Research progress on polyphenolic substances as α-glucosidase inhibitors

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Abstract. The global prevalence of type 2 diabetes mellitus (T2DM) has surged, creating a significant health and economic burden. While synthetic α-glucosidase inhibitors (AGIs) like acarbose are used to manage postprandial hyperglycemia, their clinical application is limited by adverse gastrointestinal side effects and contraindications. This has spurred the search for safer and tolerable alternatives from natural sources. Plant-derived polyphenols are considered highly promising candidates. In recent years, there have been continuous research achievements on natural polyphenolic substances as inhibitors of α-glucosidase. This article provides a review of polyphenol substances as AGIs from the perspectives of their sources and structural characteristics, screening and extraction techniques, mechanism research, and bioavailability challenges. The purpose of this article is to provide a theoretical reference for the search for more efficient, low-cost, and environmentally friendly α-glucosidase inhibitors.

Keywords: Polyphenols, α-glucosidase inhibitor, Natural products, Inhibitory.

1. Introduction

Diabetes mellitus (DM) is a prevalent chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. It is estimated that the number of adults (20–79 years) living with diabetes reached 589 million in 2024, and the corresponding global diabetes-related health expenditures exceeded 1 trillion USD annually, accounting for 12% of total global health spending. The number of DM patients is projected to rise to 853 million by 2050[1]. On the other side, DM is always associated with severe complications that significantly reduce quality of life and increase mortality, including cardiovascular diseases (with a 72% higher risk of heart attack in type 2 diabetes mellitus (T2DM) patients), nephropathy, retinopathy, and neuropathy [2].

Among the various types of diabetes, T2DM is the most common, accounting for approximately 90% of all cases. Unlike type 1 diabetes, which requires insulin replacement therapy, a key target for T2DM management is inhibiting the activity of α-glucosidase, which is a family of enzymes located on the brush border of small intestinal epithelial cells [3]. These enzymes catalyze the hydrolysis of complex carbohydrates (e.g., starch, sucrose, maltose) into simple monosaccharides (glucose and fructose) by breaking α-1,4 and α-1,6 glycosidic bonds [4]. Alpha-glucosidase inhibitors (AGIs) have been clinically used for decades as effective agents to manage T2DM, especially acarbose, voglibose, and miglitol. However, it was reported that they can cause some side effects, such as flatulence, diarrhea, and abdominal pain, due to undigested carbohydrates reaching the colon and undergoing fermentation by gut microbiota [5]. Additionally, these drugs are contraindicated in patients with renal impairment, liver cirrhosis, and gastrointestinal disorders, restricting their application [6]. These challenges have motivated the search for safer, more tolerable alternatives, particularly from natural sources.

Natural products, especially plant-derived bioactive compounds, have gained more and more attention as potential AGIs due to their diverse biological activities, low toxicity, and wide availability. These compounds exhibit a range of health benefits, including antioxidant, anti-inflammatory, and hypoglycemic effects [7]. Numerous studies have demonstrated the α-glucosidase inhibitory activity of natural polyphenols. Finally, the challenges and future directions in developing polyphenol-based AGIs for clinical applications will also be addressed. By synthesizing current knowledge, this review

seeks to advance understanding of natural polyphenols as AGIs and facilitate the development of novel therapeutic strategies for T2DM.

2. Types and sources of natural polyphenols as α-glucosidase inhibitors

Natural polyphenols can be categorized into flavonoids (e.g., quercetin, kaempferol) and non-flavonoids (e.g., phenolic acids such as caffeic acid, sinapic acid, and gallic acid). They usually exist in plants as free phenols, soluble bound phenols, or insoluble bound phenols. The bound phenols can further be divided into esterified phenols and glycosylated phenols, among others. A large number of phenolic compounds derived from plants have shown significant α-glucosidase inhibitory activity. They have the advantages of minimal side effects and high inhibitory activity.

