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# Identification of sesquiterpene glycosides from *Dendrobium nobile* and their α-glycosidase and α-amylase inhibitory activities

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**Abstract**

*Dendrobium nobile* is a traditional Chinese medicine and functional food in China, with anti-aging, immunity-enhancing, glucose-lowering and lipid-lowering health functions. In recent years, the research value of *D. nobile* has attracted the attention of more and more experts and scholars. Today, phytochemical investigation of the stems of *Dendrobium nobile* Lindl., led to the isolation of five sesquiterpene glycosides, including dendromoniliside D (**1**), dendronobiloside A (**2**), dendronobiloside C (**3**), dendronobiloside D (**4**), dendroside G (**5**) and their α-amylase and α-glycosidase inhibitory activities were also investigated. Among them, dendromoniliside D (**1**), dendroside G (**5**) were first isolated from *D. nobile*. And dendronobiloside A (**2**) and dendronobiloside C (**3**) exhibited better inhibitory activity against α-glycosidases, respectively. In the case of α-amylase inhibition, dendroside G (**5**) has a relatively good effect. These results suggest that sesquiterpene glycosides of *D. nobile* have potential hypoglycemic activity and deserve further research and development.

**Keywords:** *Dendrobium nobile*; isolation and identification; sesquiterpene glycosides; α-amylase; α-glycosidase.

**Practical Application:** The investigation of sesquiterpene glycosides provides the important information for consumers and researchers to understand *Dendrobium nobile* chemical constituents and bioactivites.

## 1 Introduction

In recent years, the research and development of functional products made from herbs has attracted increasing attention (Ruiz-Cisneros et al., 2022; Wang et al., 2022a; Wang et al., 2022b; Yin et al., 2022). The genus *Dendrobium* contains approximately 1100 species, which is one of the largest genera in the family Orchidacea, and mainly distributed in southwestern Asia, Europe and Australia, such as China, Thailand, Myanmar and Vietnam (Yu et al., 2015). In traditional medicine, several *Dendrobium* species are used for various diseases or as beverages (Cakova et al., 2017; Xu et al., 2013). Among them, the stems of *D. nobile* is the most dominant sources of Shihu, a famous traditional Chinese medicine (Chinese Pharmacopoeia Commission, 2020) and used as a tonic to nourish Yin, clear heat, nourish stomach, and replenish body fluid (Cakova et al., 2017; Shin et al., 2017; Xu et al., 2017). In term of pharmacological effects, *D. nobile* exhibits effects of regulating lipid metabolism, antioxidant activity, protecting the nervous system, anti-immune activity, antifibrosis, antitumor, and others. Previous phytochemical investigations on *D. nobile* indicated that diversified compounds, including sesquiterpene glycosides, alkaloids, bibenzyls, plysaccharides and phenanthrenes have been isolated from this plant (Lam et al., 2015; Thanh et al., 2017; Wang et al., 2019; Xu et al., 2013; Xu et al., 2017). Among them, protecting the nervous system, regulating lipid metabolism has been closely related to alkaloids (Huang et al., 2019; Lv et al., 2020). However, for the effect of anti-immune activity, sesquiterpene glycosides were found to stimulate the proliferation of the proliferation of B cells *in vitro* (Lu et al., 2022). Specifically, picrotoxane sesquiterpene glycosides were considered as key intermediates in the biosynthesis of dendrobine, a major quality marker in *D. nobile* (Gong et al., 2021). In the present continuation of phytochemical investigation of *D. nobile*, five sesquiterpene glycosides, including dendromoniliside D (**1**), dendronobiloside A (**2**), dendronobiloside C (**3**), dendronobiloside D (**4**), dendroside G (**5**) were isolated and elucidated by HR-ESI-MS, NMR spectroscopic analyses, and their α-amylase and α-glycosidase inhibitory activities were also investigated.

## 2 Experimental

### *2.1 General experimental procedures*

In the separation process, the column chromatography (CC) was performed by silica-gel (100-200 and 300-400 mesh, Qingdao Marine Chemical Co., Qingdao, China), and Sephadex LH-20 (GE Healthcare, Marlborough, MA). The TLC detection was carried by heating silica gel plate (Qingdao Marine Chemical Co., Qingdao, China) spayed with 10% $H_2SO_4$ in ethanol.

