Regular Article

Three New Lignan Glycosides from the *Firmiana simplex*

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In our quest for structurally intriguing compounds from Korean medicinal plant sources, chromatographic separation of the 80% MeOH extract from *Firmiana simplex* resulted in the isolation and identification of three new lignan glycosides (1–3), together with six known lignan glycosides (4–9). The structures of 1–3 were determined on the basis of spectroscopic analyses, including extensive 2D-NMR and enzyme hydrolysis. Nitric oxide (NO) production was evaluated in the lipopolysaccharide-activated microglial cell line, BV-2 to investigate the anti-neuroinflammatory effects of the isolated compounds (1–9). Compound 7 marginally inhibited NO levels with IC_{50} values of 59.83 μM.

Key words *Firmiana simplex*; Sterculiaceae; lignan glycoside; nitric oxide; neuroinflammatory effect

Introduction

Neuroinflammation is a major cause underlying neurodegenerative conditions.[1)] Nitric oxide (NO) is a key marker of neuroinflammation and is excessively produced by activated microglia when the inflammatory signaling is activated resulting in the production of reactive oxygen species (ROS) and nitrogen species (RNS). They induce glial cell activation and neuronal cell degeneration or death.[2)] Hence, the measurement of NO production is a critical screening technique for the evaluation of anti-neuroinflammatory and neuroprotective compounds derived from natural products.

Firmiana simplex (Sterculiaceae) is a deciduous tree widely distributed in Southeast Asia, Korea and China.[3)] The seeds of *F. simplex* have been used as Korean traditional medicine for the treatment of diarrhea and stomach disorders.[4)] Several flavonoids, lignans, and fatty acids have been isolated from *F. simplex*. Some compounds and extracts of *F. simplex* have been shown to exhibit antimicrobial and hepatoprotective activities.[4–7)] A preliminary investigation of *F. simplex* led to the isolation and structural elucidation of cytotoxic triterpenoids and anti-inflammatory lignans.[8,9)] Further investigations yielded three new lignan glycosides, designated as firmiside A–C (**1**–**3**) (Fig. 1) and six known lignan glycosides (**4**–**9**) from EtOAc and BuOH fractions of *F. simplex*, and evaluated for their anti-inflammatory activities (**1**–**9**).

Results and Discussion

Compound **1** was obtained as a colorless gum with a negative optical rotation ($[\alpha]_D^{25}$ −27.0). The molecular formula of **1** was determined as $C_{26}H_{28}O_{12}$ using positive-mode high-resolution (HR)-FAB-MS data at *m/z* 555.1470 $[M+Na]^+$ (Calcd for $C_{26}H_{28}NaO_{12}$, 555.1473). The ^{1}H-NMR spectrum revealed two sets of 1,3,4-trisubstitued aromatic protons at [δ_H 6.94 (1H, d, J = 2.0 Hz, H-2′), 6.88 (1H, dd, J = 8.5, 2.0 Hz, H-6′), 6.82 (1H, d, J = 1.5 Hz, H-2), 6.80 (1H, dd, J = 7.5, 1.5 Hz, H-6), 6.71 (1H, d, J = 7.5 Hz, H-5), 6.70 (1H, d, J = 8.0 Hz, H-5′)], two methylenedioxy protons at δ_H 5.83 (4H, s, –OH_2O–), two oxygenated methine protons at δ_H 4.77 (1H, d, J = 4.0 Hz, H-7′) and 4.72 (1H, s, H-7), two oxygenated methylene protons at δ_H 4.43 (1H, t, J = 8.0 Hz, H-9′a), 4.05 (2H, s, H-9), and 3.67 (1H, m, H-9′b), and one methine proton at δ_H 3.65 (m, H-8′). The ^{1}H- and ^{13}C-NMR spectra of **1** (Tables 1 and 2) were very similar to those of paulownin, which was isolated from *Rehmannia glutinosa*.[10)] The major difference was the presence of an additional sugar group [δ_H 4.52 (1H, d, J = 1.0 Hz, H-1″), 3.65 (1H, m, H-6″a), 3.54 (1H, dd, J = 12.0, 5.0 Hz, H-6″b), 3.35 (1H, t, J = 9.5 Hz, H-5″), 3.01 (1H, dd, J = 9.0, 3.0 Hz, H-3″), 2.92 (1H, ddd, J = 10.0, 5.0, 2.5 Hz, H-5″), and 2.84 (1H, d, J = 3.0 Hz, H-2″) in the ^{1}H-NMR spectrum; δ_C 98.4 (C-1″), 78.3 (C-5″), 75.2 (C-3″), 72.6 (C-2″), 68.1 (C-4″), 62.7 (C-6″)] in the ^{13}C-NMR spectrum. The identity of β-D-mannopyranosyl sugar moiety was confirmed by comparing the coupling constant (J = 1.0 Hz) and ^{13}C-NMR data with values reported in the literatures.[11–13)] Its position was assigned as C-8′ by heteronuclear multiple bond correlation (HMBC) of H-1″/C-8 (Fig. 2). The configuration of furofuran moiety in **1** was to be same as that of (+)-paulownin and (+)-1-hydroxysyringaresinol 1-glucoside based on the NMR data and optical rotation.[10,14)] In addition, the *trans*/*trans* configuration of 7-H/8-OH and 7′-H/8′-H in the furofuran moiety was confirmed by comparison with the chemical shift differences.[15)] Thus, the structure of **1** was determined (Fig. 1), and named firmiside A.

