

A new rearranged eudesmane sesquiterpene and bioactive sesquiterpenes from the twigs of *Lindera glauca* (Sieb. et Zucc.) Blume

Jae Sik Yu¹ · Jiwon Baek¹ · Hyun Bong Park² · Eunjung Moon³ · Sun Yeou Kim⁴ · Sang Un Choi⁵ · Ki Hyun Kim¹ 

Received: 27 June 2016 / Accepted: 6 September 2016 / Published online: 12 September 2016
© The Pharmaceutical Society of Korea 2016

Abstract A new rearranged eudesmane sesquiterpene, named eudeglaucone (**1**), and five known sesquiterpenes including (+)-faurione (**2**) and four eudesmane-type sesquiterpenes (**3–6**), were isolated from the twigs of *Lindera glauca* (Sieb. et Zucc.) Blume. The structure of **1** was elucidated by a combination of extensive spectroscopic analyses, including extensive 2D NMR (¹H-¹H COSY, HMQC, HMBC, and NOESY) and HR-MS. Compound **1** was a relatively rare rearranged eudesmane sesquiterpene in terpenoids. All isolates were evaluated for their antiproliferative activities against four human tumor cell lines (A549, SK-OV-3, SK-MEL-2, and HCT-15). Compounds **3** and **6** showed significant cytotoxicity against SK-MEL-2 and HCT-15 cell lines with IC₅₀ values ranging from 9.98 to 12.20 μM. We also investigated the anti-neuroinflammatory activities of the isolates (**1–6**) in the

lipopolysaccharide (LPS)-stimulated murine microglia BV-2 cell line by measuring nitric oxide (NO) levels. All isolates significantly inhibited NO production with IC₅₀ values of 3.67–26.48 μM without inducing cell toxicity.

Keywords *Lindera glauca* · Lauraceae · Sesquiterpene · Cytotoxicity · Anti-inflammation

Introduction

Lindera glauca (Sieb. et Zucc.) Blume (*Lauraceae*) is a deciduous shrub widely distributed in Korea, Japan, and China (Lee 1998). *L. glauca* has been used to treat various diseases in Korean traditional medicine (Park et al. 2014; Chung and Shin 1990). Traditionally, its fruit has been applied in the treatment of symptoms of paralysis, abdominal pain, and speech disorders. Its roots have also been used as a remedy for extravasation, contusion, and pain due to rheumatoid arthritis. Most importantly, the extract of this tree has long been used to cure cancers in Korean traditional medicine (Park et al. 2014; Chung and Shin 1990), and its effectiveness is supported by our preliminary study showing that the MeOH extract of *L. glauca* twigs had excellent cytotoxic activity against A549, SK-OV-3, SK-MEL-2, and HCT-15 cells in a sulforhodamine B (SRB) bioassay (Kim et al. 2014). Previous phytochemical investigations on *L. glauca* revealed a variety of bioactive compounds including sterols (Chang et al. 2000; Huh et al. 2011), alkaloids (Chang et al. 2000, 2001), butanolides (Chang et al. 2000; Seki et al. 1994, 1995), sesquiterpenoids (Nii et al. 1983), diarylpropanoids (Huh et al. 2012), flavonoids (Chang et al. 2000), and phenolic compounds (Chang et al. 2000). However, the constituents associated with the anti-tumor activity from *L. glauca* have

Electronic supplementary material The online version of this article (doi:10.1007/s12272-016-0838-1) contains supplementary material, which is available to authorized users.

✉ Ki Hyun Kim
khkim83@skku.edu

- ¹ School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea
- ² Department of Chemistry, Yale University, New Haven, CT 06520, USA
- ³ Charmzone R&D Center, Charmzone Co. LTD., 318 Yeongdong-daero, Gangnam-gu, Seoul 06177, Republic of Korea
- ⁴ College of Pharmacy, Gachon University, #191 Hambakmoero, Yeonsu-gu, Incheon 406-799, Republic of Korea
- ⁵ Korea Research Institute of Chemical Technology, Daejeon 305-600, Republic of Korea

not been investigated thoroughly. In the course of our search for the anti-tumor constituents from *L. glauca*, we recently reported the isolation and identification of several lignan derivatives with cytotoxic activity as well as anti-inflammatory activity from the MeOH extract of *L. glauca* (Kim et al. 2014; Suh et al. 2015).

