFP), which could specifically hydrolyzed the glycosidic bonds of bound polyphenols resulting in a 48.20% degradation of bound polyphenols and a substantial increase in free phenolic content. The inhibitory capacity against AG and α-amylase of the fermented PFP extract were both significantly enhanced. And 38 phenolic compounds as potential dual inhibitors were further identified by computer-aided screening.

In summary, microbial fermentation is not only a simple "component release" process, but also a complex process of "bioconversion and metabolic remodeling". Through strategic selection of microbial strains, it is not only possible to increase the content of active substances, but also to convert them into more bioactive forms or even generate new active metabolites. Thus, systematically enhancing the inhibitory efficiency of natural AGIs [9].

4 Enzymatic hydrolysis and microbial fermentation for bioactive peptide

Dietary proteins serve as a significant natural source of AGIs. Presently, converting them into bioactive peptides through enzymatic hydrolysis or microbial fermentation represents an effective approach to obtaining highly efficient AGIs [3]. Bioactive peptides have gained considerable attention in recent years due to their advantages, including low molecular weight, rapid absorption, high activity, and low toxicity.

Enzymatic hydrolysis is the mainstream method for preparing bioactive peptides, which has the advantages of strong process controllability and facilitating structure-activity relationship studies. Various proteases are employed for bioactive peptide production, including alkaline protease, trypsin, dispase, papain, and pepsin. However, different protease types influence both peptide yield and AGI activity. Moreover, multi-enzyme synergistic hydrolysis yields superior results compared to single-enzyme hydrolysis. It is primarily due to the distinct cleavage sites and mechanisms of different proteases, which generate peptides with varying amino acid compositions [23, 24]. Furthermore, the molecular weight, size, and sequence composition of active peptides are closely related to their AGI inhibitory activity. For example, Kittisak et al. used ultrafiltration fractionation to separate peptides from crude longan seed protein and found that peptide fractions <1 kDa exhibited the highest biological activity. They also discovered that a smaller molecular size plays a crucial role in enhancing AGI inhibitory activity [25].

Microbial fermentation is another significant method for obtaining bioactive peptides. It utilizes the complex protease systems produced by microbial cells to hydrolyze proteins, offering advantages such as low cost, a mild process, and the potential for multi-component synergistic effects. For instance, the powder of fermented *Porphyra yezoensis* by *Bacillus subtilis* (PFPOB) had stronger AG inhibitory activity than acarbose [9]. Molecular docking studies showed that the inhibitory activity of PFPOB may be attributed to peptide segments GPGDFL and SPPPPPA, which can form hydrogen bonds, hydrophobic interactions, van der Waals forces, and electrostatic interactions with key amino acid residues in AG active sites. So that they would compete for binding sites between enzymes and substrates, changing enzyme conformation, and thus inhibiting AG activity. *B. subtilis* isolated from Hawaijar can ferment soybeans to produce soy protein isolate, which could not only exhibited AG inhibitory activity but also demonstrated multiple benefits in animal models, for example improving glucose tolerance and insulin sensitivity [26].

In a word, as for bioactive peptide production, enzymatic hydrolysis and microbial fermentation represents not mutually exclusive but complementary strategies. Enzymatic hydrolysis offers high controllability, facilitating structure-activity relationship studies, while, more complex microbial fermentation systems had the potentiality of generating unique peptide profiles with distinct activities and multifunctional properties that are difficult to obtain via enzymatic methods. Future development should focus on integrating synthetic biology approaches to engineer microorganisms for "customized" secretion of specific proteases, enabling targeted production of bioactive peptides [27].

5 Metabolomics and synthetic biology in AGI research

Metabolomics, a vital component of systems biology, aims to comprehensively analyze small-molecule metabolites in biological systems through qualitative and quantitative methods, revealing their dynamic patterns under physiological, pathological, or external interventions [3].