α-Glycosidase (100 U), α-amylase (50 U), p-Nitrophenyl-α-D-glucopyranoside (PNPG, 99%), acarbose and DNS reagents were purchased from Beijing Solexpo Technology Co.

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NMR spectra were recorded on a Varian INOVA AS 400 instrument (Agilent, USA) with TMS as internal standard. ESIMS data were collected by a UPLC–Q/TOF-MS system including a 1290 Infinity II UPLC system (Agilent, USA) and an Agilent 6545 Q/TOF-MS system (Agilent, MA, USA). The absorbance was recorded by a microplate spectrophotometer (Thermo, USA).

### *2.2 Plant materials*

*D. nobile* were collected from the Good Agricultural Practices (GAP) bases located in Chishui City, China in 2019 and authenticated by Associate Professor Daopeng Tan (pharmacognosy, Zunyi medical university). A voucher specimen (No. 201906) was deposited in the herbarium of Zunyi medical university.

### *2.3 Extraction and isolation*

The air-dried *D. nobile* (5.0 kg) were cut into slices and then extracted with 75 L 70% EtOH by reflux extraction three times. The combined extraction solution was concentrated under vacuum to yield a viscous residue. The crude extract residue (500 g) was fractionated through an AB-8 macroporous resin column and eluted by water and 50% methanol sequentially. The 50% methanol fraction was concentrated through evaporating the solvent to obtain the total sesquiterpene glycosides extract (206 g). The total sesquiterpene glycosides extract was then subjected to reverse phase ODS column chromatography and yield five subfractions (Fr.1~5). semi-preparative HPLC and Sephadex LH-20 column were employed to purified aforesaid subfractions, and finally yielded five compounds, including **1** (35 mg), **2** (44 mg), **3** (27 mg), **4** (256 mg), **5** (55 mg).

### *2.4 α-Glucosidase inhibition activity*

The α-glucosidase inhibitory activity was determined by the microplate method (Purnomo et al., 2021). In a 96-well plate, 50 μL of phosphate buffer solution (PBS, pH 6.8), 50 μL of sample solution, 10 μL of α-glucosidase solution (1 U/mL, pH 6.8 PBS) were added separately. After shaking and mixing well, reaction solution was incubated at 37 °C for 15 min, and then added 40 μL of 5 mmol/L PNPG, continue to incubate for 15 min at 37 °C. At last, the reaction was terminated by adding 40 μL of sodium carbonate solution. Before and after incubation, the absorbance was recorded at 405 nm on a microplate spectrophotometer. Acarbose was used as a positive reference. The a-glucosidase inhibition activity was expressed as inhibition (%) and was calculated as Equation 1:

$$. Inhibition\ (\%) = (1 - \Delta A_{sample} / \Delta A_{control}) \times 100\% \quad (1)$$

### *2.5 α-Amylase inhibition activity*

The α-amylase inhibitory activity was measured by microplate method (Purnomo et al., 2021). 50 μL sample solution, 50 μL 2.5 U/mL α-amylase were added in a 96-well plate, shaking and mixing, and incubating at 37 °C for 10 min, then added 100 μL 1.5% soluble starch solution, mixing, react at 37 °C for 10 min, immediately add 300 μL DNS for color development, cooling to room temperature after boiling water bath at 95 °C for 10 min, adding 1000 μL PBS diluted to 1500 μL. Before and after incubation, the absorbance was recorded at 405 nm on a microplate spectrophotometer (Thermo). Acarbose was used as a positive reference. The a-amylase inhibition activity was also expressed as Equation 1.

### *2.6 Molecular docking studies*

To investigate the binding modes of dendronobiloside A, dendronobiloside C and dendroside G, a docking simulation was performed targeting the crystal structure of α-glucosidase and α-amylase (Purnomo et al., 2021). The crystal structures were retrieved from the PDB, and the a-glycosidase (PDB code: 1MFU) and a-amylase (PDB code: 3BAJ) were pre-docked using the Autodock software. The 3D structures of dendronobiloside A, dendronobiloside C and dendroside G were built by ChemBioDraw Ultra14.0 and then converted to PDBQT coordinateds using AutoDockTools. The rotatable bonds in the ligand were assigned with AutoDock Tools, and the ligand docking was performed with the AutoDock Vina. Construct 2D maps of protein-ligand interactions using LigPlot software to analyze the interaction forces between protein and ligand binding. Construct 3D maps of protein-ligand interactions using PyMOL software to view the binding sites between proteins and ligands.