In our ongoing search for bioactive constituents from the twigs of *L. glauca*, we further investigated the MeOH extract of *L. glauca* twigs to search for other types of compounds associated with anti-tumor activity. As a result, a new rearranged eudesmane sesquiterpene, named eudeglaucone (**1**), together with five known sesquiterpenes including faurinone (**2**) and four eudesmane-type sesquiterpenes (**3–6**), were isolated from the most active CHCl₃-soluble fraction of the MeOH extract (Fig. 1). The structure of **1** was elucidated by a combination of extensive spectroscopic analyses, including 2D NMR (¹H-¹H COSY, HMQC, HMBC, and NOESY) and HR-MS. The current report describes the isolation and structure elucidation of the compounds **1–6**, as well as their bioactive properties.

Materials and methods

General experimental procedures

Optical rotations were measured on a Jasco P-1020 polarimeter using methanol as a solvent. IR spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer using methanol as a solvent. UV spectra were recorded using an Agilent 8453 UV-Vis spectrophotometer. HR-ESI MS and ESIMS spectra were recorded on a Micromass QTOF2-MS. LC/MS analysis was performed on an Agilent 1200 Series HPLC/6130 Series mass spectrometer. NMR spectra, including ¹H-¹H COSY, HMQC, HMBC, NOESY experiments, were recorded on a Varian UNITY INOVA 500 NMR spectrometer operating at 500 MHz (¹H) and 125 MHz (¹³C), with chemical shifts given in ppm (δ).

Semi-preparative HPLC was conducted with a Shimadzu Prominence HPLC System with SPD-20A/20AV Series Prominence HPLC UV-Vis Detectors (Shimadzu). Silica gel 60 (Merck, 230–400 mesh) and RP-C₁₈ silica gel (Merck, 230–400 mesh) were used for column chromatography. The packing material for molecular sieve column chromatography was Sephadex LH-20 (Pharmacia Co. Ltd). Merck precoated silica gel F₂₅₄ plates and RP-18 F_{254s} plates were used for TLC. Spots were detected on TLC under UV light or by heating after spraying with anisaldehyde-sulfuric acid.

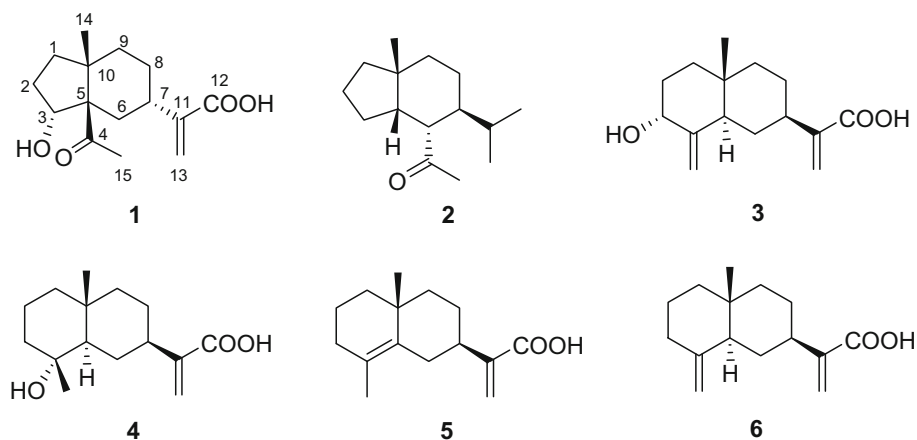
Plant materials

The twigs of *L. glauca* (Sieb. et Zucc.) Blume were collected from Hongcheon, Chungcheongbuk-do, Korea, in March 2010. Samples of plant material were identified by one of the authors (K. H. Kim). A voucher specimen (SKKU 2010-3B) has been deposited in the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

Extraction and isolation

The pulverized twigs of *L. glauca* (6 kg) were extracted twice with 80 % aqueous MeOH (2 × 4 h) under reflux, and then filtered. The filtrate was concentrated under vacuum to afford a crude MeOH extract (120 g), which was suspended in distilled water (2 L) and successively partitioned with hexane, CHCl₃, EtOAc, and *n*-BuOH, yielding 2.5, 13.3, 7.6, and 17.5 g of residues, respectively. Each fraction was evaluated for its cytotoxicity against A549, SK-OV-3, SK-MEL-2, and HCT-15 cells using the SRB bioassay. The most active fraction was the CHCl₃-soluble fraction, which we selected for phytochemical investigation. The CHCl₃-soluble fraction (13.3 g) was separated over RP-C₁₈ silica gel (230–400 mesh, 300 g) column chromatography using a gradient of increasing MeOH in

