Phenylpropanoids from Liparis nervosa and their in vitro antioxidant and α-glucosidase inhibitory activities

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Abstract

Eleven phenylpropanoids were isolated from the whole grass of *Liparis nervosa*, an orchidaceous medicinal plant. Their structures were elucidated as (+)-Syringaresinol (1), (-)-Syringaresinol-4-O-β-D-glucopyranoside (2), Sinapaldehyde (3), Coniferyl aldehyde (4), Syringin (5), Sinapaldehyde glucoside (6), 2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (7), C-Veratroylglycol (8), 7S, 7'S, 8R, 8'R-icariol A₂ (9), Erigeside 2 (10), and Methylsyringin (11) by comparing the spectroscopic data and physicochemical constants from the isolated compounds with the data reported in the literature. Compounds 1 and 9 were found to have potent *in vitro* antioxidant activities in the DPPH and ABTS assays, and their IC₅₀ values were lower than those of vitamin C. More importantly, compound 9 had a strong α-glucosidase inhibitory activity with an IC₅₀ value of 43.76 ± 2.03 µM, which was much lower than that of acarbose (IC₅₀ = 273.12 ± 11.84 µM), indicating that compound 9 has the potential for the development of hypoglycemic drugs. In conclusion, the present study suggests that phenylpropanoids may be the additional representative type of active constituents in *L. nervosa*, which provides a new line of evidence to understand this medicinal plant.

Introduction

The genus *Liparis* belongs to the family Orchidaceae and approximately 250 species are inclusive in the genus all over the world [1]. *Liparis nervosa* (Thunb. ex A. Murray) Lindl., a member of the genus *Liparis*, is a plant widely distributed in tropical and subtropical regions [1]. In China, it is mainly found in the south areas, and the whole grass of *L. nervosa* is used in traditional Chinese medicine for a long time to treat hemorrhagic and inflammatory diseases [2]. Modern pharmacological studies have revealed that *L. nervosa* possesses antioxidant [3], anti-inflammatory [4], tumor cytotoxic [5], and hemostatic effects [6]. Available researches on the phytochemical composition of *L. nervosa* have shown that phenanthrenes [5], pyrrolizidine alkaloids [4, 7, 8] and nervogenic acids [9, 10] are its main secondary metabolites. Through the natural selection process, natural products possess a unique and vast chemical diversity [11]. Therefore, whether *L. nervosa* has other representative types of secondary metabolites attracts our attention. Our previous phytochemical study has reported biphenanthrenes with the tumor cytotoxic activities from the small and medium polar fractions of *L. nervosa* [5]. The aim of the present study was to isolate and identify the major constituents present in the large polar fraction of this plant. Additionally, the *in vitro* antioxidant and α-glucosidase inhibitory activities of the isolated compounds were evaluated as well. Taken together, this study aimed to provide a theoretical basis for the in-depth research of this medicinal plant.

Results And Discussion

Structural elucidation

Eleven compounds were purified following fractionation of the *n*-butanol fraction by chromatographic techniques. Their structures were identified by comparing their 1D NMR, HR-ESI-MS, and optical rotation...
with those reported in the literature (Fig. 1). The 1D NMR, HR-ESI-MS, and HPLC spectra of all the compounds are summarized in Supplementary Information File.

(+) -Syringaresinol (1)

White crystal; [α]_D^20 = +124.5 (c = 0.006 MeOH); HR-ESI-MS (m/z): 441.1527 [M+Na]^+. 1H-NMR (CD_3OD, 600 MHz) δ: 6.66 (4H, s, H-2, 2′, 6, 6′), 4.72 (2H, d, J = 4.2 Hz, H-7, 7′), 4.26 (2H, dd, J = 6.6, 9.0 Hz, H-9a, 9′a), 3.88 (2H, dd, J = 3.0, 9.0 Hz, H-9b, 9′b), 3.84 (12H, s, 3, 3′, 5, 5′-OCH_3), 3.14 (2H, m, H-8, 8′); 13C-NMR (CD_3OD, 150 MHz) δ: 149.5 (C-3, 3′, 5, 5′), 136.4 (C-4, 4′), 133.3 (C-1, 1′), 104.7 (C-2, 2′, 6, 6′), 87.8 (C-7, 7′), 72.9 (C-9, 9′), 57.0 (3, 3′, 5, 5′-OCH_3), 55.7 (C-8, 8′). The data are consistent with those reported in reference [12].