Compound **2** was obtained as a colorless gum. The molecular formula of **2** was determined as $C_{27}H_{32}O_{12}$ based on the molecular ion peak $[M+Na]^+$ at *m/z* 571.1785 (Calcd for $C_{27}H_{32}NaO_{12}$, 571.1786) on HR-FAB-MS. The ^{1}H- and ^{13}C-NMR spectra of **2** (Tables 1 and 2) were almost identical to those of 5-methoxybalanophonin, which was isolated from the same plant source,[9)] except for the additional glucose moiety [δ_H 4.91 (1H, d, J = 8.0 Hz, H-1″), 3.79 (1H, m, H-6″a), 3.68 (1H, m, H-6″b), 3.50 (1H, m, H-2″), 3.43 (1H, m, H-5″), 3.42 (1H, m, H-4″), and 3.22 (1H, m, H-3″) in the ^{1}H-NMR spectrum; δ_C 105.0 (C-1″), 78.1 (C-3″), 77.6 (C-5″), 75.8 (C-2″), 71.4 (C-4″), and 62.4 (C-6″)] in the ^{13}C-NMR spectrum. The coupling constant (J = 8.0) of the H-1″ suggested β-glucose.[16)] The linkage of the glucose moiety was deduced by HMBC cross peaks of H-1″/C-4 (Fig. 2). Enzyme hydrolysis of **2** yielded the

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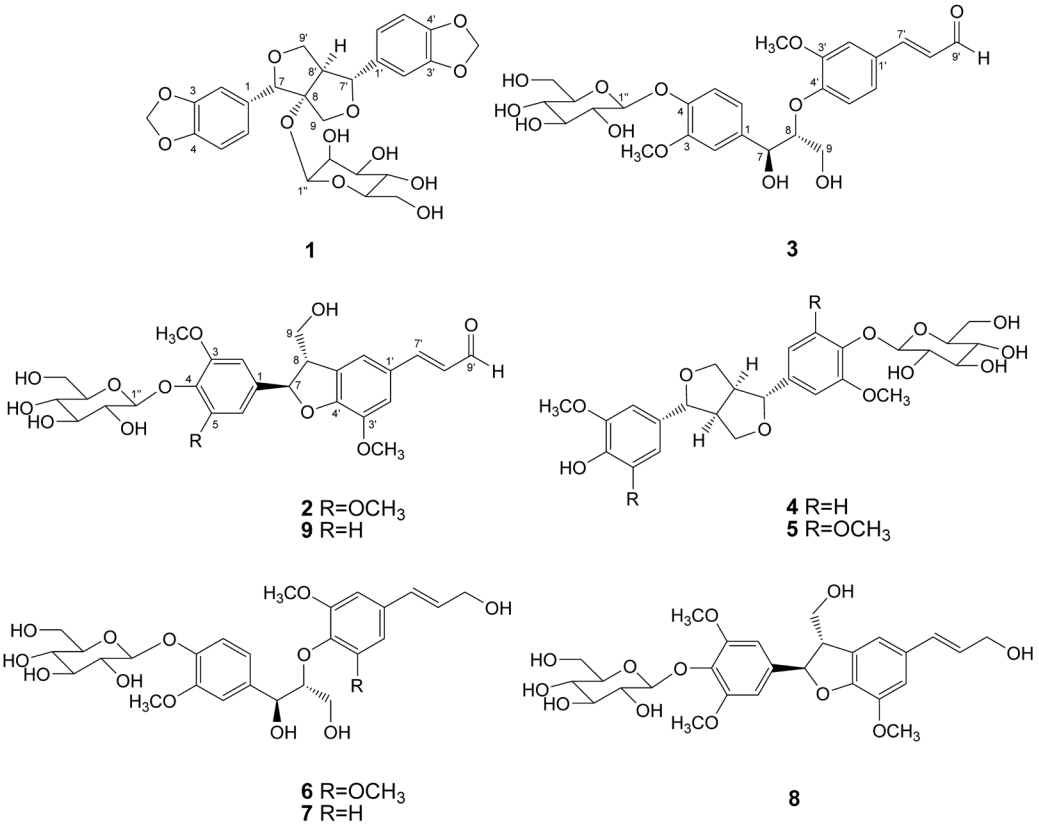