Fig. 1 Chemical structures of **1–6**



H₂O from 50 to 100 % to give four fractions (C1–C4). Fraction C3 (2.1 g) was applied to a Sephadex LH-20 column using a solvent system of CH₂Cl₂–MeOH (1:1) to yield eight subfractions (C31–C38). Subfraction C36 (135 mg) was further purified by semi-preparative HPLC using a 250 × 10 mm i.d., 10 μm, Econosil RP-18 column (Alltech, Nicholasville, KY, USA) using isocratic elution with 75 % MeOH/H₂O (flow rate; 2 mL/min) to yield compound **2** (4 mg). Subfraction C37 (120 mg) was purified by semi-preparative HPLC using the same column with an isocratic solvent system of 75 % MeOH/H₂O (flow rate; 2 mL/min) to obtain compounds **3** (3 mg) and **4** (3 mg). Compound **5** (3 mg) was isolated from subfraction C38 (275 mg) by the purification of semi-preparative HPLC using the same column with 90 % MeOH/H₂O. Fraction C4 (1.5 g) was separated over RP-C₁₈ silica gel (230–400 mesh, 50 g) column chromatography using a solvent system of 80 % MeOH/H₂O to give 12 subfractions (C4A–C4L). Subfraction C4A (180 mg) was separated over a pre-packed C18 Sep-Pak cartridge (10 g, Waters) using 90 % MeOH/H₂O, and further purified by semi-preparative HPLC using a 250 × 10 mm i.d., 10 μm, Econosil RP-18 column (Alltech) using isocratic elution with 70 % MeOH/H₂O (flow rate; 2 mL/min) to furnish compound **1** (7 mg). Subfraction C4B (85 mg) was purified by semi-preparative HPLC using the same column with an isocratic solvent system of 95 % MeCN/H₂O (flow rate; 2 mL/min) to give compound **6** (9 mg).

Eudeglaucone (**1**): colorless gum; $[\alpha]_D^{25}$ –20.5 (*c* 0.30, MeOH); UV (MeOH) λ_{\max} (log ϵ) nm 208 (3.8); IR (neat) ν_{\max} cm⁻¹: 3421, 2938, 2831, 1685, 1455, 1256, 1032; ¹H (CD₃OD, 500 MHz) and ¹³C (CD₃OD, 125 MHz) NMR data, see Table 1; HR-ESIMS (positive-ion mode) *m/z*: 289.1421 [M+Na]⁺ (calcd for C₁₅H₂₂O₄Na, 289.1416).

In vitro cytotoxicity test

A sulforhodamine B (SRB) bioassay was used to determine the cytotoxicity of each isolated compound against four cultured human tumor cell lines (Song et al. 2014). The assays were performed at the Korea Research Institute of Chemical Technology. The cell lines used were A549 (non-small cell lung carcinoma), SK-OV-3 (ovary malignant ascites), SK-MEL-2 (skin melanoma), and HCT-15 (colon adenocarcinoma). Each tumor cell line was inoculated over standard 96-well flat-bottom microplates and then incubated for 24 h at 37 °C in a humidified atmosphere of 5 % CO₂. The attached cells were then incubated with the serially diluted isolates. After continuous exposure to the compounds for 48 h, the culture medium was removed from each well and the cells were fixed with 10 % cold trichloroacetic acid at 4 °C for 1 h. After washing with tap

Table 1 ¹H (500 MHz) and ¹³C (125 MHz) NMR data of **1** in CD₃OD^a (δ in ppm)

Position	1	
	δ_H	δ_C
1	1.70 m	37.3 t
	1.47 m	
2	2.26 m	32.8 t
	1.78 m	
3	4.36 dd (8.5, 4.5)	78.6 d
4		215.4 s
5		64.6 s
6	2.06 dd (13.5, 3.5)	31.4 t
	1.99 br d (13.5)	
7	3.22 m	35.9 d
8	1.68 m	26.5 t
	1.47 m	
9	1.87 m	37.1 t
	1.42 m	
10		43.3 s
11		147.4 s
12		172.5 s
13	6.13 s	121.6 t
	5.62 s	
14	0.96 s	21.8 q
15	2.15 s	28.9 q

^a The assignments were based on ¹H–¹H COSY, HMQC, and HMBC experiments. Well-resolved couplings are expressed with coupling patterns and coupling constants in Hz in parentheses

water, the cells were stained with 0.4 % SRB dye and incubated for 30 min at room temperature. The cells were washed again and then solubilized with 10 mM unbuffered Tris base solution (pH 10.5). The absorbance was measured spectrophotometrically at 520 nm with a microtiter plate reader. Doxorubicin (purity \geq 98 %, Sigma) was used as a positive control. The cytotoxicities of doxorubicin against the A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines were IC₅₀ 0.002, 0.012, 0.001, and 0.109 μM, respectively. Tested compounds were demonstrated to be pure as evidenced by NMR and HPLC analyses (purity \geq 95 %).

