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Mechanism of inhibition of α-glucosidase activity by bavachalcone

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Abstract

Bavachalcone is an important active component of the traditional Chinese medicine Fructus Psoraleae. The inhibitory effect of bavachalcone on α-glucosidase activity is reported for the first time and the mechanism elucidated by molecular docking. The inhibition of α-glucosidase by bavachalcone (IC50 15.35 ± 0.57 μg/mL) was significantly superior to acarbose (IC50 2.77 ± 0.09 mg/mL). Inhibition type was mixed competitive and non-competitive. Molecular docking suggested this inhibition stems from hydrogen bonds formed with the trp391, arg428, and trp710 residues of α-glucosidase.

Keywords: bavachalcone; α-glucosidase; inhibition mechanism; fluorescence spectroscopy; molecular docking.

Practical Application: This work systematically studied the mechanisms of the inhibitory effects of bavachalcone on α-glucosidase, which is expected to provide a theoretical basis for the screening and development of new, safe, and effective α-glucosidase inhibitors from rich natural sources.

1 Introduction

A-Glucosidase (EC 3.2.1.20), a carbohydrate hydrolase, is widely distributed on the brush edge of small intestinal mucosa and has an important impact on glycosyl structure. It can hydrolyze glycosidic bonds in various sugar compounds in an endonucleolytic or exonucleolytic manner, producing monosaccharides, oligosaccharides, or glycosaminoglycans that lead to an increase in postprandial blood glucose (Daub et al., 2020; Ismail et al., 2020; Attjioui et al., 2020). Postprandial hyperglycemia is the main risk factor leading to the development and progression of type 2 diabetes. Inhibition of α-glucosidase activity slows down carbohydrate digestion, thereby reducing glucose absorption into the blood and controlling blood sugar levels. Such inhibition is considered an important clinical verification target for treatment of non-insulin-dependent diabetes mellitus (Ye et al., 2019; Khan et al., 2019; Syabana et al., 2021). At present, the commonly used α-glucosidase inhibitors are biosynthetic or semi-biosynthetic drugs such as acarbose and voglibose. These drugs are expensive and have varying degrees of adverse side effects (mainly gastrointestinal reactions such as abdominal discomfort, nausea, and vomiting (Wehmeier & Piepersberg, 2004; Smith et al., 2021). There is a need to develop new α-glucosidase inhibitors that are safe, effective, and clinically beneficial.

Psoralea corylifolia is the dried fruit of the legume Psoralea corylifolia L. Many studies have shown that it contains a variety of active components, such as monoterpenols, monoterpenol dimers, flavonoids, chalcone, coumarins, isoflavones, and fatty acids (Hollander, 1992). It displays anti-inflammatory, cardiovascular protective, and hypoglycemic properties, and good pharmacological activity (Corrêa et al., 2008; Xu et al., 2019; Pietro et al., 2013). Bavachalcone is a chalcone compound with a 1,3-diphenylpropenone skeleton (Figure 1) isolated from the traditional Chinese medicine Fructus Psoraleae. Natural chalcone compounds often contain phenolic hydroxyl groups, for example, isoglycyrrhizin in licorice and safflower aglycon in safflower. Such compounds possess great flexibility and can bind to different receptors, giving them a wide range of biological activities (Park et al., 2008; Song et al., 2018; Yanqi & Shuang, 2015), such as inhibition of bone cell differentiation and bacteriostatic, anti-inflammatory, antiviral, and antitumor properties. In 1996, Tsujihara designed a series of phloridin derivatives with dihydrochalcone skeletons, using phloridin as the precursor (Tsujihara et al., 1996). The strongest hypoglycemic activity was observed when hydroxyl or methoxy groups were introduced into position 4 of the B ring. However, activity decreased when methoxy or hydroxyl groups were also substituted at position 2 or 3 of the B ring. The simultaneous introduction of methoxy groups at both positions 2 and 3 of the B ring had no effect on hypoglycemic activity, while the presence of hydroxyl groups at position 4 of the A ring had little effect on activity. The molecular conformation of bavachalcone shows that it has the potential to resist hyperglycemia and, therefore, may be valuable in the development of functional foods and drugs for the treatment of type II diabetes. However, there have been few reports on its inhibitory effects on α-glucosidase and non-enzymatic glycosylation. In view of this, the mechanisms of the inhibitory effects of bavachalcone on α-glucosidase were systematically studied using enzyme kinetics and molecular simulation, providing a theoretical basis for the screening and development of new, safe, and effective α-glucosidase inhibitors from rich natural sources.