Fig. 1. Chemical Structures of Compounds **1**–**9**

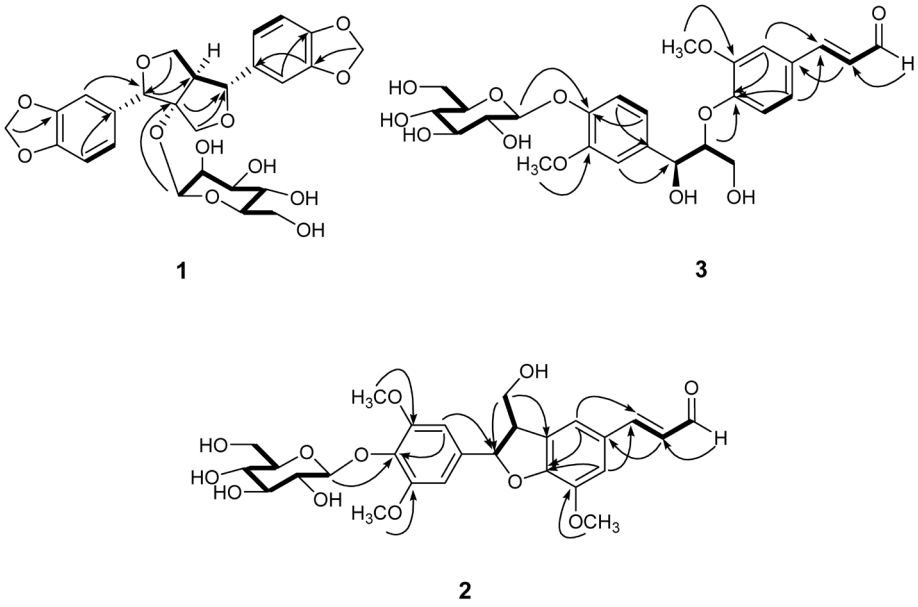

Fig. 2. Key HMBC and ^{1}H–^{1}H-COSY Correlations of **1**–**3**

aglycone (**2a**) and D-glucose. The aglycone (**2a**) was identified as 5-methoxybalanophonin by ^{1}H-NMR spectrum,[17] whereas D-glucose was identified by co-TLC [$CHCl_3$–MeOH–H_2O (2 : 1 : 0.2), *Rf* value: 0.20] with an authentic sample and by optical rotation $[\alpha]_D^{25}$ +52.1 ($c = 0.04$, H_2O).[18] The *trans*-configuration between H-7 and H-8 was confirmed by coupling constant (5.5 Hz).[19] The circular dichroism (CD) spectrum showed negative cotton effect at 236 nm and positive Cotton effect at 226 and 344, confirming the absolute configurations as (7*R*) and (8*S*).[20,21] Thus, the structure of **2** was determined (Fig. 1), and named firmiside B.