Determination of NO content

BV-2 microglia cells (4 × 10⁴ cells/well in 96 well plates) were treated with the samples to be tested for 30 min before exposure to 100 ng/mL of LPS. After 24 h incubation, nitrite in culture medium was measured to assess NO production in BV-2 microglia cells using Griess reaction. The supernatant (50 μL) was harvested and mixed

with an equal volume of Griess reagent (1 % sulfanilamide, 0.1 % *N*-1-naphthylethylenediamine dihydrochloride in 5 % phosphoric acid). After 10 min, the absorbance at 540 nm was measured using a microplate reader. Sodium nitrite was used as a standard to calculate the NO_2^- concentration. *N*^G-Monomethyl-L-arginine (L-NMMA, purity ≥ 98 %, Sigma, USA), a well-known NOS inhibitor, was tested as a positive control. Cell viability was assessed by a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) assay.

Results

Structural elucidation of isolated compounds

Compound **1** was isolated as an optically active colorless gum. The molecular formula of **1** was determined as $\text{C}_{15}\text{H}_{22}\text{O}_4$ from its positive mode HR-ESIMS data at m/z 289.1421 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{Na}$, 289.1416), which was compatible with the ^1H and ^{13}C NMR data. Its IR spectrum exhibited characteristic absorptions of hydroxy (3421 cm^{-1}) and conjugated carboxylic (1685 cm^{-1}) groups. The ^1H and ^{13}C NMR spectral data (Table 1) of **1**, in combination with HMQC, indicated a total of 15 carbon signals, including one tertiary methyl group [δ_{H} 0.96 (3H, s); δ_{C} 21.8], one characteristic acetyl moiety composed of one methyl signal [δ_{H} 2.15 (3H, s); δ_{C} 28.9] and a carbonyl carbon signal [δ_{C} 215.4], and one oxygenated methine signal [δ_{H} 4.36 (1H, dd, $J = 8.5, 4.5$ Hz); δ_{C} 78.6]. The NMR data also showed an olefinic methylene signal [δ_{H} 6.13 (1H, s) and 5.62 (1H, s); δ_{C} 21.8], one quaternary carbon [δ_{C} 147.4], and a carboxyl signal [δ_{C} 172.5], whose characteristic resonances indicated the presence of an allylic acid moiety in the molecule (Ceccherelli et al. 1985; Oksuz and Topcu 1991; Leon et al. 2009). The ^1H and ^{13}C NMR spectra of **1** were shown to have a rearranged-type sesquiterpene skeleton. The correlations in the ^1H - ^1H -COSY and HMQC spectra revealed the presence of two proton-bearing structural fragments, $-\text{CH}_2\text{CH}_2\text{CH}-\text{OH}$ (a) and $-\text{CH}_2\text{CHCH}_2\text{CH}_2-$ (b) (Fig. 2). Detailed HMBC analysis showed the correlation of H-14

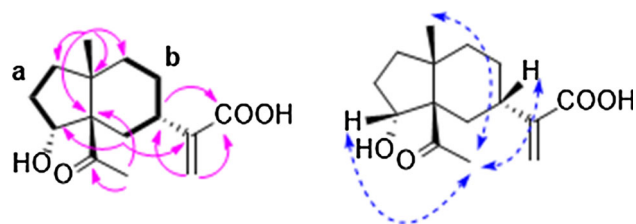


Fig. 2 Key ^1H - ^1H COSY (bold), HMBCs (continuous pink arrow), and NOESY correlations (dotted blue arrow) of **1**