### *2.7 Statistical analysis*

The experimental results including α-glucosidase and α-amylase activity assay were expressed as mean value ± standard deviation (n = 3), and data were analyzed using the Origin software (Version 8.0).

## 3 Results and discussion

### *3.1 Structure elucidation*

All structures of compounds **1**~**5** were elucidated and identified as dendromoniliside D (**1**) (Ye & Zhao, 2002), dendronobiloside A (**2**) (Thanh et al., 2017), dendronobiloside C (**3**) (Ye & Zhao, 2002), dendronobiloside D (**4**) (Ye & Zhao, 2002), dendroside G (**5**) (Ye & Zhao, 2002) (Figure 1), respectively, by ESIMS, NMR spectroscopic analyses and direct comparison of their data with the literature.

Dendromoniliside D: white amorphous powder; ESI-MS: m/z = 491.2198 $[M+FA-H]^-$ ($C_{21}H_{34}O_{10}$); $^1H$ NMR (600 MHz, $C_5D_5N$): 4.21 (d, J = 6.0 Hz, H-2), 4.51 (m, H-3), 2.08 (m, H-4), 2.38 (m, H-5), 2.71 (m, H-6), 2.07, 1.61 (m, H-7), 2.37, 2.08 (m, H-8), 3.22 (s, H-9), 1.40 (s, H-10), 3.91, 4.20 (m, H-11), 1.38 (m, H-13, 14), 4.88 (d, J = 6.0 Hz, H-1'), 4.02 (m, H-2'), 4.25 (m, H-3'), 4.22 (m, H-4'), 4.01 (m, H-5'), 4.41, 4.54 (m, H-6'); $^{13}C$ NMR (150 MHz, $C_5D_5N$): $^{13}C$ NMR (150 MHz, $C_5D_5N$): 50.8 (C-1), 73.8 (C-2), 86.0 (C-3), 54.6 (C-4), 47.2 (C-5), 45.7 (C-6), 27.2 (C-7), 29.7 (C-8), 44.5 (C-9), 23.4 (C-10), 74.3 (C-11), 69.4 (C-12), 30.7 (C-13), 31.1 (C-14), 180.2 (C-15), 105.3 (C-1'), 75.5 (C-2'), 79.0 (C-3'), 72.0 (C-4'), 79.0 (C-5'), 63.2 (C-6') (Ye & Zhao, 2002).

Dendronobiloside A: white amorphous powder; ESI-MS: m/z = 609.3135 $[M+FA-H]^-$ ($C_{27}H_{48}O_{12}$); $^1H$ NMR (600 MHz, $C_5D_5N$): 2.10 (m, H-1), 1.28 (m, H-2), 1.09, 1.30 (m, H-3), 1.09,

1.22 (m, H-4), 2.05 (m, H-6), 1.50, 2.00 (m, H-7), 1.50,1.87 (m, H-8), 2.10 (m, H-9), 3.88 (m, H-10), 2.05 (m, H-11), 3.57 (t, J = 12.0 Hz, H-12), 4.29 (m, H-12), 1.06 (s, H-13), 0.86 (d, J = 6.0 Hz,, H-14), 0.76 (d, J = 6.0 Hz,, H-15), 4.87 (d, J = 6.0 Hz, H-1'), 4.06 (m, H-2'), 4.27 (m, H-3'), 4.24 (m, H-4'), 3.99 (m, H-5'), 4.41, 4.58 (m, H-6'), 4.87 (d, J = 6.0 Hz, H-1"), 4.06 (m, H-2"), 4.28 (m, H-3"), 4.26 (m, H-4"), 4.04 (m, H-5"), 4.43, 4.61 (m, H-6"); $^{13}$C NMR (150 MHz, $C_5D_5N$): 36.9 (C-1), 39.7 (C-2), 20.5 (C-3), 27.6 (C-4), 42.2 (C-5), 52.0 (C-6), 26.7 (C-7), 23.0 (C-8), 48.9 (C-9), 71.8 (C-10), 27.4 (C-11), 71.8 (C-12), 24.2 (C-13), 22.2 (C-14), 15.8 (C-15), 105.6 (C-1'), 75.7 (C-2'), 79.2 (C-3'), 72.3 (C-4'), 79.0 (C-5'), 63.4 (C-6'), 105.2 (C-1"), 75.6 (C-2"), 79.1 (C-3"), 72.3 (C-4"), 79.0 (C-5"), 63.4 (C-6") (Thanh et al., 2017).

