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ORIGINAL ARTICLE

Chemical Composition from the Leaves of *Lindera fragrans* Oliv.

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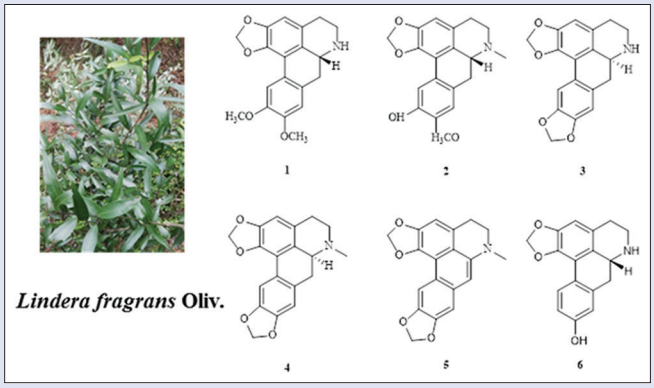
ABSTRACT

Background: One hundred known species belong to the genus *Lindera* (*Lauraceae*) and rich in chemical structure types. The branch leaves of *Lindera fragrans* Oliv. show the special curative effect of treating gastroenteritis and gastric ulcer. There are not comparatively detailed reports carried on studying the chemical composition and bioactivity of *L. fragrans*. **Objective:** This paper reports the chemical investigation and biological evaluation of the *L. fragrans*. **Materials and Methods:** The petroleum ether and ethyl acetate soluble part of *L. fragrans* was isolated using chromatographic methods, and the structures of these compounds were identified by comparison of their spectroscopic data with those reported in the literature. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide method was used to determine the antitumor activity of the isolated compounds. **Results:** Twelve compounds were isolated from the leaves of *L. fragrans* and classified as six alkaloids (1–6), three flavonoids (7–9), two aromatics (10 and 11), and one anthraquinone (12). The study of antitumor activity showed that compounds 3–5 had weak antitumor activities with the half maximal inhibitory values ranging from 71.97 to 94.69 μM. **Conclusion:** All of these compounds were isolated from this plant for the first time and compounds 3–6, 8, and 9 were first reported from the genus *Lindera*. Compounds 3–5 exhibited weak antitumor activities.

Key words: Alkaloids, antitumor, chemical composition, flavones, *Lindera fragrans* Oliv.

SUMMARY

- The chemical investigation of the leaves of *Lindera fragrans* Oliv. resulted in the isolation of 12 compounds
- The 12 compounds include six alkaloids (1–6), three flavonoids (7–9), two aromatics (10 and 11), and one anthraquinone (12)
- The isolated compounds 3–9 were evaluated for their antitumor activities
- The chemotaxonomic significance of all the isolations was summarized.



The chemical investigation of the leaves of *Lindera fragrans* resulted in the isolation of 12 compounds including six alkaloids (1–6), three flavonoids (7–9), two aromatics (10 and 11), one anthraquinone (12). The isolated compounds 3–9 were evaluated for their cytotoxicity against melanoma, glioma, and hepatoma cells by MTT method.

Abbreviations used: EtOAc: Ethyl acetate; *n*-BuOH: *N*-butyl alcohol; MCI: Middle chromatogram isolated; HPLC: High-performance liquid chromatography; MS: Mass spectrometer; NMR: Nuclear magnetic resonance; TLC: Thin-layer chromatography; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; IC_{50}: Half maximal inhibitory; B16: Melanoma cells; C6: Glioma cells; HepG2: Hepatoma cells.