(δ_{H} 0.96)/C-1 (δ_{C} 37.2), C-5 (δ_{C} 64.5), C-9 (δ_{C} 37.1), and C-10 (δ_{C} 43.3), H-15 (δ_{H} 2.15)/C-4 (δ_{C} 215.4) and C-5 (δ_{C} 64.6), H-6 (δ_{H} 2.06 and 1.99)/C-3 (δ_{C} 78.6) and C-11 (δ_{C} 147.4), H-7 (δ_{H} 3.22)/C-12 (δ_{C} 172.5), and H-13 (δ_{H} 6.13)/C-7 (δ_{C} 35.9) and C-12 (δ_{C} 172.5) (Fig. 2), which suggested that the planar structure of **1** was identical to that of 3 α -hydroxyisophion-11(13)-en-12-oic acid, a known isophionane-type sesquiterpene (Garcez et al. 2010). However, there was a major difference between the two compounds in the ^{13}C chemical shifts of the allylic acid moiety [δ_{C} 175.1 (C-12), 153.1 (C-11), 117.6 (C-13) in 3 α -hydroxyisophion-11(13)-en-12-oic acid] (Garcez et al. 2010), which suggested that compound **1** is a stereoisomer of 3 α -hydroxyisophion-11(13)-en-12-oic acid.

The relative stereochemistry of **1** was established from the observed data of the NOESY experiment. The *cis*-fused hydrindane system of **1** was assigned by the chemical shift of the methyl of C-14 (δ_{C} 21.8) (Todorova and Tsankova 1999), which was supported by NOESY correlation between H-14 and H-15 (Fig. 2). The OH group of C-3 was established as being in the α -position by the observed coupling constants of H-3 ($J = 8.5, 4.5$ Hz) and its downfield shift (δ_{H} 4.36) caused by the neighboring acetyl group (Todorova and Tsankova 1999). The β -orientated H-3 was further confirmed by the NOESY correlation of H-3/H-15 (Fig. 2). Finally, the NOESY correlation of H-7/H-15 indicated a β -orientated H-7 (Fig. 2), which confirmed that compound **1** is an epimer of 3 α -hydroxyisophion-11(13)-en-12-oic acid. Determination of the absolute configuration in natural products is crucial because it provides essential information for both molecular mode of action and total synthesis of bioactive compounds. The determination of the absolute configuration of **1** was attempted by using the modified Mosher's method (Kim et al. 2011, 2015a, b). However, the reaction failed to yield the corresponding acylation product, possibly due to steric hindrance at C-3/C-5. So the absolute configuration of **1** remains unknown. On the basis of the above data, the structure of **1** was elucidated as shown in Fig. 1 and named eudeglaucone.

The known compounds were identified as (+)-faurinone (**2**) (Bos et al. 1983), 3 α -hydroxycostic acid (**3**) (Ceccherelli et al. 1985), ilicic acid (**4**) (Oksuz and Topcu 1991), γ -costic acid (**5**) (Leon et al. 2009), and costic acid (**6**) (Watanabe et al. 2005) by comparing the physico-chemical and spectroscopic data with previously reported data. Besides the known sesquiterpenes, other known lignan derivatives such as lyoniresinol, linderuca A, linderuca C, (+)-9'-*O*-(*E*)-feruloyl-5,5'-dimethoxyariciresinol, and (+)-5,5'-dimethoxyariciresinol were also isolated and identified, however, they were all compounds previously reported from this plant by our group (Kim et al. 2014; Suh et al. 2015).

Biological activities

The cytotoxic activities of all the isolates **1–6** were evaluated by determining their inhibitory effects on human tumor cell lines, including A549 (non-small cell lung carcinoma), SK-OV-3 (ovary malignant ascites), SK-MEL-2 (skin melanoma), and HCT-15 (colon adenocarcinoma) using the SRB bioassay (Song et al. 2014), since all of the compounds **1–6** were isolated from the CHCl₃-soluble fraction of the MeOH extract, which showed potent cytotoxicity against the tumor cell lines. Some eudesmane-type sesquiterpenes have been reported to possess cytotoxic activity against cancer cell lines in recent studies (Zhang et al. 2015; Zhao et al. 2014; Nie et al. 2014; Cheng et al. 2013). However, no reports are available regarding the evaluation of cytotoxic activities of the rearranged eudesmane sesquiterpenes. The results (Table 2) demonstrated that compounds **3** and **6** showed significant cytotoxicity against SK-MEL-2 and HCT-15 cell lines with IC₅₀ values ranging from 9.98 to 12.20 μM. However, other compounds including the new compound, rearranged eudesmane sesquiterpene (**1**) were inactive (IC₅₀ > 30.0 μM). These results suggested that the exomethylene unit at C-4 in eudesmane-type sesquiterpenes may play a positive role in mediating the cytotoxicity against SK-MEL-2 and HCT-15 cell lines.