Dendronobiloside C: white amorphous powder; ESI-MS: m/z = 605.2825 $[M+FA-H]^-$ ($C_{27}H_{44}O_{12}$); $^1$H NMR (600 MHz, $C_5D_5N$): 1.99, 3.03 (m, H-2), 2.13,2.35 (m, H-3), 5.96 (s, H-5), 2.62 (brs, H-6), 1.10 (m, H-7), 1.11,1.56 (m, H-8), 2.08,2.58 (m, H-9), 4.29,4.56 (m, H-11), 2.01 (m, H-12), 0.69 (d, J = 6.0 Hz, H-13), 0.85 (d, J = 6.0 Hz, H-14), 4.38, 4.60 (m, H-15), 4.89 (d, J = 6.0 Hz, H-1'), 4.08 (m, H-2'), 4.28 (m, H-3'), 4.26 (m, H-4'), 3.97 (m, H-5'), 4.40, 4.58 (m, H-6'), 4.89 (d, J = 6.0 Hz, H-1"), 4.08 (m, H-2"), 4.28 (m, H-3"), 4.26 (m, H-4"), 3.98 (m, H-5"), 4.40, 4.58 (m, H-6"); $^{13}$C NMR (150 MHz, $C_5D_5N$): 137.3 (C-1), 27.3 (C-2), 29.4 (C-3), 135.6 (C-4), 127.7 (C-5), 40.5 (C-6), 45.6 (C-7), 21.8 (C-8), 29.0 (C-9), 126.8 (C-10), 73.7 (C-11), 27.2 (C-12), 16.2 (C-13), 22.2 (C-14), 68.3 (C-15), 103.5 (C-1'), 75.7 (C-2'), 79.0 (C-3'), 72.2 (C-4'), 79.1 (C-5'), 63.3 (C-6'), 104.4 (C-1"), 75.7 (C-2"), 79.1 (C-3"), 72.3 (C-4"), 79.1 (C-5"), 63.4 (C-6") (Ye & Zhao, 2002).