With the rapid development of separation and identification technologies, an increasing number of polyphenolic AGIs have been discovered. The structural characteristics, physicochemical properties, and biological activities of natural polyphenols vary significantly depending on plant sources, preparation methods, and other factors. Meanwhile, phenolic compounds in rapeseed oil could also inhibit α-glucosidase, obviously through spectroscopic and molecular docking analyses [8]. Jia et al. investigated the potential of 27 dietary flavonoid compounds as AGIs [5]. Four compounds, catechin, myricetin, tiliroside, and cinnamic tannin D1, were isolated from the n-butanol extract of the traditional plant Potentilla erecta, among which cinnamic tannin D1 exhibited excellent α-glucosidase inhibitory activity [9]. Zhou et al. identified 32 polyphenolic compounds from the free phenols in sorghum ethanol extracts [2]. Among these, naringin, chrysanthemum glycoside, glycine, and apigenin exhibited strong inhibitory activity against α-glucosidase. Yang et al reported that the efficacy of natural polyphenols is closely related to specific structural features and interaction patterns with enzymes [10]. They found that hydroxylation modification can significantly enhance inhibitory potency. For example, myricetin, with five hydroxyl groups on A- and B-rings, exhibits higher α-glucosidase inhibition ability than quercetin, which has four hydroxyl groups. By contrast, methylation modification reduces inhibition activity, since the IC50 value significantly increases. Double flavonoids (e.g., amentoflavone, hinokiflavone) exhibit even stronger activity than monoflavonoids, due to their dual aromatic rings.

3. Screening of natural polyphenols

The screening of AGIs includes in vivo screening and in vitro screening, ranging from traditional in vitro assays using 4-nitrophenol-α-D-glucopyranoside (pNPG) or natural substrates (starch, sucrose) to advanced approaches like high-throughput screening, molecular docking, and Caco-2 cell models, which have enabled efficient identification of potent polyphenolic AGIs. These techniques not only streamline the discovery process but also provide insights into structure-activity relationships, aiding in the design of more effective inhibitors.

The traditional activity-guided method is the primary approach for screening AGIs, which focuses on the overall activity of α-glucosidase. Generally, these methods involve repeated extraction and separation to obtain target monomeric compounds, followed by screening based on activity analysis. It mainly includes screening based on pNPG as a substrate, screening based on the Caco-2 cell model, screening based on immobilized enzymes, etc [11]. However, in these screening strategies, the acquisition of compounds cannot be synchronized with their activity evaluation, and the separation of compounds has low throughput, long cycles, high costs, and trace active ingredients are easily lost.

Therefore, in recent years, with the rapid development of separation technology and detection technology, a large number of new screening methods have emerged, significantly improving the screening speed and accuracy of natural polyphenolic AGIs. For example, Gao et al. used affinity selection mass spectrometry (AS-MS) to high-throughput screen 19 AGI candidates from tea leaves, 14 of which were classified as galloylated polyphenols [12]. Among these potential AGIs, some were previously reported compounds, such as Epigallocatechin gallate, pigallocatechin gallate, naringin,

and quercetin, while 12 compounds were identified for the first time. By combining affinity ultrafiltration, five phenolic compounds with high affinity for α-glucosidase were screened from *Mallotus furetianus* Muell-Arg extract [13]. Five potential AGIs were screened from the 70% ethanol extract of *Aquilaria* leaf tea by a targeted bioaffinity ultrafiltration HPLC/MS method. Chen et al. established a high-throughput activity profiling analysis platform and screened 28 AGIs from *Polygonum cuspidatum*, among which the phenolic compounds catechin-3-O-galloyl and procyanidin exhibited strong inhibitory activity [14] [3].

Molecular docking has gradually been used in the screening of polyphenol AGIs in recent years. Taking human α-glucosidase as a target, using molecular docking methods combined with ADME and Lipinski properties, Shi et al. screened and identified 10 promising AGIs from 76 plant chemicals, including two common carbon glycosides, vitexin and isovitexin, and their aglycone apigenin [15]. A study using Discovery Studio 2.5 to dock 44 flavonoids with α-glucosidase (PDB: 3TOP) found that compounds like HT15, HT18, and HT7 had LibDockScore > 137, indicating strong binding affinity [16]. Similarly, kaempferol-3-O-rutinoside, screened from Tartary buckwheat, forms three hydrogen bonds with ASP69 [17].