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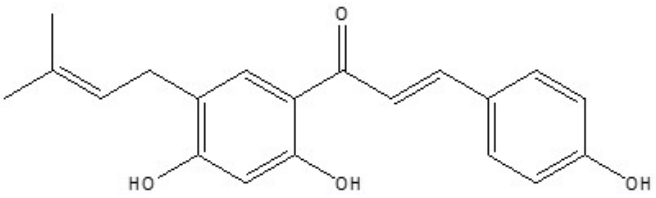

Figure 1. Chemical structure of bavachalcone.

2 Experimental

2.1 Chemicals

Bavachalcone was purchased from Shanghai Yuanye Biotechnology Co. Ltd., acarbose and *p*-nitrophenol (*p*NP) from Shanghai Aladdin Biochemical Technology Co. Ltd., and α-glucosidase (from Saccharomyces cerevisiae) and *p*-nitrobenzene-α-glucopyranoside (*p*NP-G) from Sigma-Aldrich. Other chemicals were of analytical grade.

2.2 α-Glucosidase inhibition assay

As previously described (Geng et al., 2016), 1 mL of α-glucosidase (0.2 U/mL) and 1 mL of bavachalcone at various concentrations were mixed in test tubes and heated for 10 min in a 37 °C water bath. Control tubes contained 1 mL phosphate buffer (0.1 M, pH 6.8) instead of bavachalcone sample. *p*NP-G substrate solution (1 mM, 1 mL) was added and incubated for 20 min. The reaction was terminated by addition of ethanol (0.5 mL) and absorbance was measured at 405 nm. The inhibition rate was calculated as follows (Equation 1):

$$\text{α-Glucosidase inhibitory activity (\%)} = \frac{A_{Control} - A_{Sample}}{A_{Control}} \times 100\% \quad (1)$$

2.3 Type of inhibition of α-glucosidase

The type of inhibition produced by bavachalcone was determined from a Lineweaver-Burk plot. *p*NP-G (0.2, 0.4, 0.6, 0.8, or 1.0 mmol/L), bavachalcone (0, 20, or 50 μg/mL) and α-glucosidase (0.2 U/mL) were mixed. The reciprocal of *p*NP-G concentration (1/[S]) was plotted against the reciprocal of reaction rate (1/V) to create a Lineweaver-Burk double reciprocal curve.

2.4 Fluorescence spectrometry

As previously described (Hua et al., 2018), 1 mL of sample solution at various concentrations was mixed with 4 mL of enzyme solution and incubated at 30 °C for 10 min. Fluorescence spectra in the emission wavelength range 320-380 nm were recorded using an excitation wavelength of 295 nm and excitation and emission slit widths of 10 nm.

2.5 Molecular docking

The molecular structure of bavachalcone was optimized using density functional theory (B3LYP/6-31G+). The crystal structure of α-glucosidase was downloaded from the RCSB PDB database (http://www.rcsb.org/). Molecular docking of bavachalcone and α-glucosidase was carried out based on the Lamarckian genetic algorithm (LGA) using AutoDock 4.2 molecular simulation software (Yue et al., 2018).

2.6 Statistical analysis

Each test was based on three replicate measurements and the significance of variance was analyzed using SPSS software. Results are expressed as mean ± standard deviation.

