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Sesquiterpenes and lignans from the flower buds of *Daphne genkwa* and their nitric oxide inhibitory activities

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ABSTRACT

Chemical investigation of the *Daphne genkwa* has led to the isolation of four sesquiterpenes (**1a/1b**, **2**, and **3**), including one pair of sesquiterpene enantiomers (**1a/1b**), **1a** is a new compound (+)-4-hydroxy-10-epirotundone, and twelve lignans (**4–15**). Their structures were elucidated by spectroscopic analysis, and the absolute configurations of **1a/1b** were determined by CD analysis. All compounds were examined for their inhibitory effects on the nitric oxide (NO) production induced by lipopolysaccharide (LPS) in BV-2 microglial cells, and compounds **7–10** exhibited pronounced inhibition on NO production with IC₅₀ values in the range of 5.8–10.2 μM, being more active than the positive control, quercetin (IC₅₀ = 17.0 μM).

Keywords: *Daphne genkwa*; Sesquiterpene; Lignan; Nitric Oxide

1. Introduction

Daphne genkwa (Thymelaeaceae) is widely distributed in Korea and mainland China and is a well-known traditional oriental medicine. The flower buds of this plant (“Yuanhua”) are mainly used for diuretic, antitussive, expectorant, and antitumor purposes. (Han et al. 2016). Previous phytochemical studies have indicated that Yuanhua contains different types of chemical components, including flavonoids (Liang et al. 2012, Xie et al. 2011), coumarins (Park et al. 2006), lignans (Okunishi et al. 2001), diterpenoids (Li et al. 2015, Zhan et al. 2005, Zhang et al. 2006). Previous phytochemical studies mainly focus on the nonpolar part of *D.genkwa* extracts, especially the daphnane-type diterpenes. However, the polar part of *D.genkwa* extracts were few studies. In our screening program aimed at the discovery of novel NO inhibitors from natural resource (Zhu et al. 2015), the EtOAc fraction of the ethanolic extract of *D. genkwa* showed a certain inhibitory activity against the lipopolysaccharide (LPS)-induced NO production in BV-2 microglial cells. Subsequent chemical investigation led to the isolation of four sesquiterpenes and twelve lignans, including one new compound (Figure 1). Bioassay verified that 16 compounds were responsible for the NO inhibitory activities of the EtOAc fraction, with IC₅₀ values ranging from 5.8 to 36.0 μ M. Herein, details of the isolation, structural elucidation, and NO inhibitory activities of these compounds were described.

2. Results and discussion

Compound **1** (**1a/1b**), a yellow powder, had the molecular formula C₁₅H₂₂O₂, as determined by HRESIMS at m/z 257.1492 [M + Na]⁺ (calcd 257.1512), corresponding to five degrees of unsaturation. The IR spectrum exhibited absorption bands for an α,β -unsaturated carbonyl moiety (1691 and 1638 cm⁻¹). The ¹H NMR spectrum (Table S1) of **1** showed two methyl singlets [δ_{H} 1.76 (3H, s, CH₃-13) and 1.46 (3H, s, CH₃-15)], a doublet signal 1.12 (3H, d, J = 7.2, CH₃-14), an exocyclic methylene group [(δ_{H} 4.78 (1H, d, J = 1.4, CH₂-12) and 4.75 (1H, dd, J = 1.4, 1.4, CH₂-12)], and

a series of aliphatic methylene multiplets. The ^{13}C NMR spectrum (Table S1) in combination with DEPT experiments resolved 15 carbon resonances attributable to a ketone group (δ_{C} 204.6), two double bonds (δ_{C} 173.6, 149.2, 144.9, and 110.0), one oxygenated sp^3 quaternary carbons, two sp^3 methines, four sp^3 methylenes, and three methyls. As three of the five degrees of unsaturation were accounted for by one ketone and two double bonds, the remaining degrees of unsaturation required that **1** was dicyclic system. The NMR data of **1** were identical to those of 4-hydroxy-10-epirotundone, which was isolated from *Joannesia princeps* (Achenbach and Benirschke 1997). The planar structure of **1** was further secured by detailed analyses of its 2D NMR data (Figure S1). The relative configuration of **1** was established by NOESY experiment and by comparison of its 1D NMR data with those of 4-hydroxy-10-epirotundone. The NOE interactions (Figure S2) of H-10/H-14, H-9 β , and H-8 β , H₃-15/H-6 β and H-3 β suggested that H-10 and H₃-15 were cofacial and were assigned to be β -oriented randomly. The NOE interaction H-7/H₃-14 assigned H-7 as α .