4. Extraction of natural polyphenols

In recent years, extensive research has been conducted on the preparation of AGIs from plant polyphenols. Among various extraction methods, solvent extraction remains the primary method for extracting plant polyphenols. Traditional solvents used for polyphenol extraction primarily include water, methanol, ethanol, acetone, and ethyl acetate, which significantly influence the content. By comparing the effects of water, 70% methanol, 70% ethanol, acetone, and ethyl acetate on raspberry extracts, Li et al. found that the water extract and 70% ethanol extract had the highest total polyphenol content [18]. For different types of brown algae, Xie et al. found that acetone was the optimal solvent for extracting brown algae phenolic compounds, which showed higher content of phenolic compounds than methanol and ethanol extracts. Meanwhile, acetone extracts from *Sargassum pallidum* and *Undaria pinnatifida Suringar* exhibited the highest α-glucosidase inhibitory activity, even higher than that of the acarbose control group [19]. However, extracted polyphenols from Aquilaria sinensis leaf-tea with acetone and ethyl acetate showed low content and low α-glucosidase inhibitory activity [3].

New solvents are being continuously developed and applied. These solvents are often combined with auxiliary methods to enhance the extraction efficiency of plant polyphenols. For example, DESs-UAE not only increased the extraction yield but also significantly reduced the extraction time [20]. Moreover, the α-glucosidase inhibitory activity of the extract was also higher than that of other traditional methods, which may be attributed to the higher yield of free phenols. Cao et al. reported a method using microwave-assisted extraction based on ionic liquids (IL-MAE) to enhance polyphenol extraction from papaya leaves [21].

Pre-treatment is one of the effective means to preserve the plant polyphenol. For instance, electron beam irradiation (EBI) pretreatment can effectively reduce the compactness of plant cell wall structures, creating numerous irregular pores on the cell walls, thereby promoting the dissolution of polyphenolic compounds [4]. Therefore, combining EBI pretreatment with supercritical solvent-assisted extraction, the content of free phenols in the extract of persimmon leaves was increased [22]. Microbial fermentation has also been proven to be a particularly promising method for the extracted polyphenols, since they have the ability to break down the complex structures and generate novel bioactive metabolites. For example, after being fermented by *Lactobacillus fermentum* and *Lactobacillus plantarum*, the total phenolic content increased significantly. [23] The total phenolic content and antioxidant capacity of wheat after being solid-state fermented by *Ganoderma lucidum* were obviously higher than those of unfermented wheat. [24]

5. Inhibitory mechanism of natural polyphenols on α-glucosidase

Mechanistic studies have deepened the understanding of how polyphenols inhibit α-glucosidase. Especially, the introduction of spectroscopic techniques and computational methods played important roles in deepening the understanding and elucidation.

Spectroscopic techniques, including fluorescence spectroscopy (FS), circular dichroism (CD), and synchronous fluorescence (SF), are widely used to elucidate the interaction between inhibitors and α-glucosidase. The CD spectra indicated that Silibinin binds to the enzyme's non-active site, thereby disrupting the microenvironment of the active sites[10]. As for *Flos Trollii* polyphenols, they could reduce α-helix content of α-glucosidase from 32.0% to 20.3% and increase β-sheet content from 19.3% to 26.8%, while SF spectroscopy indicated Trp residues were more sensitive to ligand binding than Tyr residues [25]. The 3D FS revealed that after bingding with young apple polyphenols, the intrinsic fluorescence intensity of α - glucosidase decreased by 32.43%, emission peaks shifted blue by 4 nm, indicating a change—in the FS, CD, and UV spectroscopy, Zhao et al. confirmed that the formation of non-fluorescent complexes will induce conformational changes in α-glucosidase, such as a decrease in α - helix content and changes in β - folding stability [22]. These techniques collectively confirm that natural inhibitors impair α-glucosidase activity by inducing conformational changes, rather than merely competing for the active site.

Computational methods are employed to further confirm the binding mode between inhibitors and enzymes, identify key amino acid residues in the enzyme active site, and assist in the design of inhibitor structures. Therefore, multi-spectroscopic techniques have become a powerful tool to decode the interaction between natural inhibitors and α-glucosidase, addressing limitations of traditional in vitro assays. During the investigation of the inhibitory mechanism of Apigenin B2 isolated from rapeseed, multispectral analysis (FS, FTIR, CD) indicated that it primarily interacts with α-glucosidase. Molecular dynamics simulations revealed that proanthocyanidin B2 forms a stable complex with α-glucosidase for over 200 ns, confirming the stability of the interaction between the inhibitor and the enzyme [8]. Gao et al. elucidated that the galloylated polyphenols screened from tea leaves would non-competitively inhibit α-glucosidase activity, using methods such as enzyme kinetics, FS, CD, and molecular docking [12]. For buckwheat hull polyphenols, molecular docking revealed they form hydrogen bonds with TRP344 and ARG346 of α-glucosidase, while FS confirmed static quenching of the enzyme's tryptophan residues, confirming hydrophobic interactions as the main driving force [26].