3 Results and discussion

To evaluate the feasibility of using bavachalcone as an α-glucosidase inhibitor, its inhibitory activity towards α-glucosidase was determined using acarbose as a positive control (Figure 2). Inhibition rates gradually increased with increasing concentration. Bavachalcone at 30 μg/mL inhibited α-glucosidase by 75.36%, while the inhibition rate with 5 mg/mL acarbose was only 71.80%. The IC50 values for bavachalcone and acarbose were 15.35 ± 0.57 μg/mL and 2.77 ± 0.09 mg/mL, respectively, showing that the inhibitory performance of bavachalcone was significantly superior to acarbose. Chalcones and flavonoids in plant extracts are generally considered to have good chemical stability and α-glucosidase inhibition properties. Phloridin and its polymers have been shown to be effective inhibitors of α-glucosidase with IC50 values of 0.21 mg/mL and 0.12 mg/mL, respectively(Zhou HY et al.,2021). In keeping with these reports, this study shows that food-derived bavachalcone is an excellent α-glucosidase inhibitor with potential applications in functional foods and medicines.

To investigate the type of inhibition bavachalcone exerts on α-glucosidase, the enzymatic hydrolysis rate of *p*NP-G was analyzed at various bavachalcone concentrations and the linear regression of 1/[S] to 1/V plotted in Figure 3. The lines in this Lineweaver-Burk plot intersect in quadrant II, with the Michaelis constant (K_m) increasing gradually and the maximum reaction rate (V_{max}) gradually decreasing with rising bavachalcone concentration. Thus, bavachalcone exerted mixed inhibition on α-glucosidase (Worawalai et al., 2019), both competitively and non-competitively.

Fluorescence spectrometry is the most widely used technique for studying interactions between drug molecules and enzymes under physiological conditions and can determine the binding constant, number of binding sites, and thermodynamic parameters of an interaction (Liu et al., 2017). The type of interaction between a small molecule and an enzyme and the effect bound substances have on molecular conformation can also be obtained from fluorescence spectra. There are two types of fluorescence quenching: dynamic and static. In dynamic quenching the quencher collides with the fluorescent group to reduce their fluorescence absorption. Static quenching is when non-fluorescent complexes are formed by the combination of fluorophores and other substances. The dynamic quenching constant will increase with increasing temperature, while the static quenching constant will decrease (Lakowicz, 2006). It is generally thought the maximum dynamic quenching constant of biological macromolecules is 2.0×10^{10} $L\cdot mol^{-1}\cdot S^{-1}$.

Figure 4 illustrates the fluorescence changes of α-glucosidase when mixed with bavachalcone at various temperatures. Under