Compound **3** was obtained as a colorless gum. The molecular formula of **3** was determined as $C_{26}H_{32}O_{12}$ by HR-FAB-MS *m/z* 559.1785 $[M + Na]^+$ (Calcd 559.1786). The ^{1}H- and ^{13}C-NMR spectra of **3** (Tables 1 and 2) were comparable to those of *erythro*-guaiacylglycerol-*β*-coniferyl aldehyde ether, which was isolated from the same plant source,[9] except for the additional glucose moiety [δ_H 4.86 (1H, d, $J = 8.0$ Hz,

Table 1. ^{1}H (700 MHz) NMR Data of **1**–**3** in CD_3OD (δ in ppm)[a)]

Position	1	2	3
1	—	—	—
2	6.82 (d, 1.5)	6.76 s	7.15 (d, 2.0)
3	—	—	—
4	—	—	—
5	6.71 (d, 7.5)	—	7.14 (d, 8.0)
6	6.80 (dd, 7.5, 1.5)	6.76 s	6.99 (dd, 8.0, 1.5)
7	4.72 s	5.70 (d, 5.5)	4.98 (d, 5.0)
8	—	3.58 m	4.56 (q, 5.0)
9	4.05 s	3.93 m, 3.85 m	3.83 m, 3.58 (dd, 12.0, 6.0)
1′	—	—	—
2′	6.94 (d, 2.0)	7.27 br s	7.31 (d, 2.0)
3′	—	—	—
4′	—	—	—
5′	6.70 (d, 8.0)	—	7.09 (d, 8.0)
6′	6.88 (dd, 8.5, 2.0)	7.30 br s	7.21 (dd, 8.5, 2.0)
7′	4.77 (d, 4.0)	7.64 (d, 16.0)	7.61 (d, 16.0)
8′	3.65 m	6.71 (dd, 15.5, 8.0)	6.71 (dd, 16.0, 8.0)
9′	4.43 (t, 8.0), 3.67 m	9.61 (d, 8.0)	9.61 (d, 8.0)
1″	4.52 (d, 1.0)	4.91 (d, 8.0)	4.86 (d, 8.0)
2″	2.84 (d, 3.0)	3.50 m	3.49 m
3″	3.01 (dd, 9.0, 3.0)	3.22 m	3.40 m
4″	3.35 (t, 9.5)	3.42 m	3.41 m
5″	2.92 (ddd, 10.0, 5.0, 2.5)	3.43 m	3.47 m
6″	3.65 m, 3.54 (dd, 12.0, 5.0)	3.79 m, 3.68 m	3.88 m, 3.71 m
3-OCH_3		3.85 s	3.85 s
5-OCH_3		3.85 s	
3′-OCH_3		3.96 s	3.92 s
–OCH_2O–	5.83 s		
–OCH_2O–	5.83 s		

a) Assignments were based on 2D-NMR including HMQC and HMBC. Well-resolved couplings are expressed with coupling patterns and coupling constants in Hz in parentheses.

Table 2. ^{13}C (175 MHz) NMR Data of **1**–**3** in CD_3OD (δ in ppm)[a)]

Position	1	2	3
1	131.6	139.3	137.1
2	108.5	104.6	112.5
3	149.4	154.4	150.6
4	148.6	135.8	147.5
5	109.1	154.4	117.5
6	121.0	104.6	120.5
7	88.8	89.7	73.4
8	99.7	54.8	85.5
9	75.4	64.5	62.0
1′	135.5	129.6	129.3
2′	108.4	114.2	112.7
3′	149.1	145.9	151.6
4′	148.7	152.5	152.7
5′	108.9	130.8	117.0
6′	121.4	119.7	124.5
7′	87.5	156.0	155.3
8′	57.8	127.4	127.7
9′	72.7	196.2	196.2
1″	98.4	105.0	102.8
2″	72.6	75.8	75.0
3″	75.2	78.1	78.3
4″	68.1	71.4	71.4
5″	78.3	77.6	77.9
6″	62.7	62.4	62.5
3-OCH_3		56.5	56.7
5-OCH_3		56.5	
3′-OCH_3		56.5	56.7
–OCH_2O–	102.5		
–OCH_2O–	102.5		

a) Assignments were based on 2D-NMR including HMQC and HMBC.