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INTRODUCTION

The genus *Lindera* (*Lauraceae*) widely distributes in tropics and subtropics. The wide geographical distribution makes *Lindera* plants rich in chemical structure types. At present, more than 300 chemical constituents have been found in the genus *Lindera* including sesquiterpenes, alkaloids, flavonoids, lignans, and butyrolactones. Among them, eucalyptus, urea alkanes, furan cyclosporine, and isoquinoline alkaloids (apophine alkaloids) are the characteristic chemical constituents of the genus *Lindera*.[1] *Lindera fragrans* Oliv. is mainly distributed in Hunan, Hubei, and Sichuan in China and its

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branch leaves are the main medicinal parts in treating gastroenteritis and gastric ulcer.[2] At present, no comparatively detailed research had addressed the chemical composition and bioactivity of *L. fragrans*. Previous phytochemical studies on *Lindera nacusua* (D. Don) Merr. by our group reported the isolation and identification of anthraquinones, gamma-butanolides, phenolic glycosides, phenolic acid amides, and cerebroside.[3]

MATERIALS AND METHODS

Plant material

The leaves of *L. fragrans* were collected from Jiange County, Sichuan Province, China, and identified by Prof. Liang-Ke Song (Southwest Jiaotong University). Voucher specimen (XYZ001) was deposited at the Laboratory of Traditional Chinese Medicinal Chemistry, Southwest Jiaotong University, China.

Extraction and isolation

The air-dried leaves of *L. fragrans* (2.9 kg), after comminution, extracted with 95% ethanol 3 times. After removal of solvent under reduced pressure, the extract (270 g) was suspended in water followed by successive partition with petroleum ether, ethyl acetate (EtOAc), and *n*-butanol, respectively.

Then, the petroleum ether soluble part (104.1 g) was subjected on silica gel column with a gradient solvent petroleum ether/acetone (100:1–1:1, v:v) to give 13 fractions (P1–P13). Fraction P7 (769 mg) was chromatographed over a Sephadex LH-20 column ($CHCl_3$/MeOH, 1:1, v:v) to give compound 1 (2 mg). Fraction P9 (2949 mg) was separated on middle chromatogram isolated, which elution system was CH_3OH/acetone (1:0–0:1, v:v), to afford six fractions (P9-1–P9-6). Fraction P9-5 (113 mg) was further purified with a Sephadex LH-20 column ($CHCl_3$/MeOH, 1:1, v:v) to yield compound 2 (5.6 mg). Silica gel column chromatography was used to further purify the EtOAc extract (61.5 g), which elution solvent was CH_2Cl_2/CH_3OH (100:1–1:1, v:v) and 12 subfractions were obtained (E1–E12). Fraction E10 (10.2 g) was separated on RP-18 (MeOH/H_2O, 30%–100%, v:v) to give 10 subfractions (E10-1–E10-10). Fraction E10-9 (408 mg) was further purified on Sephadex LH-20 (MeOH) to give compound 12 (5 mg); compound 7 (32 mg) was obtained from fraction E10-5 (507 mg) in the same way. Fraction 10-4 was loaded on silica gel column using CH_2Cl_2-CH_3OH (30:1–1:1, v:v) as eluent and then produced six fractions (E10-4-1–E10-4-6). Compounds 11 (6 mg) and 10 (5 mg) were purified by semi-preparative high-performance liquid chromatography (HPLC) using 55% MeOH in H_2O from E10-4-6 (213 mg). Compound 9 (10 mg) was isolated by Sephadex LH-20 (MeOH) from fraction E10-4-4 (123 mg). Fraction E10-6 (925 mg) was submitted to Sephadex LH-20 (MeOH) and semi-preparative HPLC to yield compounds 8 (48 mg), 6 (3.1 mg), and 4 (9 mg). Fraction E10-8 was subjected to Sephadex LH-20 (MeOH) to afford fractions E10-8-1–E10-8-4. Fraction E10-8-3 (167 mg) was further separated by Sephadex LH-20 ($CHCl_3$/MeOH, 1:1, v:v) and semi-preparative HPLC to produce compounds 5 (3 mg) and 3 (4.6 mg).