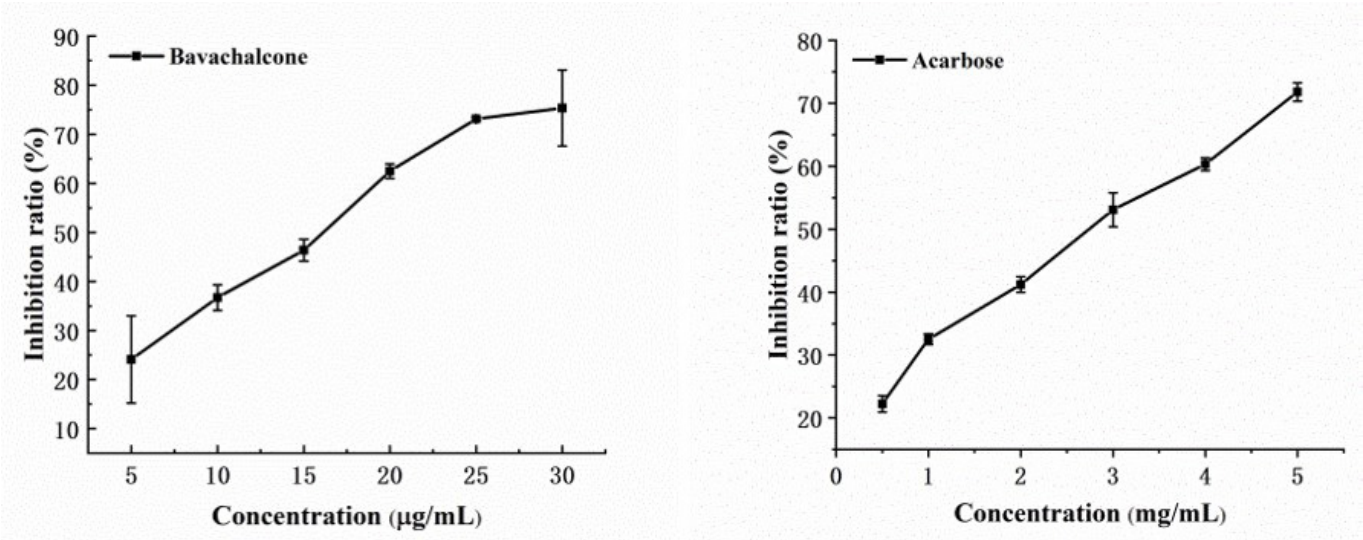

Figure 2. Inhibitory effect of bavachalcone and acarbose (control) on α-glucosidase.

280 nm excitation, α-glucosidase exhibited maximum fluorescence at emission wavelengths around 330 nm. α-Glucosidase fluorescence intensity decreased consistently as bavachalcone concentration increased, indicating that the two molecules interacted. The fluorescence data at various temperatures were analyzed using the Stern-Volmer equation (Equation 2). The quenching constants (k_q) for bavachalcone at 25 °C, 30 °C, and 37 °C were 0.2914×10^{12}, 0.2460×10^{12}, and 0.2117×10^{12}, respectively (Table 1). These are much higher than the maximum dynamic fluorescence quenching constant of 2.0×10^{10} L·mol^{-1}·s^{-1} for biological macromolecules, indicating that bavachalcone formed complexes with α-glucosidase, initiating static fluorescence quenching of the enzyme.

$$F_0 / F = k_q \cdot \tau 0[\mathrm{Q}] + 1 \quad (2)$$

The binding constant (k_a) and number of binding sites (n) of bavachalcone with α-glucosidase during static fluorescence quenching can be calculated from the double logarithmic Equation 3. Bavachalcone and α-glucosidase binding constants were greater than 10^4 orders of magnitude, indicating a strong interaction (Table 2). As temperature increased, the binding constant rose significantly and the number of binding sites (around one) increased slightly. It is speculated that heat not only accelerates the movement of the two compounds in solution, thus promoting binding, but also distends the α-glucosidase structure, exposing more binding sites.

$$\lg\left[\left(F_0 - F\right)/F\right] = \lg k_a + n \lg[\mathrm{Q}] \quad (3)$$

To elucidate the binding process of bavachalcone and α-glucosidase, the thermodynamic constants of their interaction were calculated using the van't Hoff (Equation 4) and Gibbs free energy (Equation 5) equations.

$$\ln K = -\Delta H_0 / RT + \Delta S_0 / R \quad (4)$$

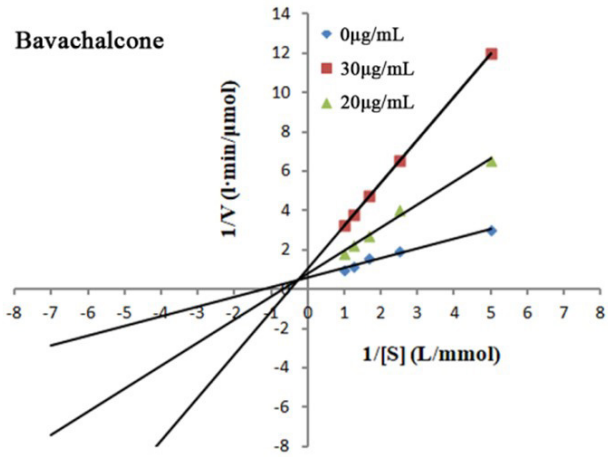

Figure 3. Lineweaver-Burk plot of inhibition of α-glucosidase by bavachalcone.