Compound **1** was primarily obtained with the specific rotation being almost zero and no cotton effect in its electronic circular dichroism (ECD), indicating a near racemic nature. Subsequent chiral resolution of **1** afforded the anticipated enantiomers **1a** and **1b**, which showed mirror image-like ECD curves (Figure S3) and opposite specific rotation ($[\alpha]_{\text{D}}^{20}$ +57 in **1a**, $[\alpha]_{\text{D}}^{20}$ -69 in **1b**). The absolute configurations (ACs) of **1a** and **1b** were determined by CD analysis (Snatzke 1965). The CD curve of **1a** showed a positive Cotton effect at 317 nm ($\Delta\epsilon$ +4.54) that was attributed to the $n \rightarrow \pi^*$ transition of an α,β -unsaturated ketone and a negative Cotton effect (255 nm, $\Delta\epsilon$ -3.85) that was attributed to the $\pi \rightarrow \pi^*$ transition of an α,β -unsaturated ketone. Thus, the absolute configuration of **1a** was determined to be 4*S*, 7*S*, 10*S* and **1a** was given a trivial name (+)-4-hydroxy-10-epirotundone. Consequently, the 4*R*, 7*R*, 10*R* configurations were defined in **1b**.

By comparison of their observed and reported NMR data, the known compounds **2–15** were identified as oleodaphnal (**2**) (Taninaka et al. 1999), (4*S*,5*R*,7*S*)-4,11-dihydroxy-guaia-1(2), 9(10)-dien (**3**) (Li et al. 2016),

threoguaiacylglycerol- β -O-4-coniferyl (**4**) (Cutillo et al. 2003), longifloroside B (**5**) (Wang et al. 2009), *threo*-3,3'-dimethoxy-4,8'-oxyneoligna-9,4',7',9'-tetraol-7(8)-ene (**6**) (Wang et al. 2009), (–)-nortrachelogenin (**7**) (Zhang et al. 2013), (–)-Matairesin (**8**) (Youssef and Frahm 1995), (+)-isolariciresinol (**9**) (Jutiviboonsuk et al. 2006), (–)-secoisolariciresinol(**10**) (Hong et al. 2006), lariciresinol (**11**) (Subbaraju et al. 1991), (–)-justiciresinol (**12**), syringaresinol (**13**) (Niu et al. 2001), medioresinol (**14**) (Li et al. 2008), and pinoresinol (**15**) (Páska et al. 2002). All compounds were evaluated for their inhibitory effects on the NO production in LPS-induced BV-2 microglial cells using the Griess assay. Compounds **1a**, **1b**, **2**, and **3** were inactive (< 50% inhibition at 50 μ M), while compounds **4–6** and **11–15** showed moderate inhibitory activities with IC₅₀ values ranging from 16.8 to 36.0 μ M. Compounds **7–10** showed remarkable inhibitory activities with IC₅₀ values of 5.8 to 10.2 μ M, respectively, more active than the positive control quercetin (IC₅₀ = 17.0 μ M), a well-known NO inhibitor (Table 1).

3. Experimental

3.1. General methods

Optical rotations were measured on a Rudolph Autopol I automatic polarimeter. IR spectra were determined on a Bruker Tensor 37 infrared spectrophotometer. NMR spectra were measured on a Bruker AM-400/600 spectrometer at 25°C. HRESIMS was performed on a Waters Micromass Q-TOF spectrometer. A Shimadzu LC-20 AT equipped with an SPD-M20A PDA detector was used for HPLC. Both a YMC-pack ODS-A column (250 \times 10 mm, S-5 μ m, 12 nm) and a chiral column (Phenomenex Lux, cellulose-2, 250 \times 10 mm, 5 μ m) were used for semipreparative HPLC separation. Silica gel (300–400 mesh, Qingdao Haiyang Chemical Co., Ltd.), C₁₈ reversed-phase silica gel (12 nm, S-50 μ m, YMC Co., Ltd.), and Sephadex LH-20 gel (Amersham Biosciences) were used for column chromatography (CC). All solvents were of analytical grade (Shanghai Chemical Reagents Company, Ltd.).