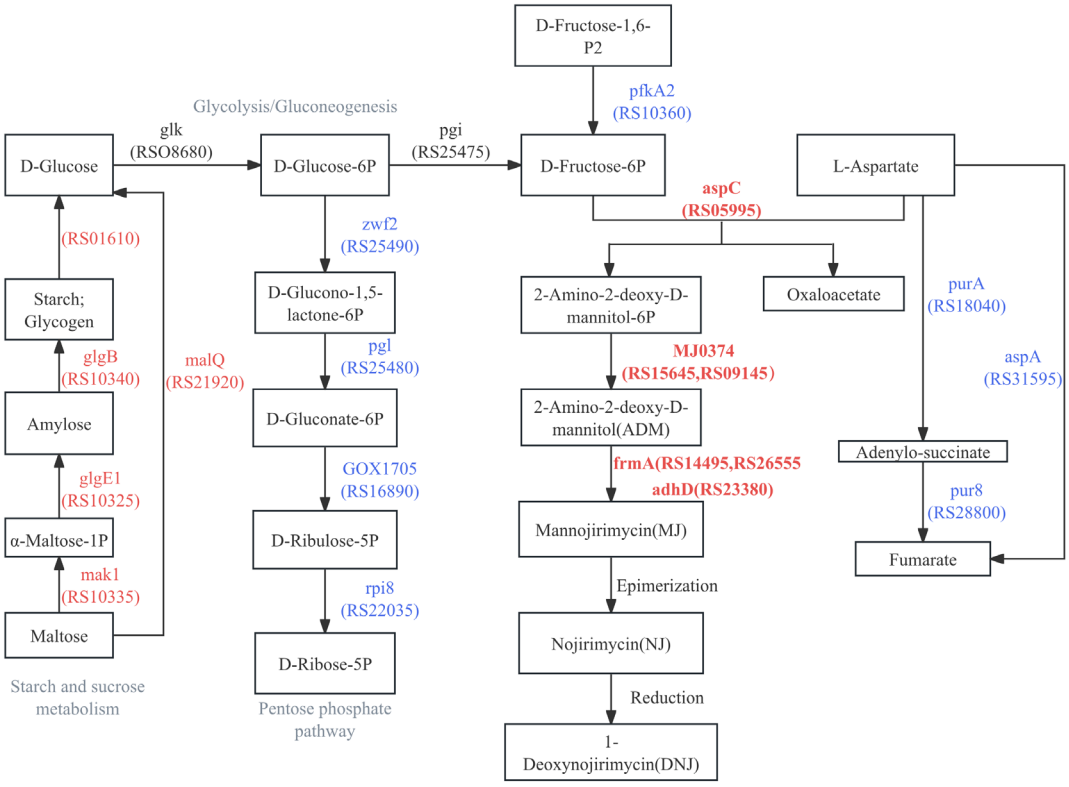

Fig. 3. Putative DNJ biosynthesis pathway in S.lavendulae.[11]

In natural AGI research, targeted/broad-targeted metabolomics has emerged as an effective tool for uncovering global chemical composition changes during fermentation. As reported by Wang and Zhao, this technology not only quantitatively described changes in key active components (e.g., flavonol aglycones) but also revealed core metabolic pathways regulating fermentation through KEGG pathway analysis (e.g., flavonoid biosynthesis, isoflavonoid biosynthesis pathways) [2, 20]. It enables a systems-level understanding of the material basis and metabolic mechanisms underlying fermentation-enhanced AG inhibitory activity.

Synthetic biology achieves efficient synthesis of target products through the design, construction, and optimization of biological systems. Xin et al. [11] discovered that mulberry seed polysaccharides significantly promote 1-deoxynojirimycin (DNJ) synthesis of *Streptomyces lavendulae*. Transcriptomic analysis revealed four key metabolic pathways for DNJ biosynthesis and identified six critical genes, including aspC, MJ0374-1/2, frmA-1/2, and adhD (Fig.3). This establishes a robust theoretical foundation for future genetic engineering of strains to substantially enhance the yield of natural AGIs like DNJ, representing a paradigm shift from "discovering" natural AGIs to "creating" high-yield AGIs.

6 Conclusion and outlook

Biotechnology has been comprehensively integrated into all aspects of natural AGI research. Molecular docking reveals interaction mechanisms of AG and inhibitors at the atomic level, guiding rational design of highly effective inhibitors; Microbial fermentation, as a powerful bioconversion platform, enhances the inhibitory activity and bioavailability of natural products through degradation, transformation, and system remodeling. Bioactive peptides have become an effective approach for

obtaining potent AGIs, greatly enriching the sources and types of natural AGIs. Metabolomics and synthetic biology advance this field toward more systematic and precise directions by providing insights and enabling creation, respectively.

In the future, the width and depth of biotechnology in the related researches on natural AGIs would be further strengthened. Specifically, molecular docking technology will guide the customized design of potent inhibitors at multiple scales and promote the development of composite AGI with synergistic effects. The biotransformation and metabolic remodeling mechanisms of microbial fermentation processes should be more utilized, which will benefit for achieving the targeted transformation of potential AG inhibitory substances into higher activity structures, even new active metabolites through specific microorganisms. With the development of metabolomics and synthetic biology, biocatalysts such as enzymes and microorganisms can be customized through the design, construction, and optimization of biological systems, realizing the shift of "discovering" natural AGI to "creating" high-yield AGI.

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