Cytotoxicity bioassay

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide method, as previously described,[4] was used to determine the antitumor activity of the isolated compounds 3–9 against three cell lines: melanoma, glioma, and hepatoma cells (B16, C6, and HepG2 cells), respectively. These cells were provided by West China School of Pharmacy, Sichuan University; dimethyl methyl sulfate (DMSO) was purchased from Sigma-Aldrich, and Dulbecco's modified Eagle Medium was purchased from GIBCO BRL. Half maximal inhibitory (IC_{50}) values were calculated by Reed and Muench's method.

RESULTS

The present study reports 12 known compounds, including six alkaloids (1–6), three flavones (7–9), two aromatics (10 and 11), and one anthraquinone (12). All of them were first isolated from this plant and compounds 3–6, 8, and 9 were first reported from the genus *Lindera*.

Twelve compounds [Figure 1] were identified as nordicentrine (1),[5] phanostenine (2),[6] cryptodorine (3),[7] neolitsine (4),[8] dehydroneolitsine (5),[9] anolobin (6),[10] kaempferol-3-*O*-α-L-rhamnoside (7),[11] kaempferol-3,7-*O*-α-L-dir hamnoside (8),[12] kaempferol-3-*O*-β-D-xylopyranosyl-(1 → 2)-α-L -rhamnopyranoside (9),[13] *p*-methoxyphenylacetic acid (10),[14] 4-methoxycinnamic acid (11),[15] demethylmacrosporine I (12),[16] by analysis of mass spectrometry and nuclear magnetic resonance (NMR) data and comparison with those in the literature.

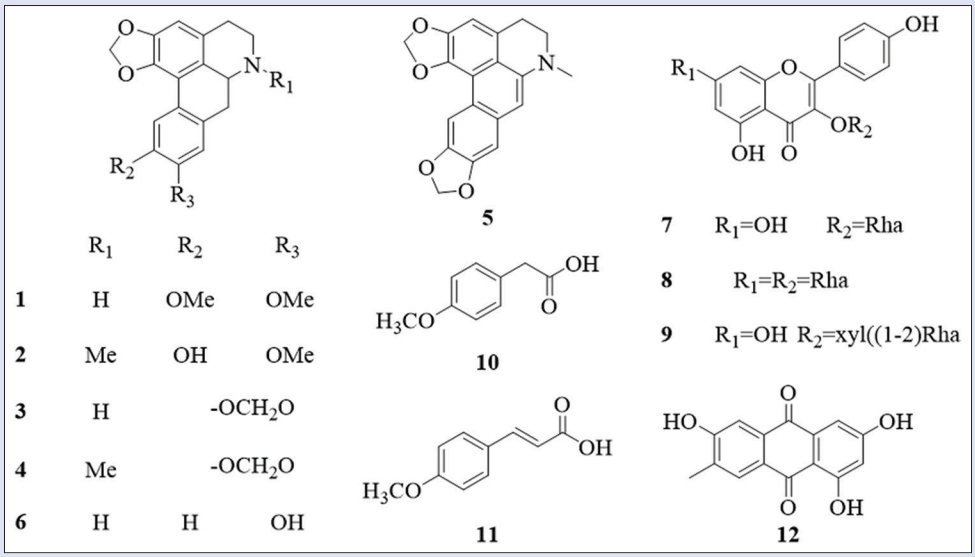

Figure 1: Structures of compounds 1–12 isolated from *Lindera fragrans* Oliv.

Nordicentrine (1)

$C_{19}H_{19}NO_4$, colorless oil; HRESI-MS(+): *m/z* = 326.1314 $[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.61 (1H, s, H-11), 6.73 (1H, s, H-8), 6.47 (1H, s, H-3), 6.04 (1H, br, -OCH_2O-), 5.89 (1H, br, -OCH_2O-), 3.87 (6H, s, 9, 10-OCH_3), 3.79 (1H, m, H-6a), 3.44 (1H, br, H-5), 2.57 (5H, m, H-4, 5, 7), 1.98 (1H, s, *N*-H).