3.2. Materials

The flower buds of *D. genkwa* were collected from Huangshan city, Anhui Province, P. R. China, in August 2013. The plant material was identified by Professor Lu-Ping Qin and A voucher specimen (Accession number SDGZ-201308) has been deposited at Central Laboratory, Shanghai Seventh People's Hospital, Shanghai University of TCM.

3.3. Extraction and isolation

The air-dried powder of the flower buds of *D. genkwa* (15 kg) was extracted with 95% EtOH (3 × 10 L) at rt to give 1.5 kg of crude extract. The extract was suspended in H₂O (3 L) and successively partitioned with petroleum ether (PE, 3 × 3 L), EtOAc (3 × 3 L), and *n*-BuOH (3 × 3 L) to yield three corresponding portions. The EtOAc extract (256 g) was subjected to MCI gel CC eluted with a MeOH/H₂O gradient (1:9 → 10:0) to afford Fr. I–Fr. VI. Fr. I (50.0 g) was subjected to silica gel chromatography using hexane/EtOAc mixtures (v/v 1:0 → 0:1) to afford four fractions Ia–Id. Fr. Ib (3.4 g) was subjected to silica gel chromatography using PE–Acetone mixtures (v/v 1:0, 15:1, 10:1, 1:1) to yield three fractions, Fr. Ib (1–3). Fr. Ib2 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 7:3, 3 mL/min) to give **11** (10 mg, *t_R* 12 min) and **12** (6.9 mg, *t_R* 13 min). Fr. Id (2.8 g) was loaded onto a Sephadex LH-20 column and eluted with CH₂Cl₂-MeOH (1:1) to yield four fractions, Fr. Id (1–4). Fr. Id2 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 7:3, 3 mL/min) to give **15** (3.7 mg, *t_R* 10 min), **14** (5.4 mg, *t_R* 11 min), and **13** (10.4 mg, *t_R* 12 min). Fr. II (17.8 g) was loaded onto a Sephadex LH-20 column and eluted with CH₂Cl₂-MeOH (1:1) to four fractions IIa–IIc. Fr. IIb (2.7 g) was subjected to silica gel chromatography using PE–Acetone mixtures (v/v 1:0, 15:1, 10:1, 1:1) to yield five fractions, Fr. IIb (1–5). Fr. IIb2 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 7:3, 3 mL/min) to give **9** (5.6 mg, *t_R* 14 min) and **10** (6.3 mg, *t_R* 15 min). Fr. IIb3 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 7:3, 3 mL/min) to give **7** (7 mg, *t_R* 11

min) and **8** (8 mg, t_R 12 min). Fr. IId (3.0g) was subjected to silica gel chromatography using PE–Acetone mixtures (v/v 1:0, 15:1, 10:1, 1:1) to yield three fractions, Fr. IId (1–3). Fr. IId1 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 7:3, 3 mL/min) to give **4** (3.6 mg, t_R 13 min), **5** (5.6 mg, t_R 14 min), and **6** (6.3 mg, t_R 15 min). Fr. III (8.8 g) was loaded onto a Sephadex LH-20 column and eluted with CH₂Cl₂-MeOH (1:1) to afford three fractions Fr. IIIa–IIIc. Fr. IIIc (2.4 g) was subjected to silica gel chromatography using PE–Acetone mixtures (v/v 1:0, 15:1, 10:1, 1:1) to yield four fractions, Fr. IIIc (1–4). Fr. IIIc2 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 8:2, 3 mL/min) to give **1** (10.6 mg, t_R 14 min), followed by semipreparative chiral HPLC with Phenomenex Lux, cellulose-2 column (CH₃OH/H₂O, 9:1, 3 mL/min) to give **1a** (4.1 mg, t_R 10 min) and **1b** (3.5 mg, t_R 11 min). Fr. IIIc3 was purified using semipreparative HPLC with a YMC-pack ODS-A column (MeOH/H₂O, 8:2, 3 mL/min) to give **2** (4.3 mg, t_R 14 min) and **3** (5.7 mg, t_R 15 min).