The anti-neuroinflammatory activities of the isolates **1–6** were also evaluated by measuring the levels of nitric oxide (NO) produced in lipopolysaccharide (LPS)-activated microglia BV-2 cells (Ko et al. 2015). Recently, several eudesmane sesquiterpenes were reported to inhibit LPS-induced NO production in BV-2 microglial cells (Tian et al. 2013; Wang et al. 2014; Jiang et al. 2013). However, research on the NO inhibitory effect of rearranged

eudesmane sesquiterpenes in LPS-stimulated murine microglia BV-2 cells has not been reported until now. Microglia, the immune resident cells of the brain, have been implicated in the pathogenesis of a variety of neurodegenerative diseases including Parkinson's disease and Alzheimer's disease (Wilms et al. 2007; McGeer and McGeer 1995). Under pathological conditions, microglia cells are over-activated and produce a variety of pro-inflammatory mediators including NO (Yang et al. 2015; Kim et al. 2015a, b), which consequently leads to various neurodegenerative conditions of the CNS. In this study, the isolated compounds **1–6** significantly inhibited NO levels in LPS-stimulated BV-2 cells with IC₅₀ values in the range of 3.67–26.48 μM (Table 3). None of the compounds showed any significant cellular toxicity up to 20 μM (Table 3). In particular, compound **2** potently inhibited LPS-stimulated NO production with an IC₅₀ value of 3.67 μM, and the new compound, rearranged eudesmane sesquiterpene (**1**) (IC₅₀ = 15.90 μM) along with compounds **2** (IC₅₀ = 3.67 μM), **4** (IC₅₀ = 14.92 μM), and **6** (IC₅₀ = 12.13 μM) displayed better inhibitory activity on NO production than the positive control, N^G-nonomethyl-L-arginine (NMMA), a well-known NOS inhibitor (IC₅₀ = 18.35 μM). Regarding to the other known lignan derivatives, they were not evaluated for the cytotoxic and anti-inflammatory activities in this study since we already reported the biological data of them (Kim et al. 2014; Suh et al. 2015).

Table 2 Cytotoxicity of compounds **1–6** against four cultured human tumor cell lines using the SRB bioassay in vitro

Compound	IC ₅₀ (μM) ^a			
	A549	SK-OV-3	SK-MEL-2	HCT-15
1	>30.0	>30.0	>30.0	>30.0
2	>30.0	>30.0	>30.0	>30.0
3	>30.0	>30.0	10.25	9.98
4	>30.0	>30.0	>30.0	>30.0
5	>30.0	>30.0	>30.0	>30.0
6	>30.0	>30.0	12.20	11.60
Doxorubicin ^b	0.002	0.012	0.001	0.109

^a IC₅₀ value of compounds against each tumor cell line, which was defined as the concentration (μM) that caused 50 % inhibition of cell growth in vitro

^b Doxorubicin served as a positive control

Table 3 Inhibitory effect of compounds **1–6** isolated from *L. glauca* on NO production in lipopolysaccharide (LPS)-activated BV-2 cells

Compound	IC ₅₀ (μM) ^a	Cell viability (%) ^b
1	15.90	106.6 ± 3.0
2	3.67	105.5 ± 3.9*
3	26.48	102.7 ± 4.5*
4	14.92	103.6 ± 1.0
5	24.44	106.1 ± 1.0
6	12.13	105.7 ± 2.2
NMMA ^c	18.35	98.2 ± 4.5*

Only **p*-value < 0.05 was indicated as statistically significant

^a IC₅₀ value of each compound was defined as the concentration (μM) that caused 50 % inhibition of NO production in LPS-activated BV-2 cells

^b Cell viability after treatment with a 20 μM concentration of each compound is expressed as a percentage (%) of the LPS-only treatment group. Results are averages of three independent experiments, and the data are expressed as mean ± SD. Statistical comparisons were performed using a one-way ANOVA test with Student's *t* test