Phanostenine (2)

$C_{19}H_{19}NO_4$, colorless oil; HRESI-MS(+): *m/z* = 326.1386 $[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.60 (1H, s, H-11), 6.79 (1H, s, H-8), 6.50 (1H, s, H-3), 6.07 (1H, br, -OCH_2O-), 5.92 (1H, br, -OCH_2O-), 3.98 (3H, s, 9-OCH_3), 3.71 (1H, m, H-6a), 3.20 (2H, m, H-7), 3.06 (2H, m, H-4), 2.66 (2H, m, H-5), 2.61 (3H, s, *N*-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.0 (C-10), 145.6 (C-9), 145.3 (C-2), 141.9 (C-1), 130.2 (C-7a), 129.4 (C-3a), 126.5 (C-3b), 122.8 (C-11a), 116.8 (C-11b), 114.4 (C-11), 110.0 (C-8), 106.7 (C-3), 100.8 (-OCH_2O-), 62.2 (C-6a), 56.2 (9-OCH_3), 53.1(C-5), 43.7 (*N*-CH_3), 33.3 (C-7), 22.7 (C-4).

Cryptodorine (3)

$C_{18}H_{15}NO_4$, colorless oil; HRESI-MS (+): *m/z* = 310.1012$[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.58 (1H, s, H-11), 6.77 (1H, s, H-8), 6.59 (1H, s, H-3), 6.13, 5.97 (2H, d, *J* = 1.37 Hz, -OCH_2O-), 6.00, 5.98 (2H, d, *J* = 1.40 Hz, -OCH_2O-), 3.47 (1H, s, H-6a), 2.08 (1H, s, *N*-H)

Neolitsine (4)

$C_{19}H_{17}NO_4$, colorless crystals; HRESI-MS (+): *m/z* = 324.1223 $[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.56 (1H, s, H-11), 6.70 (1H, s, H-8), 6.47 (1H, s, H-3), 6.01-5.93 (2H, d, *J* = 1.32 Hz, -OCH_2O-), 5.91-5.88 (2H, d, *J* = 1.32 Hz, -OCH_2O-), 3.13 (1H, m, H-6a), 3.1 (2H, m, H-7), 3.0 (2H, m, H-4), 2.6 (2H, m, H-5), 2.5 (3H, s, *N*-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.8 (C-2), 146.7 (C-9), 146.6 (C-7), 142.0 (C-1), 129.6 (C-7a), 126.4 (C-3a), 126.1 (C-11c), 124.5 (C-11a), 116.7 (C-11b), 108.7 (C-11), 107.5 (C-8), 106.9 (C-3), 101.0 (-OCH_2O-), 100.7 (-OCH_2O-), 62.2 (C-3a), 53.5 (C-5), 43.7 (*N*-CH_3), 34.5 (C-7), 27.3 (C-4).

Dehydroneolitsine (5)

$C_{19}H_{15}NO_4$, yellow powder; HRESI-MS(+): *m/z* = 344.1086$[M+Na]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.38 (1H, s, H-11), 7.59 (1H, s, H-8), 6.73 (1H, s, H-3), 6.51 (1H, s, H-7), 6.05, 5.94 (2H, d, *J* = 1.39 Hz, -OCH_2O-), 5.96, 5.92 (2H, d, *J* = 1.91 Hz, -OCH_2O-), 2.61 (3H, s, *N*-CH_3).

Anolobin (6)

$C_{17}H_{15}NO_3$, colorless oil; HRESI-MS(+): *m/z* = 282.1134$[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.21 (1H, br, H-11), 8.05 (1H, brd, *J* = 7.97 Hz, H-10), 7.27 (1H, d, *J* = 2.07 Hz, H-8), 6.54 (1H, s, H-3), 6.06, 5.93 (2H, d, *J* = 1.32 Hz, -OCH_2O-), 3.13 (1H, dd, *J* = 14.01, 4.59 Hz, H-6a), 2.77 (1H, s, *N*-H).