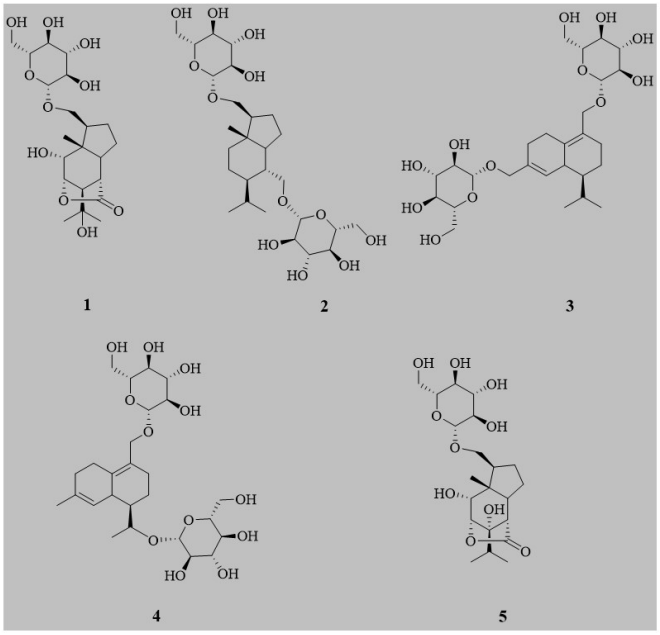


**Figure 1.** Structures of compounds 1~5 isolated from *D. nobile*.

Dendronobiloside D: white amorphous powder; ESI-MS: m/z = 605.2826 $[M+FA-H]^-$ ($C_{27}H_{44}O_{12}$); $^1$H NMR (600 MHz, $C_5D_5N$): 1.95, 3.02 (m, H-2), 1.97 (m, H-3), 5.54 (s, H-5), 2.62 (brd, J = 7.0 Hz, H-6), 1.50 (m, H-7), 1.15,1.52 (m, H-8), 1.99, 2.52 (m, H-9), 1.61 (s, H-11), 2.42 (m, H-12), 0.86 (d, J = 6.0 Hz, H-13), 3.59, 4.08 (m, H-14), 4.39, 4.62 (m, H-15), 4.89 (d, J = 6.0 Hz, H-1'), 4.06 (m, H-2'), 4.28 (m, H-3'), 4.24 (m, H-4'), 3.99 (m, H-5'), 4.43, 4.60 (m, H-6'), 4.88 (d, J = 6.0 Hz, H-1"), 4.06 (m, H-2"), 4.28 (m, H-3"), 4.24 (m, H-4"), 3.99 (m, H-5"), 4.43, 4.60 (m, H-6"); $^{13}$C NMR (150 MHz, $C_5D_5N$): 137.4 (C-1), 27.5 (C-2), 33.2 (C-3), 134.7 (C-4), 124.7 (C-5), 40.0 (C-6), 40.9 (C-7), 22.5 (C-8), 28.9 (C-9), 126.4 (C-10), 23.9 (C-11), 33.7 (C-12), 11.6 (C-13), 74.8 (C-14), 68.3 (C-15), 105.5 (C-1'), 75.7 (C-2'), 79.0 (C-3'), 72.2 (C-4'), 79.1 (C-5'), 63.4 (C-6'), 103.4 (C-1"), 75.7 (C-2"), 79.0 (C-3"), 72.3 (C-4"), 79.1 (C-5"), 63.4 (C-6") (Ye & Zhao, 2002).

Dendroside G: white amorphous powder; ESI-MS: m/z = 491.2149 $[M+FA-H]^-$ ($C_{21}H_{34}O_{10}$); $^1$H NMR (600 MHz, $C_5D_5N$): 2.75 (d, J = 4.0 Hz, H-1), 2.21 (m, H-2), 2.11 (m, H-3), 1.65, 2.41 (m, H-4), 3.56 (m, H-5), 4.17 (s, H-7), 5.02 (s, H-8), 2.05 (m, H-11), 1.14 (d, J=6.0 Hz, H-12), 1.13 (d, J=6.0 Hz, H-13), 4.22, 4.50(m, H-14), 1.25 (m, H-15), 4.88 (d, J = 6.0 Hz, H-1'), 4.02 (m, H-2'), 4.25 (m, H-3'), 4.23 (m, H-4'), 4.01 (m, H-5'), 4.42, 4.55 (m, H-6'); $^{13}$C NMR (150 MHz, $C_5D_5N$): $^{13}$C NMR (150 MHz, $C_5D_5N$): 55.1 (C-1), 48.2 (C-2), 27.2 (C-3), 29.4 (C-4), 44.7 (C-5), 49.1 (C-6), 75.9 (C-7), 90.4 (C-8), 180.0 (C-9), 81.8 (C-10), 29.7 (C-11), 16.9 (C-12), 16.0 (C-13), 74.0 (C-14), 25.3 (C-15), 105.3 (C-1'), 75.5 (C-2'), 79.0 (C-3'), 72.1 (C-4'), 79.0 (C-5'), 63.3 (C-6') (Ye & Zhao, 2002).

### *3.2 Enzyme inhibition activity*

The inhibitory activity of compounds **1**~**5** isolated from *D. nobile* against α-glucosidase and α-amylase were assayed by microplate method. The results were showed in Table 1. Among them, dendronobiloside A (**2**) and dendronobiloside C (**3**) exhibited better inhibitory activity against α-glycosidases. To further investigate the dose-dependent effects of dendronobiloside A (**2**) and dendronobiloside C (**3**) on α-glucosidase inhibitory activity, the IC50 values were determined to be 299.7 ± 2.38 μg/mL (dendronobiloside A, **2**) and 537.8 ± 2.33 μg/mL (dendronobiloside C, **3**), respectively. In the case of α-amylase inhibition, dendroside G (**5**) has a relatively good effect. Furthermore, its IC50 value was determined to be 1.06 ± 0.06 mg/mL (dendroside G, **5**).