H-1″), 3.88 (1H, m, H-6″a), 3.71 (1H, m, H-6″b), 3.49 (1H, m, H-2″), 3.47 (1H, m, H-5″), 3.41 (1H, m, H-4″), and 3.40 (1H, m, H-3″) in the ^{1}H-NMR spectrum; δ_C 102.8, 78.3, 77.9, 75.0, 71.4, and 62.5] in the ^{13}C-NMR spectrum. The coupling constant ($J = 8.0$ Hz) of the anomeric proton suggested to be β-form of glucose.[16] The position of glucose was assigned at C-4 by the HMBC experiment, showing correlation with H-1″/C-4 (Fig. 2). Enzyme hydrolysis of **3** yielded an *erythro*-guaiacylglycerol-β-coniferyl aldehyde ether (**3a**), which was identified based on ^{1}H-NMR data.[22] The D-glucose was confirmed by co-TLC [$CHCl_3$–MeOH–H_2O (2 : 1 : 0.2), *Rf* value: 0.20] with standard sample and by optical rotation value {$[\alpha]_D^{25}$ +75.0 ($c = 0.05$, MeOH)}.[18] The *erythro* configuration of H-7 and H-8 was confirmed by coupling constant (5.5 Hz), and CD spectrum exhibited negative cotton effect at 232 nm, confirming the absolute configurations as (7*S*) and (8*R*).[23,24] Thus, the structure of **3** was determined (Fig. 1), and named firmiside C.

The seven known lignans were identified as (+)-pinoresinol 4-*O*-β-D-glucopyranoside (**4**),[25] (+)-syringaresinol 4′-*O*-β-D-glucopyranoside (**5**),[26] armaoside (**6**),[27] 4-[(1*S*,2*R*)-1,3-dihydroxy-2-[4-[(1*E*)-3-hydroxy-1-propenyl]-2-methoxyphenoxy]propyl]-2-methoxyphenyl β-D-glucopyranoside (**7**),[28] scorzonoside (**8**),[29] and balanophonin 4-*O*-β-D-glucopyranoside (**9**)[30] based on their spectroscopic data compared with the reported data in the literature.

To study the anti-inflammatory effect of compounds (**1**–**9**), we tested their inhibitory effect on nitric oxide (NO) production by lipopolysaccharide (LPS)-stimulated microglial cells.[31] Among the isolates, the compound **7** weakly inhibited LPS-stimulated NO production with IC_{50} values of 59.83 μM (Table 3). However, none of the compounds showed significant cytotoxicity to the microglial cells.

Experimental

General Experimental Procedures Optical rotations were measured on a JASCO P-1020 polarimeter. UV spectra were recorded with a Shimadzu UV-1601 UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan). IR spectra were recorded on a JASCO FT/IR-4600 spectrometer. FAB and HR-FAB mass spectra were obtained using a JEOL JMS700 mass spectrometer. NMR spectra were recorded on a Bruker AVANCEIII 700 NMR spectrometer operating at 700 MHz (^{1}H) and 175 MHz (^{13}C) with chemical shifts expressed in ppm (δ). Preparative HPLC was performed using a Gilson 306 pump with a Shodex refractive index detector and a Phenomenex Luna 10 μm column (250 × 10 mm). Silica gel 60 (Merck, Darmstadt, 70–230 mesh, and 230–400 mesh) and RP-C_{18} silica gel (Merck, 230–400 mesh) were used for col-

Table 3. Inhibitory Effects of Compounds **1–9** on NO Production in LPS-Activated BV-2 Cells

Compounds	IC_{50}[a] (μM)	Cell viability[b] (%)
1	265.79	106.35 ± 6.40
2	197.44	116.47 ± 2.33
3	90.1	118.48 ± 50.20
4	96.33	93.13 ± 4.78
5	237.34	92.61 ± 7.41
6	117.37	108.5 ± 7.18
7	59.83	113.61 ± 3.65
8	436.92	111.32 ± 3.65
9	353.8	116.83 ± 5.8
L-NMMA[c]	24.78	106.46 ± 4.96

a) IC_{50} value of each compound was defined as the concentration (μM) inducing 50% inhibition of NO production in LPS-activated BV-2 cells. *b*) Cell viability after treatment with 20 μM of each compound was determined by MTT assay and expressed as a percentage (%). The results represent the averages of three independent experiments, and the data are expressed as mean ± S.D. *c*) L-NMMA represents positive control.

umn chromatography. TLC was performed using Merck precoated silica gel F_{254} plates and RP-18 F_{254s} plates. Spots were detected under UV light or by heating after spraying with 10% H_2SO_4 in EtOH (v/v).