Kaempferol-3-O-α-L-rhamnoside (7)

$C_{21}H_{20}O_{10}$, yellow powder; HRESI-MS(+):*m/z* = 433.1130$[M+H]^+$; *m/z* = 455.0946$[M+Na]^+$; ^1H NMR (600 MHz, CD_3OD): δ = 7.76–7.74 (2H, d, *J* = 8.8 Hz, H-2', 6'), 6.91-6.93 (2H, d, *J* = 8.8 Hz, H-3', 5'), 6.33 (1H, d, *J* = 2.1 Hz, H-8), 6.18 (1H, d, *J* = 2.1 Hz, H-6), 5.37 (1H, d, *J* = 1.7 Hz, H-1"), 4.23 (1H, dd, *J* = 1.7 Hz, 3.3 Hz, H-2"), 3.70-3.72 (1H, m, H-3"), 3.32-3.33 (1H, m, H-4"), 3.30-3.31 (1H, m, H-5"), 0.92 (3H, d, *J* = 5.7 Hz, H-CH_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 178.2 (C-4), 164.6 (C-7), 161.6 (C-5), 160.2 (C-4'), 157.9 (C-9), 157.2 (C-2), 134.8 (C-3), 130.6 (C-2', 6'), 121.3 (C-1'), 115.1 (C-3', 5'), 104.5 (C-10), 102.1 (C-1'), 98.5(C-6), 93.4 (C-8), 71.8 (C-3"), 70.75 (C-5"), 70.69 (C-4"), 70.58 (C-2"), 16.3 (C-6").

Kaempferol-3, 7-O-α-L-dirhamnoside (8)

$C_{27}H_{30}O_{14}$, yellow crystals; HRESI-MS(+): *m/z* = 601.1313$[M+Na]^+$, ^1H NMR (600 MHz, CD_3OD): δ = 7.77-7.74 (2H, d, *J* = 8.88 Hz, H-2H, d, RESI-MS(+): e (8) 160*J* = 8.88 Hz, H-

3H, d, RESI-MS(+): e (8*J* = 2.09 Hz, H-8), 6.42 (1H, d, *J* = 2.09 Hz, H-6), 5.53 (1H, d, *J* = 1.78 Hz, H-1), 5.53 (1H, d,): *J* = 2.01 Hz, H-1), 5.53 (1H, d,):*J* = 6.16 Hz, -CH_3), 0.90 (3H, d, *J* = 5.70 Hz, -CH_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 182.5 (C-4), 166.2 (C-7), 165.7 (C-5), 164.5 (C-4'), 162.5 (C-9), 160.7 (C-2), 139.1 (C-3), 134.7 (C-2', 6'), 125.0 (C-1'), 119.2 (C-3', 5'), 110.2 (C-10), 106.2 (C-1"), 103.2 (C-6), 102.2 (C-1'"), 98.2 (C-8), 20.8 (C-6'"), 20.4 (C-6").

Kaempferol-3-O-β-D-xylopyranosyl-(1→2)-α-L-rhamnopyranoside (9)

$C_{26}H_{28}O_{14}$, yellow powder; HRESI-MS(+): *m/z* = 587.1370$[M+Na]^+$, ^1H NMR (600 MHz, CD_3OD) δ = 7.91-7.90 (2H, d, *J* = 8.08 Hz, H-2H, d, -MS(+): osyl-(1 → 2)-α-L*J* = 8.08 Hz, H-3H, d, -MS(+): osybr, H-8), 6.42 (1H, br, H-6), 5.53 (1H, br, H-1"), 4.41 (1H, d, *J* = 2.17 Hz, H-13H, d, -MS(+): osyb*J* = 6.13 Hz, -CH_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 178.4 (C-4), 164.9 (C-7), 161.7 (C-5), 160.2 (C-4'), 157.5 (C-9), 157.1 (C-2), 133.4 (C-3), 130.6 (C-2', 6'), 121.3 (C-1'), 115.3 (C-3', 5'), 106.4 (C-1'"), 104.2 (C-10), 99.9 (C-1"), 98.6 (C-6), 93.6 (C-8), 16.6 (C-6").

