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Chemical constituents from *Lindera nacusua* (D. Don) Merr

Guo-Qing Wei [a, c], Jia-Sui Zhang [a], Jie-Ping Lei [a], Chao-Ying Ma [a, b], Yan Tong [a], He-Zhong Jiang [a, *]

[a] School of Life Science and Engineering, Southwest Jiaotong University, Chengdu 610031, PR China
[b] School of Medicine, Southwest Jiaotong University, Chengdu 610031, PR China
[c] School of Materials Science and Engineering, Southwest Jiaotong University, Chengdu 610031, PR China

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ABSTRACT

This first phytochemical investigation on the roots of *Lindera nacusua* (D. Don) Merr led to the isolation of nine compounds, including demethylmacrosporine I (**1**), emodin-6-*O*-*β*-D-gluco- pyranoside (**2**), (−)-litsenolide D1 (**3**), (−)-(2Z,3R,4S)-2-(dodec-11-ynylidene)-3-hydroxy-4-methyilbu- tanolide (**4**), 1-*O*-3,4-dimethoxy-5-hydroxyphenyl-(6-*O*-3,5-dimethoxygalloyl)-*β*-D-glucopyranoside (**5**), 1-*O*-3,4-dimethoxy-5-hydroxyphenyl-(6-*O*-va-nilloyl)-*β*-D-glucopyranoside (**6**), (E)-feruloyltyra- mine (**7**), Z-N-feruloyltyramine (**8**), and 1-*O*-*β*-D-glucopyranosyl-(2S,3R,4E,8Z)-2-[2′(R)-hydroxyhex- adecanoyl-amino]-4,8-octadecadiene-1,3-diol (**9**). The types of the compounds involved anthraquinones (**1**, **2**), γ-butanolides (**3**, **4**), phenolic glycosides (**5**, **6**), phenolic acid amides (**7**, **8**) and cerebroside (**9**). Among them, Compounds **1**–**6** and **9** were firstly isolated from the genus Lindera as well as the Lauraceae family, and the anthraquinones and cerebrosides were first found in the Lauraceae family. The chemotaxonomic significance of these compounds was also summarized.

1. Subject and source

The genus *Lindera* (Lauraceae) is comprised of approximately 100 species (Deng et al., 2011) that are distributed in the temperate and the tropical regions of Asia and North America. *Lindera nacusua* (D. Don) Merr. is widely distributed in the Guangdong, Guangxi, Fujian, Jiangxi, Sichuan, Yunnan and Tibet provinces of China, and also in Nepal, India, Myanmar and Vietnam (Li, 1982). The roots of *L. nacusua* were collected from Mount Emei, Sichuan Province, PR China, and identified by Associate Professor Liang-Ke Song (School of Life Science and Engineering, Southwest Jiaotong University). Voucher specimen (JRY0001) was deposited at the School of Life Science and Engineering, Southwest Jiaotong University (Chengdu, China).

2. Previous work

Previous phytochemical studies on the genus *Lindera* have resulted in the isolation and identification of alkaloids (Zhao et al., 2006), flavonoids (Xiao et al., 2011) and sesquiterpene (Deng et al., 2011). In recent years, many biological activities of some plants of this genus have been reported (Shimomura et al., 2010; Suh et al., 2011). However, there were no reports

* Corresponding author.
E-mail address: jianghz10@sina.com (H.-Z. Jiang).

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regarding with the chemical constituents from the phytochemistry of *L. nacusua* in previous literature. Thus, we herein present the first report on the phytochemical investigation of the roots of *L. nacusua*.

3. Present study

The dried and powdered tubers of *L. nacusua* (11.0 Kg) were extracted with 95% EtOH under percolation. The dried EtOH extract (500 g) was suspended in water followed by successive partition with petroleum ether, EtOAc, and *n*-BuOH, respectively. The EtOAc extract (206 g) was chromatographed on silica gel column (200–300 mesh) using a gradient solvent $CHCl_3$/MeOH (100:1–0:1, V: V) to afford ten fractions (1–10). Fraction 4 (33 g) was subjected to silica gel column using a gradient solvent $CHCl_3$/MeOH (100:0–10:1, V: V) to afford eight subfractions (4–1 – 4–8). The fraction 4–5 (6.3 g) was further separated on silica gel column using a gradient solvent petroleum ether/EtOAc (30:1, 20:1, 15:1, 10:1, 5:1, V: V) to yield compound **3** (81 mg) and six subfractions (4–5–1 – 4–5–6). Then compound **4** (84 mg) was purified from the fraction 4–5–5 (270 mg), by preparative HPLC (Venusil XDP-C_{18} column, 21.2 × 250 mm, 5 μm, flow rate 10.0 mL/min, UV 254 nm) with a solvent system of CH_3CN/H_2O (80:20, V: V). Fraction 4–6 (1.3 g) gel was filtrated on Sephadex LH-20 ($CHCl_3$/MeOH 1:1) to afford **1** (37 mg). Fraction 7 (49 g) was subjected to silica gel column using a gradient solvent $CHCl_3$/EtOAC (100:1–1:1, V: V) to give six subfractions (7–1 – 7–6). Fraction 7–4 (2.5 g) was further separated on Sephadex LH-20 (MeOH 100%) and by semipreparative HPLC (YMC-PACK ODS-A, 10 × 250 mm, 5 μm, flow rate 2.0 mL/min, UV 254 nm) with a solvent system of CH_3CN/H_2O (24:76) to afford **7** (54 mg) and **8** (17 mg). Fraction 8 (16 g) was chromatographed on silica gel column using a gradient solvent $CHCl_3$/acetone (50:1–1:1, V: V) to give five fractions (8–1 – 8–5). Fraction 8–4 (5.4 g) was further separated on silica gel column using a gradient solvent $CHCl_3$/MeOH (30:1, 20:1, 15:1, 10:1, 5:1, V: V) to afford five five fractions (8–4–1 – 8–4–5). Further purification of fraction 8–4–4 (678.0 mg) was submitted to Sephadex LH-20 (MeOH 100%) and semi-preparative HPLC (YMC-PACK ODS-A, 10 × 250 mm, 5 μm, flow rate 2.0 mL/min, UV 254 nm) with a solvent system of CH_3CN/H_2O (28.5:71.5) to yield **5** (10 mg) and **6** (12 mg). Compound **2** (18 mg) was purified from fraction 8–5 (1.2 g) by Sephadex LH-20 with MeOH. Fraction 9 (14 g) was chromatographed on silica gel column using a gradient solvent $CHCl_3$/MeOH (40:1, V: V) to give six fractions (9–1 – 8–6). Fraction 9–5 (1.1 g) was further separated by Sephadex LH-20 with MeOH (100%), silica gel column using a gradient solvent petroleum $CHCl_3$/MeOH (15:1, V: V), and semipreparative HPLC (YMC-PACK ODS-A, 10 × 250 mm, 5 μm, flow rate 2.0 mL/min, UV 210 nm) with a solvent system of MeOH/H2O (97.7:2.3), to yield **9** (5 mg).