6. Bioaccessibility and synergistic effect studies of phenolic substances as α-glucosidase Inhibitors

A critical gap in natural inhibitor research is the disconnect between in vitro activity and in vivo efficacy, largely due to poor bioaccessibility. After being in vitro digested by simulating the environment of the oral cavity, stomach, and intestine, Allmania nodiflora (L.) R.Br.ex Wight polyphenols showed an increased α-glucosidase inhibition (from 52% to 76%), attributed to pH-induced structural changes that enhance intestinal assimilation, which suggests in vitro assays without digestion may underestimate true in vivo activity [27]. Similarly, young apple polyphenols (chlorogenic acid, epicatechin) retain 78% of their inhibitory activity after digestion, forming stable complexes with α-glucosidase via hydrophobic interactions, indicating potential for functional food development [28]. Grain-bound polyphenols (GBPs) exhibit unique bioaccessibility profiles, since they can slowly release from covalent bonds with dietary fiber during gut microbiota fermentation, providing prolonged α-glucosidase inhibition (up to 12 hours postprandially). Wheat bran GBPs can modulate gut microbiota, activating GPR41/43 receptors to stimulate GLP-1 secretion, further enhancing glucose regulation [29]. Moreover, the combinations of polyphenols with other inhibitors have emerged as a strategy to enhance efficacy and reduce side effects. Pigallocatechin gallate combined with *Ampelopsis grossedentata* extract exhibits via π-π stacking and hydrogen bonding, reducing postprandial glucose spikes by 42% compared to single inhibitors [30]. This dual-enzyme

inhibition targets both starch hydrolysis (α-amylase) and oligosaccharide hydrolysis (α-glucosidase), addressing the limitation of single-target therapy. There is also a synergistic effect between AGIs of different inhibition types. For example, the combination of kaempferol-3-O-rutinoside from Tartary buckwheat, a non-competitive inhibitor, combined with the competitive inhibitor acarbose could reduce the dosage of acarbose by 40% and mitigate its gastrointestinal side effects [17].

7. Conclusion and perspective

The escalating global burden, coupled with the limitations of traditional AGIs, has driven extensive research into natural alternatives. Among these, plant-derived polyphenolic compounds have emerged as promising candidates, with the advantages of high efficacy, safety, and multifaceted biological activities, which align with the need for sustainable and patient-friendly T2DM management strategies. In recent years, significant progress has been achieved in the screening, preparation, and elucidation of natural polyphenolic substances. This review synthesized the current research progress on natural polyphenols as AGIs, encompassing their classification, sources, screening and preparation techniques, inhibitory mechanisms, and potential for clinical translation.

However, several challenges still hinder the translation of polyphenolic AGIs from laboratory research to clinical application. First, due to the coexistence of multiple phenolic substances in polyphenol extracts from plants, it is challenging to identify individual active components and their synergistic or antagonistic effects, making the utilization of advanced separation techniques (e.g., HPLC, UHPLC) and metabolomics approaches inevitable. Second, the composition, structure, and biological properties of polyphenols in plant extracts exhibit significant variability due to differences in plant sources, extraction methods, and extraction parameters, which hinders comparability between studies and scalability in industrial production. Lastly, the inhibition mechanism studies are most limited to in vitro or animal models, with few clinical trials validating efficacy and safety in humans. To overcome these challenges and advance the clinic application of polyphenols as AGIs, several research directions merit attention. Establish novel delivery systems to enhance the bioavailability of polyphenolic compounds, such as nanoparticles, liposomes, or plant-based carriers. Combine multi-omics approaches (e.g., proteomics, metabolomics) with computational modeling to uncover the underlying inhibitory mechanisms of polyphenols in complex systems. Develop more cost-effective, environmentally friendly, and efficient polyphenol preparation technologies. Coordinate polyphenols with other natural AGIs to develop composite AGIs.

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