p-Methoxyphenylacetic acid (10)

$C_9H_{10}O_3$, yellow oil; HRESI-MS(+): *m/z*: = 189.0634 $[M+Na]^+$; ^1H NMR (600 MHz, CD_3OD): δ = 6.78 (2H, d, *J* = 8.7 Hz, H-2, CDMS(+):), 161.7 *J* = 8.7 Hz, H-3, CDMS(+):)(H, m, H-2), 3.82 (H, m, H-2), 3.71 (3H, s, -OCH_3); ^{13}C NMR (150 MHz, CD_3OD) δ = 173.8 (C-1), 155.39 (C-4'), 129.69 (C-2', C-6'), 128.75 (C-1'), 114.38 (C-3', C-5'), 51.16 (4'-OCH3), 44.55 (C-2).

4-Methoxycinnamic acid (11)

$C_{10}H_{10}O_3$, yellow crystals; HRESI-MS(+): *m/z* = 282.1134$[M+Na]^+$; ^1H NMR (600 MHz, CD_3OD): δ = 7.58–7.56 (1H, d, *J* = 16.0 Hz, H-7), 7.42–7.41 (2H, d, *J* = 8.6 Hz, H-2, 6), 6.77-6.75 (2H, d, *J* = 8.6 Hz, H-3, 5), 6.30-6.28 (1H, d, *J* = 16.0 Hz, H-8), 3.72 (3H, s, OCH_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 169.9 (C-9), 161.4 (C-4), 146.7 (C-7), 131.3 (C-2, 6), 127.2 (C-1), 116.9 (C-3, 5), 115.0 (C-8), 52.1 (OCH_3).

Demethylmacrosporine I (12)

$C_{15}H_{10}O_5$, orange crystals; HRESI-MS(+): *m/z* = 293.0423$[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.52 (1H, s, H-5), 7.16 (1H, br d, *J* = 2.3 Hz, H-4), 7.01 (1H, s, H-8), 6.56 (1H, br d, *J* = 2.4 Hz, H-2), 2.37 (3H, s, H-15); ^{13}C NMR (150 MHz, DMSO-*d6*): δ = 190.1 (C-10), 181.7 (C-13), 166.0 (C-1), 164.9 (C-3), 161.8 (C-6), 148.6 (C-7), 135.4 (C-12), 133.1 (C-9), 124.5 (C-8), 120.9 (C-5), 113.7 (C-14), 109.3 (C-11), 109.2 (C-4), 108.3 (C-2), 22.0 (C-15).

The isolated compounds 3–9 were evaluated for their cytotoxicity against B16, C6, and HepG2 cells by MTS method. As a result, compounds 3–5 showed weak inhibitory effect against B16 cell line with IC_{50} values of 71.97, 73.63, and 94.69 μM, respectively, while the other four compounds exhibited unobvious cytotoxic activities with IC_{50} values greater than 100 μM.

DISCUSSION

This is the first report on the phytochemical investigation of *L. fragrans*. In the present paper, the compounds 1–6 got from *L. fragrans* were classified as apophine alkaloids that confirmed the chemical composition similarity in homologous plants. No related reports of the

genus *Lindera* had mentioned the compounds 3–6, which can be used to distinguish *L. fragrans* with other plants of *Lindera*. Compounds 7–9 were classified as flavonoids, which are the other major constituents in *Lindera*.

CONCLUSION

Twelve known compounds were isolated from the leaves of *L. fragrans* for the first time, and compounds 3–6, 8, and 9 were first reported from the genus *Lindera*. Compounds 3–5 exhibited weak antitumor activities with the IC_{50} values ranging from 71.97 to 94.69 μM.

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Conflicts of interest

There are no conflicts of interest.

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