^c NMMA served as a positive control

Discussion

We isolated and identified a new rearranged eudesmane sesquiterpene, eudeglaucone (**1**), together with five known sesquiterpenes including faurinone (**2**) and four eudesmane-type sesquiterpenes (**3–6**) from the twigs of *L. glauca* and evaluated their cytotoxic and anti-neuroinflammatory activities. The new compound **1** was a relatively rare rearranged eudesmane sesquiterpene in terpenoids, and to the best of our knowledge, this is the first report of the presence of the rearranged eudesmane sesquiterpene in this plant. In addition, this is the first report of the occurrence of the eudesmane sesquiterpenes in this plant, and compounds **2** and **3** were isolated from the family of Lauraceae for the first time. The co-occurrence of the rearranged eudesmane sesquiterpene **1** and eudesmane sesquiterpenes **3–6** in the same plant reinforces the biogenetic inter-relationship between the rearranged sesquiterpene and eudesmanes, and suggested the rearrangement of 4,5-epoxy-eudesmanes into the rearranged eudesmane sesquiterpenes (Garcez et al. 2010; Todorova and Tsankova 1999). Compounds **3** and **6** showed significant cytotoxicity against SK-MEL-2 and HCT-15 cell lines and all the isolated compounds **1–6** had anti-neuroinflammatory properties in murine BV-2 microglia cells. Therefore, it is possible that these compounds could be applicable in the development of treatments for activated microglia-mediated brain diseases and/or tumors.

Acknowledgments This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2015R1C1A1A02037383) and by the Ministry of Education (NRF-2012R1A5A2A28671860).

Compliance with ethical standards

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

References

- Bos R, Hendriks H, Kloosterman J, Sipma G (1983) A structure of faurinone, a sesquiterpene ketone isolated from *Valeriana officinalis*. *Phytochemistry* 22:1505–1506
- Ceccherelli P, Curini M, Marcotullio MC, Menghini A (1985) Sesquiterpene acids from *Dittrichia viscosa*. *Phytochemistry* 24:2987–2989
- Chang YC, Chang FR, Wu YC (2000) The constituents of *Lindera glauca*. *J Chin Chem Soc* 47:373–380
- Chang YC, Chen CY, Chang FR, Wu YC (2001) Alkaloids from *Lindera glauca*. *J Chin Chem Soc* 48:811–815
- Cheng XR, Zhang SD, Wang CH, Ren J, Qin JJ, Tang X, Shen YH, Yan SK, Jin HZ, Zhang WD (2013) Bioactive eudesmane and germacrane derivatives from *Inula wissmanniana* Hand.-Mazz. *Phytochemistry* 96:214–222
- Chung BS, Shin MK (1990) Dictionary of Korean folk medicine. Young Lim, Seoul
- Garcez FR, Garcez WS, Hamerski L, Miranda ACDM (2010) Eudesmane and rearranged eudesmane sesquiterpenes from *Nectandra cissiflora*. *Quim Nova* 33:1739–1742
- Huh GW, Park JH, Shrestha S, Lee YH, Ahn EM, Kang HC, Baek NI (2011) Sterols from *Lindera glauca* Blume stem wood. *J Appl Biol Chem* 54:309–312
- Huh GW, Park JH, Shrestha S, Lee YH, Ahn EM, Kang HC, Kim YB, Baek NI (2012) New diarylpropanoids from *Lindera glauca* Bl Heartwood. *Holzforschung* 66:585–590
- Jiang B, Wang WJ, Li MP, Huang XJ, Huang F, Gao H, Sun PH, He MF, Jiang ZJ, Zhang XQ, Ye WC (2013) New eudesmane sesquiterpenes from *Alpinia oxyphylla* and determination of their inhibitory effects on microglia. *Bioorg Med Chem Lett* 23:3879–3883
- Kim KH, Choi SU, Kim YC, Lee KR (2011) Tirucallane triterpenoids from *Cornus walteri*. *J Nat Prod* 74:54–59
- Kim KH, Moon E, Ha SK, Suh WS, Kim HK, Kim SY, Choi SU, Lee KR (2014) Bioactive lignan constituents from the twigs of *Lindera glauca*. *Chem Pharm Bull* 62:1136–1140
- Kim KH, Clardy J, Senger D, Cao S (2015a) Chakyunglupulins A and B, two novel 4,8,8-trimethylcyclooct-2-enone derivatives from *Barleria lupulina*. *Tetrahedron Lett* 56:2732–2734
- Kim S, Oh MH, Kim BS, Kim WI, Cho HS, Park BY, Park C, Shin GW, Kwon J (2015b) Upregulation of heme oxygenase-1 by ginsenoside Ro attenuates lipopolysaccharide-induced inflammation in macrophage cells. *J Ginseng Res* 39:365–370
- Ko W, Sohn JH, Kim YC, Oh H (2015) Viridicatol from marine-derived fungal strain *Penicillium* sp. SF-5295 exerts anti-inflammatory effects through inhibiting NF- κ B signaling pathway on lipopolysaccharide-induced RAW264.7 and BV2 cells. *Nat Prod Sci* 21:240–247
- Lee TB (1998) Coloured flora of Korea. Hyangmunsa, Seoul
- Leon LG, Donadel OJ, Tonn CE, Padron JM (2009) Tassaric acid derivatives induce G₂/M cell cycle arrest in human solid tumor cell lines. *Bioorg Med Chem* 17:6251–6256
- McGeer PL, McGeer EG (1995) The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res Rev* 21:195–218
- Nie XP, Yao F, Yue XD, Li GS, Dai SJ (2014) New eudesmane-type sesquiterpenoid from *Solanum lyratum* with cytotoxic activity. *Nat Prod Res* 28:641–645
- Nii H, Furukawa K, Iwakiri M, Kubota T (1983) A new sesquiterpene carboxylic acid from *Lindera glauca* (Sieb. et Zucc.) Blume. *Nippon Nogei Kagaku Kaishi* 57:725–732
- Oksuz S, Topcu G (1991) A eudesmanolide and other constituents from *Inula graveolens*. *Phytochemistry* 31:195–197
- Park SY, Neupane GP, Lee SO, Lee JS, Kim MY, Kim SY, Park BC, Park YJ, Kim JA (2014) Protective effects of *Pogostemon cablin* Bentham water extract on inflammatory cytokine expression in TNBS-induced colitis in rats. *Arch Pharm Res* 37:253–262
- Seki K, Sasaki T, Haga K, Kaneko R (1994) Two methoxybutanolides from *Lindera glauca*. *Phytochemistry* 36:949–951
- Seki K, Sasaki T, Wano S, Haga K, Kaneko R (1995) Linderanolides and isolinderanolides, ten butanolides from *Lindera glauca*. *Phytochemistry* 40:1175–1181
- Song JH, Choi HJ, Song HH, Hong EH, Lee BR, Oh SR, Choi K, Yeo SG, Lee YP, Cho S, Ko HJ (2014) Antiviral activity of ginsenosides against coxsackievirus B3, enterovirus 71, and human rhinovirus 3. *J Ginseng Res* 38:173–179
- Suh WS, Kim KH, Kim HK, Choi SU, Lee KR (2015) Three new lignan derivatives from *Lindera glauca* (Siebold et Zucc.) Blume. *Helv Chim Acta* 98:1087–1094