$$\Delta G_0 = \Delta H_0 - T\Delta S_0 \quad (5)$$

As shown in Table 3, the free energy change (ΔG) of the interaction between bavachalcone and α-glucosidase was negative, indicating that binding was a spontaneous process. The enthalpy change (ΔH) and entropy change (ΔS) were positive. Thus, according to thermodynamic law, the binding is a spontaneous process driven by entropy and hydrophobic forces. This may be attributed to the two hydrophobic benzene rings in bavachalcone binding to the hydrophobic pocket of the enzyme.

Molecular docking is a computer simulation technique that is often used to study the binding process between macromolecules (such as enzymes) and small molecules. It can be optimized according to the conformation of the molecules (bond length, bond angle, dihedral angle, and other parameters) and follows the principles of energy matching and geometric matching to determine the best mode of binding (Jain, 2003; Haiwei et al., 2021). The main forces acting between macromolecules and small

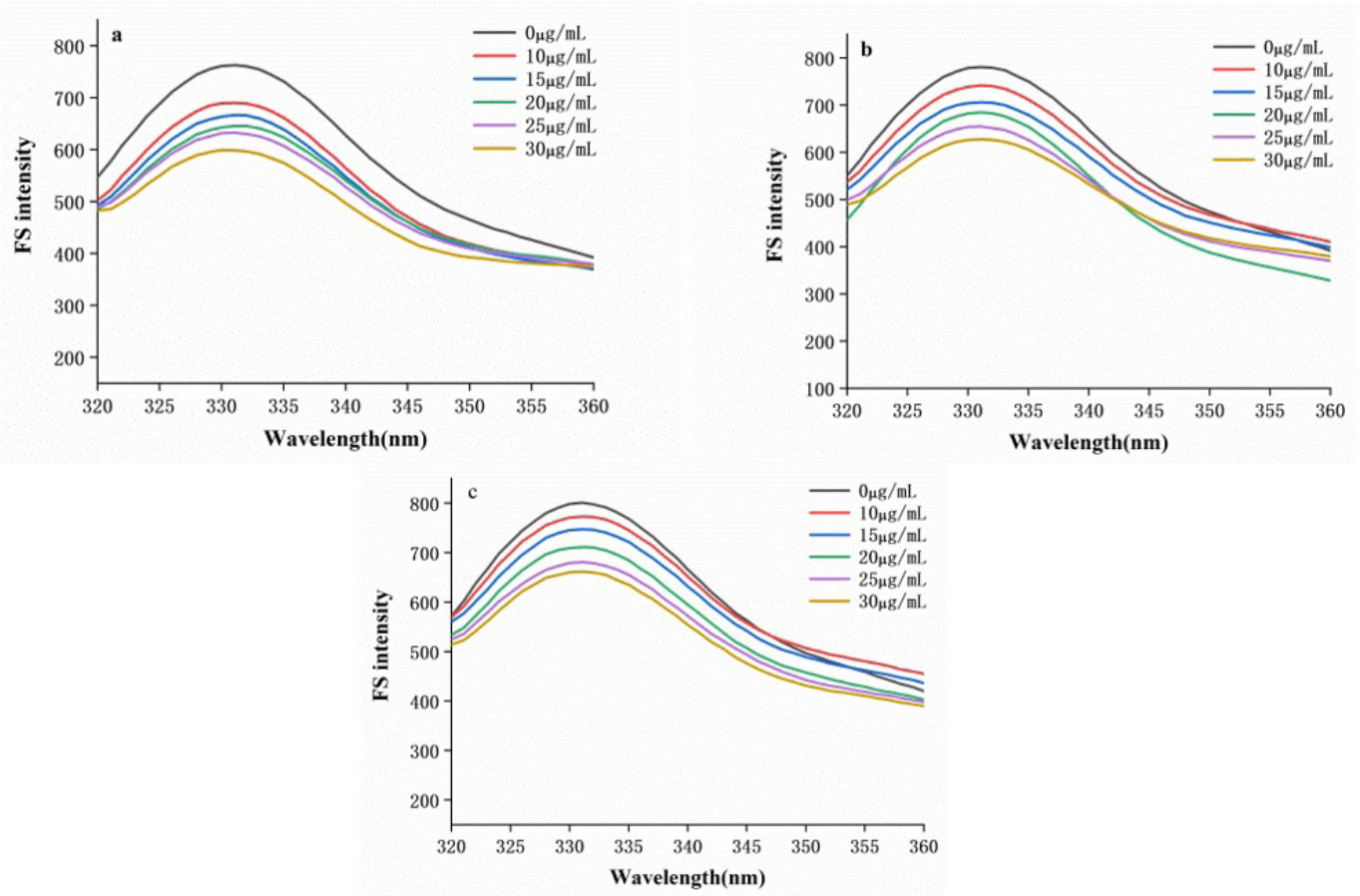

Figure 4. Effect of bavachalcone on fluorescence spectrum of α-glucosidase at 25°C (a), 30°C (b) and 37 °C (c).

Table 1. Fluorescence quenching constants of bavachalcone on α-glucosidase.

	Temperature (°C)	Stern-Volmer equation	R^2	k_q (L·mol^{-1}·s^{-1})