(-) -Syringaresinol-4-β-D-glucopyranoside (2)

White crystal; [α]_D^20 = -84.73 (c = 0.042 MeOH); HR-ESI-MS (m/z): 579.2064 [M-H]. 1H-NMR (CD_3OD, 600 MHz) δ: 6.72 (2H, s, H-2, 6), 6.66 (2H, s, H-2′, 6′), 4.86 (1H, d, J = 9.0 Hz, glc-H-1), 4.77 (1H, d, J = 4.8 Hz, H-6), 4.72 (1H, d, J = 5.4 Hz, H-2), 3.86 (6H, s, 3, 5-OCH_3), 3.85 (6H, s, H-3′, 5′); 13C-NMR (CD_3OD, 150 MHz) δ: 154.6 (C-3, 5), 149.5 (C-3′, 5′), 139.7 (C-4), 136.4 (C-4′), 135.7 (C-1), 133.2 (C-1′), 105.5 (glc-C-1), 105.0 (C-2, 6), 104.7 (C-2′, 6′), 87.7/87.3 (C-2, 6), 78.5 (glc-C-5), 78.0 (glc-C-3), 75.8 (glc-C-2), 73.1/73.0 (C-4, 8), 71.5 (glc-C-4), 62.7 (glc-C-6), 57.2/57.0 (4×OCH_3), 55.9/55.7 (C-1, 5). The data are consistent with those reported in reference [13].

Sinapaldehyde (3)

Yellow powder; HR-ESI-MS (m/z): 207.0634 [M-H]: 1H-NMR (CD_3OD, 600 MHz) δ: 9.58 (1H, d, J = 7.8 Hz, H-9), 7.58 (1H, d, J = 15.6 Hz, H-7), 6.99 (2H, br.s, H-2, 6), 6.68 (1H, dd, J = 7.8, 15.6 Hz, H-8), 3.90 (6H, s, 3, 5-OCH_3); 13C-NMR (CD_3OD, 150 MHz) δ: 196.2 (C-9), 156.5 (C-8), 151.7 (C-3), 149.8 (C-7), 141.0 (C-4), 127.2 (C-7), 126.7 (C-1), 107.8 (C-2, 6), 56.3 (3-OCH_3). The data are consistent with those reported in reference [14].

Coniferyl aldehyde (4)

Yellow powder; HR-ESI-MS (m/z): 177.0530 [M-H]: 1H-NMR (CD_3OD, 600 MHz) δ: 9.52 (1H, d, J = 7.8 Hz, H-9), 7.56 (1H, d, J = 15.6 Hz, H-7), 7.19 (1H, d, J = 1.8 Hz, H-2), 7.14 (1H, dd, J = 1.8, 7.8 Hz, H-6), 6.78 (1H, d, J = 7.8 Hz, H-5), 6.58 (1H, dd, J = 8.4, 15.6 Hz, H-8), 3.88 (3H, s, 3-OCH_3); 13C-NMR (CD_3OD, 150 MHz) δ: 196.2 (C-9), 156.0 (C-7), 151.7 (C-3), 149.5 (C-4), 127.6 (C-1), 126.2 (C-8), 125.1 (C-6), 117.5 (C-5), 111.8 (C-2), 56.3 (3-OCH_3). The data are consistent with those reported in reference [15].

Syringin (5)

White powder; HR-ESI-MS (m/z): 395.1314 [M+Na]^+. 1H-NMR (DMSO-d_6, 600 MHz) δ: 6.72 (2H, s, H-2, 6), 6.46 (1H, d, J = 15.6 Hz, H-7), 6.33 (1H, dt, J = 4.8, 15.6 Hz, H-8), 4.90 (1H, d, J = 7.8 Hz, H-1′), 4.10 (2H, d, J
= 4.8 Hz, H-9), 3.77 (6H, s, 3, 5-OCH₃), 3.01~3.60 (6H, m, Glc-H); ¹³C-NMR (DMSO-d₆, 150 MHz) δ: 152.7 (C-3, 5), 133.8 (C-4), 132.6 (C-1), 130.2 (C-7), 128.4 (C-8), 104.5 (C-2, 6), 102.5 (C-1'), 77.2 (C-3'), 76.5 (C-5'), 74.2 (C-2'), 69.9 (C-4'), 61.5 (C-9), 60.9 (C-6'), 56.3 (3, 5-OCH₃). The data are consistent with those reported in reference [16].