### *3.3 Molecular docking analysis*

To clarify the interaction between dendronobiloside A (**2**) and dendronobiloside C (**3**) and α-glucosidase, or dendroside G (**5**) and α-amylase, the molecular docking was used to simulate

**Table 1.** The α-glucosidase and α-amylase inhibition of compounds 1~5 (1.0 mg/mL).

| Targets | (1) | (2) | (3) | (4) | (5) | Acarbose |
|---|---|---|---|---|---|---|
| α-glucosidase inhibition (%) | 7.15 ± 1.18 | 70.82 ± 3.97 | 67.94 ± 0.28 | 40.61 ± 0.15 | 14.99 ± 0.53 | 96.51 ± 0.02 |
| α-amylase inhibition (%) | 46.96 ± 1.32 | 19.77 ± 0.02 | 34.94 ± 1.47 | 44.68 ± 1.68 | 51.69 ± 0.94 | 92.47 ± 0.29 |

their binding modes. After docking, the conformational clusters with the lowest binding free energy in the docked complex of dendronobiloside A (**2**) and dendronobiloside C (**3**) with α-glucosidase were shown in Fig. 2. and dendroside G (**5**) with α-amylase was shown in Fig. 3. Their lowest binding energy of -7.3 kacl/mol (dendronobiloside A, **2**), -8.4 kacl/mol (dendronobiloside C, **3**)