(+)-4-hydroxy-10-epirotundone (**1a**), a colorless powder; $[\alpha]_D^{20}$ +57 (c 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 236 (4.10) nm; CD (c 1.0×10^{-4} M, MeOH) λ_{max} ($\Delta\epsilon$) 255 ($\Delta\epsilon$ –3.85), 317 ($\Delta\epsilon$ +4.54) nm; IR (KBr) ν_{max} 2975, 1692, 1638, 1378, 1215, 1047, 880, 749 cm⁻¹; ¹H and ¹³C NMR data, see Table S1; HRESIMS m/z 257.1492 [M + Na]⁺ (calcd for C₁₅H₂₂O₂Na, 257.1512).

3.4. Cell culture and viability assay

BV-2 microglial cells were obtained from Second Military Medical University (SMMU) Cell Bank (Shanghai, People's Republic of China). Cells were plated into a 96-well plate (2×10^4 cells/well). After 24 h, they were pretreated with samples for 30 min and stimulated with 1 μ g/mL LPS for another 24 h. The cell viability of the cultured cells was assessed by MTT assay. Briefly, BV-2 cells were incubated with 200 μ L MTT solution (0.5 mg/mL in medium) for 4 h at 37 °C, and then the supernatants were removed and residues were dissolved in 200 μ L DMSO. The absorbance was detected at 570 nm using a microplate reader (Molecular Devices,

USA) and analyzed using a Soft Max Pro 5 software (Molecular Devices, USA).

3.5. Measurement of NO production

The NO concentration was measured by the Griess reaction. Briefly, BV-2 cells were treated with LPS (1.0 $\mu\text{g}/\text{mL}$) and compounds for 24 h. After that, 100 μL of culture supernatant was allowed to react with 100 μL of Griess reagent (1% sulfanilamide, 0.1% N-1-naphthylethylenediamine dihydrochloride in 5% phosphoric acid) for 10 min at rt in the dark. Then, the optical density (100 μL per well) was measured at 540 nm using a microplate reader (Molecular Devices, USA). Sodium nitrite was used as a standard to calculate the nitrite concentration. Inhibition (%) = $(1 - (A_{\text{LPS} + \text{sample}} - A_{\text{untreated}})/(A_{\text{LPS}} - A_{\text{untreated}})) \times 100$. The experiments were performed in triplicates, and the data were expressed as the mean \pm standard deviation (SD) values. Quercetin was used as a positive control.

4. Conclusions

In summary, chemical investigation led to the isolation of four sesquiterpenes and twelve lignans, including one new compound. Bioassay verified that 16 compounds were responsible for the NO inhibitory activities of the EtOAc fraction, with IC_{50} values ranging from 5.8 to 36.0 μM , and compounds **7–10** exhibited pronounced inhibition on NO production with IC_{50} values in the range of 5.8–10.2 μM , being more active than the positive control, quercetin ($\text{IC}_{50} = 17.0 \mu\text{M}$). *D. genkwa* is known as a rich source of daphnane diterpenoids (Jiang, et al. 2015). The current study not only enriched the chemo diversity of this spices by the isolation of a series of bioactive lignans, but also dig out the potential usage of this plant as anti-neuroinflammatory therapy. However, the mechanism of inhibition against NO production of these compounds requires further investigation.

Supplementary material

Supplementary data: Table S1 (1D data of **1**), figures for 2D NMR correlations of **1**, CD, IR, HRESIMS, 1D and 2D NMR spectra of **1**, ^1H and ^{13}C NMR spectra of known compounds **2–15**.

Disclosure statement

No potential conflict interest was reported by the authors.

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