The structures of compounds **1**–**9** (Fig. 1) were identified as demethylmacrosporine I (**1**) (Sandra et al., 2009), emodin-6-*O*-*β*-D-glucopyranoside (**2**) (Zhang et al., 2004), (−)-litsenolide D1 (**3**) (Tanaka et al., 1990), (−)-(2Z,3R,4S)-2-(dodec-11-ynylidene)-3-hydroxy-4-methylbutanolide (**4**) (Cheng et al., 2009), 1-*O*-3,4-Dimethoxy-5-hydroxyphenyl-(6-*O*-3,5-dimethoxygalloyl)-*β*-D-glucopyranoside (**5**) and 1-*O*-3,4-Dimethoxy-5-hydroxyphenyl-(6-*O*-vanilloyl)-*β*-D-glucopyranoside (**6**) (Fu et al., 2011), (*E*)-feruloyltyramine (**7**), *Z*-N-feruloyltyramine (**8**) (Ma et al., 2004) and 1-*O*-*β*-D-glucopyranosyl-(2S,3R,4E,8Z)-2-[2'(R)-hydroxyhexadecanoyl-amino]-4,8-octadecadiene-1,3-diol (**9**) (Jung et al., 1996), respectively, by analysis of MS and NMR data and comparison with the published data.

4. Chemotaxonomic significance

The genus *Lindera* comprising of about 100 worldwide-distributed species (Deng et al., 2011) is one of the most representatives of the Lauraceae family. This is the first report on the phytochemical investigation of *L. nacusua*. Compounds **1**–**6** and **9** were isolated for the first time from the genus *Lindera* and the family Lauraceae.

According to previous research, butanolides are widely distributed in the genus of *Lindera*, including *Lindera benzoin* (L.) Blume (Anderson et al., 1992), *Lindera glauca* (Sieb. et Zucc.) Bl (Seki et al., 1995), *Lindera communis* Hemsl (Tsai et al., 2001), and *Lindera akoensis* Hay (Yang et al., 2013), all of which belong to the Lauraceae family, Butanolides also widely occur in the family of Lauraceae, such as in the genera *Litsea* (Cheng et al., 2010), *Machilus* (Kim et al., 2013), and *Cinnamomum* (Liu et al., 2014). Butanolides **3** and **4** are reported here for the first time from the genus *Lindera* and the family Lauraceae. The occurrence of compounds **3** and **4** can be used to confirm the close chemotaxonomic relations between the related species of *Lindera* and the related genus of Lauraceae. In addition, butanolides (butyrolactones) can serve as a chemotaxonomic marker for *L. nacusua*.

The phenolic acid amides have also been found in the genera *Actinodaphne* (Tanaka et al., 1989), *Litsea* (Tanaka et al., 2009), *Cryptocarya* (Kurniadewi et al., 2010), *Lindera* (Wang et al., 2011), *Cinnamomum* (Hong et al., 2011), *Neolitsea* (Kim et al., 2013), and *Beilschmiedia* (Chen et al., 2015) of the Lauraceae family. This suggested that phenolic acid amides could serve as potential chemotaxonomic markers for the genus *Lindera* and for the family Lauraceae. Moreover, the two amides **7** and **8** were also previously isolated from *Lindera glauca*, which suggests the close chemotaxonomic relations between *L. glauca* and *L. nacusua*. Phenolic acid amides can be also used as chemotaxonomic markers for *L. nacusua*.

Compounds **5** and **6** are phenolic glycosides, and this type of compounds were previously reported only from *Dodecadenia grandiflora* Nees (Kumar et al., 2009) and *Machilus robusta* W. W. Smith (Bu et al., 2013), suggesting their narrow distribution among the genera of Lauraceae family. In addition, anthraquinones (e.g. **1** and **2**) and cerebroside (e.g. **9**) found in the Lauraceae family are reported here for the first time. These all together may provide additional chemotaxonomic markers for *L. nacusua*.

These results indicated that *L. nacusua* shared some relatively similar but largely different chemotaxonomic chemical composition compared to those of other species of *Lindera* as well as other genus of the Lauraceae family. The phytochemical