Bavachalcone	25	$F_0/F = 0.2915\times10^4[Q]+1$	0.9552	0.2914×10^{12}
	30	$F_0/F = 0.2460\times10^4[Q]+1$	0.9546	0.2460×10^{12}
	37	$F_0/F = 0.2117\times10^4[Q]+1$	0.9050	0.2117×10^{12}

Table 2. Binding parameters of bavachalcone with α-glucosidase.

	Temperature (°C)	Lineweaver-Burk equation	R^2	k_a (L·mol^{-1})	n
Bavachalcone	25	$\lg(F_0-F)/F = 0.8217\lg[Q]+2.7132$	0.9806	0.0528×10^4	0.8217
	30	$\lg(F_0-F)/F = 1.3649\lg[Q]+4.9014$	0.9908	7.9689×10^4	13.649
	37	$\lg(F_0-F)/F = 1.6520\lg[Q]+6.0221$	0.9920	105.2204×10^4	16.520

Table 3. Thermodynamic parameters of bavachalcone and α-glucosidase binding.

	Temperature (°C)	ΔH (KJ·mol^{-1})	ΔG (KJ·mol^{-1})	ΔS (J·mol^{-1}K^{-1})
Bavachalcone	25	206.32	-7.47	717.43
	30		-11.06	
	37		-16.08	

molecules include electrostatic, hydrogen bond, hydrophobic, and van der Waals forces (Koshland et al., 1962).

Molecular docking was used to elucidate the binding mechanism of bavachalcone and α-glucosidase. As shown in Figure 5A, hydrogen bonds formed between bavachalcone and the amino acid residues trp391 (two bonds of length 1.9 Å and 2.3 Å), arg428, and trp710 (two bonds of length 2.0 and 2.2 Å). Figure 5B shows that bavachalcone docked in a large hydrophobic pocket within α-glucosidase, in close proximity to the evenly distributed hydrophobic amino acids tryptophan