Sinapaldehyde-4-O-β-D-glucoside (6)

Yellow powder; HR-ESI-MS (m/z): 393.1151 [M+Na]⁺. ¹H-NMR (DMSO-d₆, 600 MHz) δ: 9.64 (1H, d, J = 8.4 Hz, H-9), 7.63 (1H, d, J = 15.6 Hz, H-7), 7.10 (2H, s, H-2, 6), 6.90 (1H, dd, J = 7.8, 15.6 Hz, H-8), 4.91 (1H, d, J = 6.6 Hz, H-1'), 3.81 (6H, s, 3, 5-OCH₃); ¹³C-NMR (DMSO-d₆, 150 MHz) δ: 194.2 (C-9), 153.4 (C-7), 152.7 (C-3, 5), 136.9 (C-4), 129.4 (C-1), 127.9 (C-8), 107.1 (C-2, 6), 102.0 (C-1'), 77.4 (C-3'), 76.6 (C-5'), 74.1 (C-2'), 69.9 (C-4'), 60.8 (C-6'), 56.5 (3, 5-OCH₃). The data are consistent with those reported in reference [17].

2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (7)

Colorless crystal; [α]₂₀° = -28.54 (c = 0.042 MeOH); HR-ESI-MS (m/z): 265.0680 [M+Na]⁺. ¹H-NMR (CD₃OD, 600 MHz) δ: 7.35 (2H, s, H-2', 6'), 5.14 (1H, dd, J = 4.8, 6.0 Hz, H-2), 3.91 (6H, s, 3′, 5′-OCH₃), 3.86 (1H, m, H-3a), 3.75 (1H, m, H-3b); ¹³C-NMR (CD₃OD, 150 MHz) δ: 199.8 (C-1), 149.2 (C-3′, 5′), 143.1 (C-4′), 126.9 (C-1'), 107.8 (C-2', 6'), 75.7 (C-2), 66.4 (C-3), 57.0 (3′, 5′-OCH₃). The data are consistent with those reported in reference [18].

C-Veratroylglycol (8)

Colorless crystal; HR-ESI-MS (m/z): 235.0570 [M+Na]⁺. ¹H-NMR (CD₃OD, 600 MHz) δ: 7.58 (1H, s, H-2), 7.57 (1H, d, J = 8.4 Hz, H-6), 6.89 (1H, d, J = 8.4 Hz, H-5), 5.11 (1H, t, J = 7.2 Hz, H-8), 3.92 (3H, s, 3-OCH₃), 3.88 (1H, m, H-9α), 3.74 (1H, m, H-9β); ¹³C-NMR (CD₃OD, 150 MHz) δ: 199.7 (C-7), 153.9 (C-4), 149.4 (C-3), 128.2 (C-1), 125.2 (C-6), 116.0 (C-5), 112.5 (C-2), 75.6 (C-8), 66.4 (C-9), 56.5 (3-OCH₃). The data are consistent with those reported in reference [19].

7S, 7′S, 8R, 8′R-icariol A₂ (9)

White powder; [α]₂₀° = -48.18 (c = 0.014 MeOH); HR-ESI-MS (m/z): 435.1673 [M-H]⁻. ¹H-NMR (CD₃OD, 600 MHz) δ: 6.74 (4H, s, H-2, 2′, 6, 6′), 4.97 (2H, d, J = 9.6 Hz, H-7, 7′), 3.87 (12H, s, 3, 3′, 5, 5′-OCH₃), 3.68 (4H, m, H-9, 9′), 2.32 (2H, m, H-8, 8′); ¹³C-NMR (CD₃OD, 150 MHz) δ: 149.5 (C-3, 3′, 5, 5′), 136.4 (C-4, 4′), 134.4 (C-1, 1′), 105.0 (C-2, 2′, 6, 6′), 84.7 (C-7, 7′), 61.8 (C-9, 9′), 57.0 (3, 3′, 5, 5′-OCH₃), 55.3 (C-8, 8′). The data are consistent with those reported in reference [20].

Erigeside 2 (10)

White powder; HR-ESI-MS (m/z): 379.1362 [M+Na]⁺. ¹H-NMR (CD₃OD, 600 MHz) δ: 6.53 (2H, s, H-2, 6), 5.95 (1H, m, H-8), 5.09 (2H, m, H-9), 4.81 (1H, d, J = 6.0 Hz, H-1′), 3.83 (6H, s, 3, 5-OCH₃), 3.47 (2H, d, J =
7.2 Hz, H-7); $^{13}$C-NMR (CD$_3$OD, 150 MHz) $\delta$: 154.3 (C-3, 5), 138.8 (C-1), 138.5 (C-8), 116.3 (C-9), 107.6 (C-2, 6), 105.7 (C-1′), 78.5 (C-3′), 78.0 (C-5′), 75.9 (C-2′), 71.5 (C-4′), 62.7 (C-6′), 57.1 (3, 5-OCH$_3$), 41.5 (C-7). The data are consistent with those reported in reference [21].