- Tian SH, Chai XY, Zan K, Zeng KW, Tu PF (2013) Three new eudesmane sesquiterpenes from *Artemisia vestita*. *Chin Chem Lett* 24:797–800
- Todorova MN, Tsankova ET (1999) New sesquiterpenoids from *Achillea clypeolata*. *Phytochemistry* 52:1515–1518
- Wang S, Sun J, Zeng K, Chen X, Zhou W, Zhang C, Jin H, Jiang Y, Tu P (2014) Sesquiterpenes from *Artemisia argyi*: absolute configurations and biological activities. *Eur J Org Chem* 2014:973–983
- Watanabe Y, Mihara R, Mitsunaga T, Yoshimura T (2005) Termite repellent sesquiterpenoids from *Callitris glaucophylla* heartwood. *J Wood Sci* 51:514–519
- Wilms H, Zecca L, Rosenstiel P, Sievers J, Deuschl G, Lucius R (2007) Inflammation in Parkinson's diseases and other neurodegenerative diseases: cause and therapeutic implications. *Curr Pharm Des* 13:1925–1928
- Yang Y, Lee J, Rhee MH, Yu T, Baek KS, Sung NY, Kim Y, Yoon KY, Kim JH, Kwak YS, Hong S, Kim JH, Cho JY (2015) Molecular mechanism of protopanaxadiol saponin fraction-mediated anti-inflammatory actions. *J Ginseng Res* 39:61–68
- Zhang L, Lin HQ, Li GS, Yue XD, Dai SJ (2015) New sesquiterpenoid derivatives from *Solanum septemlobum* with cytotoxicities. *Nat Prod Res* 29:1889–1893
- Zhao J, Wu J, Yan F (2014) A new sesquiterpenoid from the rhizomes of *Homalomena occulta*. *Nat Prod Res* 28:1669–1673