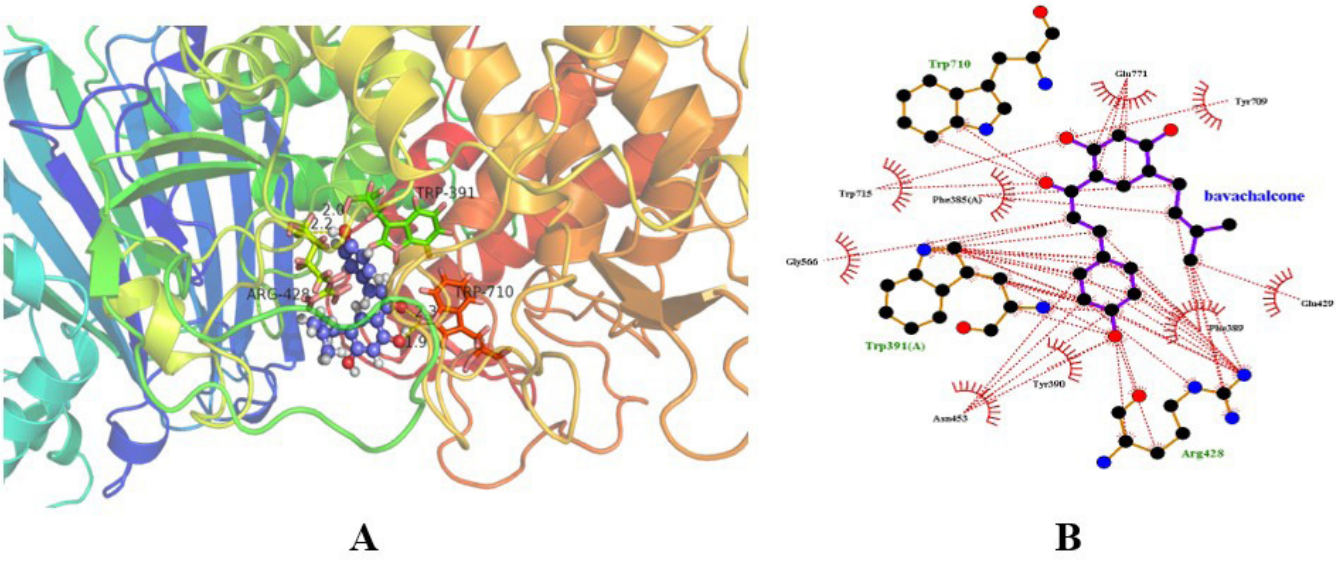

Figure 5. Molecular docking analysis of the binding of bavachalcone and α-glucosidase, including (A) hydrogen bonding, and (B) hydrophobic interactions.

and phenylalanine. This confirmed that bavachalcone binds to the active site of α-glucosidase via hydrophobic forces, causing fluorescence quenching and a decrease in enzyme activity. To more accurately describe this interaction from an energy perspective, the ONIOM computational method was used to calculate the binding free energy between the key residues of the enzyme and bavachalcone. AutoDock analysis demonstrated that the binding free energy between bavachalcone and α-glucosidase was -6.26 kcal/mol, proving they were tightly bound. These findings are similar to the interaction of phenolic acid and α-glucosidase (Xiao et al., 2015). Phenolic acid forms strong hydrogen bonds with trp391 and asp392, and has hydrophobic interactions with the benzene ring-containing residues trp391, trp710, trp715, trp789, phe385, phe389, phe444, and phe786, which all play an important role in the resulting inhibition of α-glucosidase activity.

4 Conclusions

The inhibitory effect of bavachalcone on α-glucosidase activity has been elucidated for the first time, revealing a strong, concentration-dependent effect comprising both competitive and non-competitive inhibition. Fluorescence quenching analysis showed that bavachalcone combined with α-glucosidase at a molar ratio of 1:1 driven by hydrophobic forces. Molecular docking confirmed the formation of hydrogen bonds and hydrophobic interactions between bavachalcone and specific amino acid residues in α-glucosidase. These data support the application of bavachalcone as an α-glucosidase inhibitor.

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