**Methylsyringin (11)**

White powder; HR-ESI-MS (m/z): 409.1468 [M+Na]$^+$. $^1$H-NMR (DMSO-$d_6$, 600 MHz) $\delta$: 6.77 (2H, s, H-3, 5), 6.51 (1H, d, $J$ = 16.2 Hz, H-7), 6.31 (1H, dt, $J$ = 6.0, 16.2 Hz, H-8), 4.92 (1H, d, $J$ = 6.6 Hz, H-1′), 4.02 (2H, dd, $J$ = 6.0 Hz, H-6′), 3.77 (6H, s, 2, 6-OCH$_3$), 3.58 (1H, m, H-6′a), 3.40 (1H, m, H-6′b), 3.27 (3H, s, 9-OCH$_3$), 3.19 (2H, m, H-2′, 5′), 3.13 (1H, m, H-4′), 3.03 (1H, m, H-3′); $^{13}$C-NMR (DMSO-$d_6$, 150 MHz) $\delta$: 152.7 (C-2, 6), 134.1 (C-1), 132.0 (C-4), 131.3 (C-7), 125.8 (C-8), 104.7 (C-3, 5), 102.5 (C-1′), 77.2 (C-3′), 76.5 (C-5′), 74.1 (C-2′), 72.2 (C-9), 69.9 (C-4′), 60.9 (C-6′), 57.3 (9-OCH$_3$), 56.3 (2, 6-OCH$_3$). The data are consistent with those reported in reference [22].

**Antioxidant property**

Since phenylpropanoids belong to phenolic constituents, and most of the isolated compounds have phenolic hydroxyl groups structurally, we first evaluated their in vitro antioxidant activities. The results were shown in Table 1, compounds 1 and 9 had potent in vitro antioxidant activities in the DPPH and ABTS assays, and their IC$_{50}$ values ranged from 12.35 ± 1.45 to 29.14 ± 0.63 μM, which were lower than those of the positive control vitamin C (the IC$_{50}$ values were 25.30 ± 2.05 and 40.13 ± 2.27 μM, respectively). Furthermore, compounds 2, 3 and 4 had moderate or slight in vitro antioxidant activities in both assays, and their IC$_{50}$ values ranged from 43.15 ± 0.90 to 118.47 ± 1.43 μM. Lastly, compounds 5–8, 10 and 11 with the IC$_{50}$ values exceeding 200 μM did not possess in vitro antioxidant effects.

**α-Glucosidase inhibitory activity**

Diabetes mellitus is a common disease world-wide. It has been the third dangerous sicknesses inferior to cardiopathy and cancer. Treatment of diabetes mellitus by oral α-glucosidase inhibitors is currently confined to acarbose, miglitol and voglibose marred by efficacy problems and unwanted side effects. Since the discovery of the above drugs more than three decades ago, no significant progress has been made in the drug development area of anti-diabetic α-glucosidase inhibitors [23]. Therefore, it is utmost important to find new drugs. Recently, phenylpropanoids were reported to have potent α-glucosidase inhibitory activities [24, 25]. Therefore, the α-glucosidase inhibitory activities of all the isolated compounds were then tested. The results were shown in Table 2. The IC$_{50}$ values of compounds 3, 9 and 10 ranged from 43.76 ± 2.03 to 145.88 ± 3.54 μM, which were much lower than that of the positive control acarbose (IC$_{50}$ value = 273.12 ± 11.84 μM). Among the three compounds, compound 9 showed the strongest α-glucosidase inhibitory activity with an IC$_{50}$ value of 43.76 ± 2.03 μM. On the other hand, compounds 1, 2, 4–8 and 11 did not show α-glucosidase inhibitory activities, for their IC$_{50}$ values were higher than 300 μM.
Conclusion

Our phytochemical investigations have led to the isolation of eleven phenylpropanoids from the large polar fraction of *L. nervosa*. Among the isolated phenylpropanoids, three are lignans. Compounds 2–9, and 11 were isolated from the genus *Liparis* for the first time, and compounds 1 and 10 were obtained from *L. nervosa* for the first time. The results in the present study enrich the research of phytochemistry on *L. nervosa* and indicate that phenylpropanoids may be the additional representative type of active constituents in *L. nervosa*. What’s more, our results of bioactivity screening show that *L. nervosa* may be a promising source of α-glucosidase inhibitors. More importantly, compound 9 has the strongest α-glucosidase inhibitory activity with a much lower IC$_{50}$ value than that of acarbose, indicating its potential for the development of new hypoglycemic drugs. The present study provides a new line evidence for the further study of *L. nervosa*.