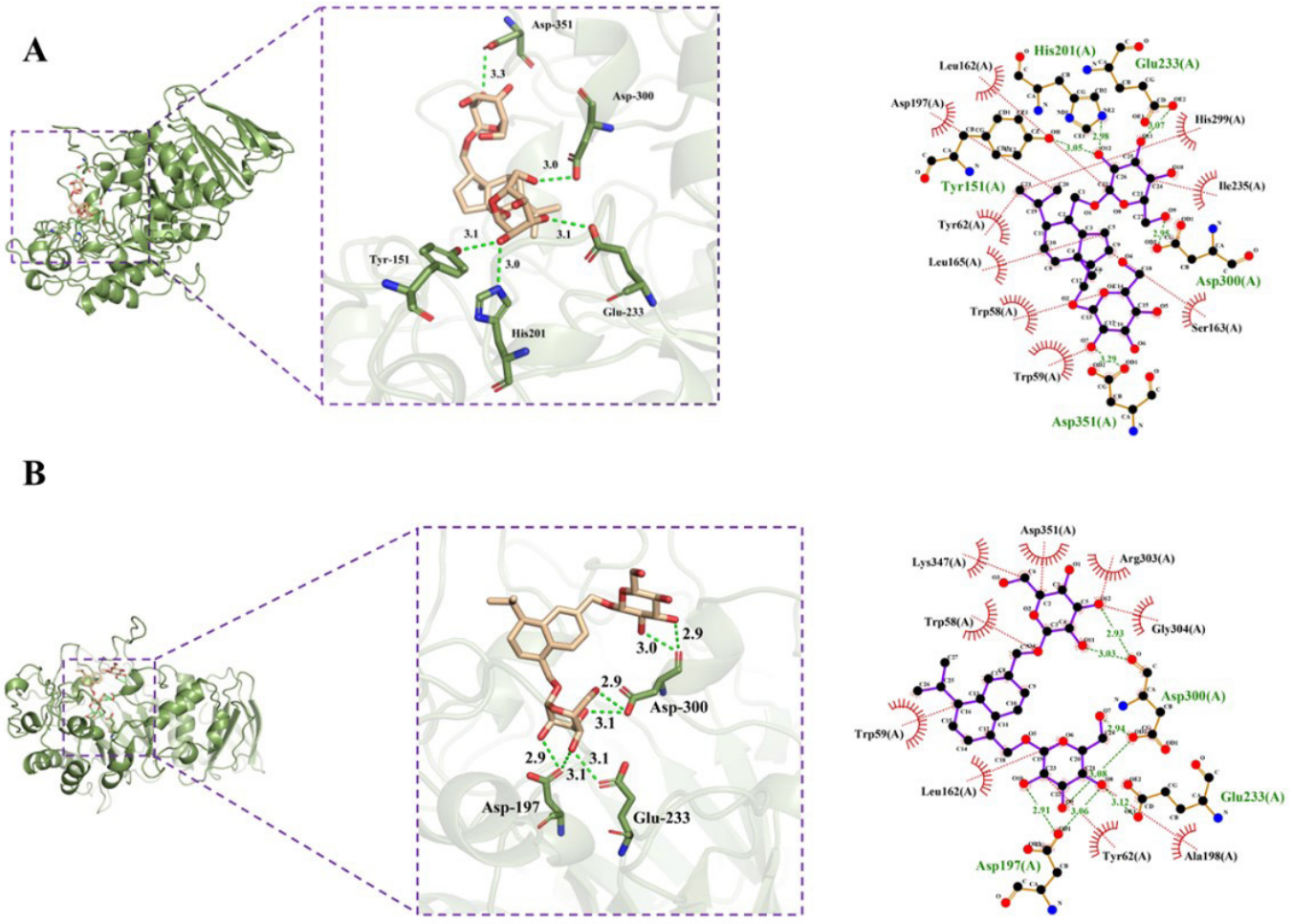


**Figure 2.** Dendronobiloside A (A) and dendronobiloside C (B) were docked to the binding pocket of the α-glucosidase.

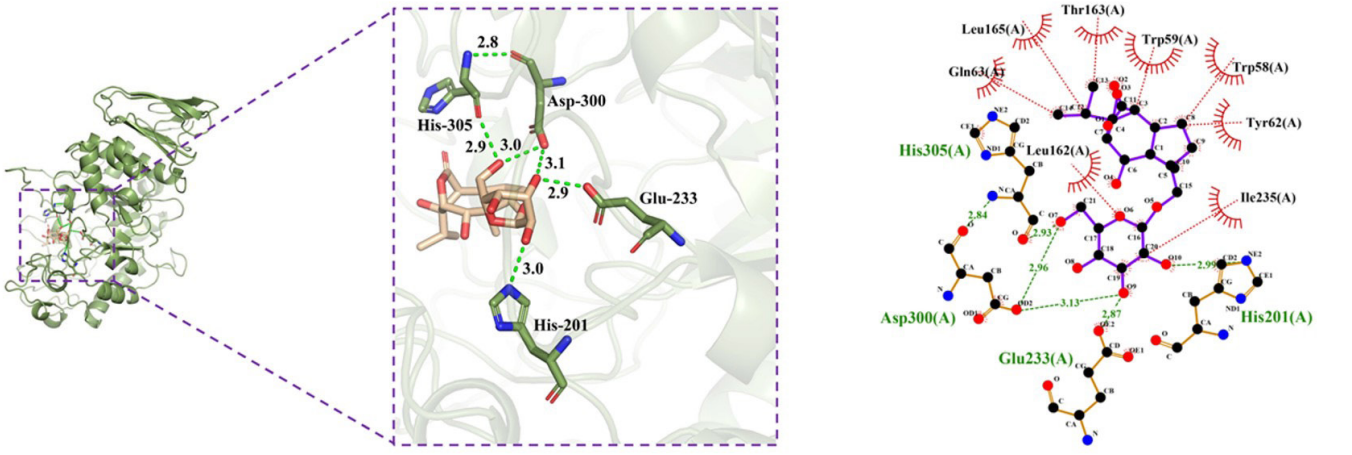


**Figure 3.** Dendroside G was docked to the binding pocket of the α-amylase.

and -8.2 kacl/mol (dendroside G, **5**) were selected as the final model. These results implied that dendronobiloside A (**2**) has larger binding affinities with α-glucosidase, and dendroside G (**5**) with α-amylase.

## 4 Conclusion

In the present study, five sesquiterpene glycosides were isolated and elucidated from *D. nobile*. And their α-amylase and α-glycosidase inhibitory activities were also investigated. The results showed that dendronobiloside A (**2**) and dendronobiloside C (**3**) exhibited better inhibitory activity against α-glycosidases, respectively. In the case of α-amylase inhibition, dendroside G (**5**) has a relatively good effect. These results suggest that sesquiterpene glycosides of *D. nobile* have potential hypoglycemic activity and deserve further research and development.

## Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Author contributions

Daopeng Tan: Investigation, Writing-original draft. Yeyang Song and Jianmei Wang: Data curation, Supervision. Chunxue Gao: Manuscript checking. Lin Qin: Manuscript checking and data analysis. Yanliu Lu and Yongxia Zhao: Writing–review and editing. Zhou Yang: Funding acquisition. Yuqi He: Funding acquisition and supervision writing.

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