Material And Methods

General experimental procedures

NMR data were obtained using a Bruker 600 NMR Avance spectrometer (Germany). Semipreparative HPLC separation was performed using an Agilent 1260 Infinity II instrument (Santa Clara, CA, USA) equipped with a ODS column (250 mm × 10 mm, 5 µm, Cosmosil, Japan) and a diode array detector (DAD). Column chromatography-based separations were conducted using Sephadex LH-20 (GE Healthcare, Sweden), silica gel (Qingdao Marine Chemistry Ltd., Qingdao, China), and ODS C$_{18}$ (Merck, Germany). HR-ESI–MS spectra were recorded using a Bruker MAXIS mass spectrometer (Germany). The absorbance of the samples in bioactivity assays was determined using a BioTek multimode plate reader (Winooski, VT, USA).

Plant material and chemicals

The whole grasses with roots of *L. nervosa* were collected in Chongqing city of China in Feb. 2014, and Prof. Hu-Yin Huai, from School of Biological Science and Technology of Yangzhou University, identified the plant. DPPH, ABTS, vitamin C, α-glycosidase, and acarbose were all purchased from Sigma-Aldrich Chemical Company (St. Louis, MO, USA).

Extraction

The plant materials were extracted with 95% ethanol and partitioned using the method described in our previous study [5] to get petroleum ether, ethyl acetate, and *n*-butanol fractions. The *n*-butanol fraction was applied to repeated column chromatography over silica gel, Sephadex LH-20 and RP-18, and then purified using semipreparative HPLC to yield compounds 1 (10.3 mg), 2 (5.0 mg), 3 (8.9 mg), 4 (3.1 mg), 5 (5.4 mg), 6 (2.2 mg), 7 (3.8 mg), 8 (6.2 mg), 9 (7.5 mg), 10 (5.3 mg), and 11 (5.9 mg).

DPPH/ABTS radical scavenging capacity
DPPH and ABTS assays were performed to evaluate the in vitro antioxidant capacities of all the isolates. The experiments were performed as described previously [26]. Vitamin C served as the positive control. The absorbance of each sample was read at 517/734 nm.

α-Glucosidase inhibitory activity

All the isolates were evaluated for their α-glucosidase inhibitory activities using the method described in the literature [27]. Acarbose served as the positive control. The absorbance of each sample was read at 405 nm.

Statistical analysis

All results are presented as means ± SD for three independent experiments. IC$_{50}$ values were calculated by SPSS statistical software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Declarations

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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### Tables

**Table 1** Radical scavenging activities of the isolated compounds against DPPH and ABTS (IC<sub>50</sub> μM)

| No. | Compounds                           | DPPH assay  | ABTS assay  |
|-----|-------------------------------------|-------------|-------------|
|     | Vitamin C                           | 25.30 ± 2.05| 40.13 ± 2.27|
| 1   | (+)-Syringaresinol                   | 16.71 ± 0.55| 25.83 ± 1.12|
| 2   | (-)-Syringaresinol-4-O-β-D-glucopyranosid | 57.64 ± 1.82| 78.66 ± 1.91|
| 3   | Sinapaldehyde                       | 83.02 ± 1.90| 43.15 ± 0.90|
| 4   | Coniferyl aldehyde                  | 118.47 ± 1.43| 86.95 ± 2.29|
| 9   | 7S, 7’S, 8R, 8’R-icariol A<sub>2</sub> | 12.35 ± 1.45| 29.14 ± 0.63|

Compounds with the IC<sub>50</sub> values exceeding 200 μM were not listed in the table.
Table 2 α-glucosidase inhibitory activities of isolated compounds (µM)

| No. | Compounds                               | IC<sub>50</sub> value   |
|-----|-----------------------------------------|-------------------------|
|  -  | Acarbose                                | 273.12 ± 11.84          |
|  3  | Sinapaldehyde                           | 98.81 ± 0.99            |
|  9  | 7S, 7′S, 8R, 8′R-icariol A₂              | 43.76 ± 2.03            |
|  10 | Erigeside 2                             | 145.88 ± 3.54           |

Compounds with the IC<sub>50</sub> values exceeding 300 µM were not listed in the table.

Figures

Figure 1

Chemical structures of compounds 1–11 isolated from L. nervosa.

Supplementary Files
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