Plant Material *F. simplex* stems (7.0 kg) were collected at Jecheon in Chungcheongbuk-do, Korea, in June 2012, and authenticated by one of the authors (K. R. Lee). A voucher specimen (SKKU-NPL-1209) was deposited at the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

Extraction and Isolation The stems of *F. simplex* (7.0 kg) were extracted with 80% MeOH under reflux. The filtered MeOH extract was concentrated under reduced pressure to yield a viscous concentrate (400 g), which was suspended in water (3.2 L) and solvent-partitioned successively to yield hexane (24 g), $CHCl_3$ (14 g), EtOAc (50 g), and BuOH (270 g) extracts. The EtOAc soluble fraction (18.0 g) was subjected to CC [RP-C_{18} (360.0 g), MeOH–H_2O 40 : 60–100 : 0]: Fractions E1–E8. Fraction E1 (14.2 g) was separated by CC (SiO_2 (100 g), $CHCl_3$–MeOH 5 : 1–1 : 1): Fractions. E11–E16. Fraction E13 (75 mg) was purified by preparative HPLC (RP-C_{18}, MeCN–H_2O 30 : 70; 2 mL/min): **9** (t_R 29.5 min; 5 mg). Fraction E4 (1.0 g) was separated over a Sephadex LH-20 (MeOH–H_2O 4 : 1) and further separated by semi-preparative HPLC (RP-C_{18}, MeCN–H_2O 40 : 60; 2 mL/min) to yield **1** (t_R 18.2 min; 2 mg). The BuOH soluble fraction (30.0 g) was separated by CC (SiO_2 (600 g), $CHCl_3$–MeOH 5 : 1–1 : 1): Fractions B1–B6. Fraction B2 (1.1 g) was subjected to CC [RP-C_{18} (40.0 g), MeOH–H_2O 30 : 70–100 : 0] and further separated by semi-prep. HPLC (RP-C_{18}; MeCN–H_2O 20 : 80; 2 mL/min) to yield **4** (t_R 19.8 min; 12 mg). Fraction B3 (2.5 g) was subjected to CC (RP-C_{18} (40.0 g), MeOH–H_2O 30 : 70–100 : 0): Fractions B31–B31-16. Fraction B32 (120 mg) was purified by preparative HPLC (RP-C_{18}, MeCN–H_2O 20 : 80; 2 mL/min): **7** (t_R 22.5 min; 15 mg) and **2** (t_R 26.1 min; 11 mg). Fraction B33 (140 mg) was purified by preparative HPLC (RP-C_{18}, MeCN–H_2O 20 : 80; 2 mL/min): **6** (t_R 16.5 min; 30 mg). Fraction B35 (120 mg) was purified by preparative HPLC (RP-C_{18}, MeCN–H_2O 20 : 80; 2 mL/min): **8** (t_R 20.5 min; 45 mg). Fraction B37 (50 mg) was purified by preparative HPLC (RP-C_{18}, MeCN–H_2O 20 : 80; 2 mL/min): **3** (t_R 12.5 min; 4 mg). Fraction B4 (8.7 g) was subjected to CC [RP-C_{18} (100.0 g), MeOH–H_2O 30 : 70–100 : 0] and further separated by semi-preparative HPLC (RP-C_{18}; MeCN–H_2O 25 : 75; 2 mL/min) to yield **5** (t_R 25.6 min; 5 mg).

Firmiside A (**1**)

Colorless gum; $[\alpha]_D^{25}$ −27.0 (c = 0.05, MeOH); UV λ_{max} (MeOH) nm (logε): 284 (1.1), 234 (1.8), 211 (2.9); ^{1}H (700 MHz) NMR data (Table 1); ^{13}C (175 MHz) NMR data (Table 2); HR-FAB-MS: 555.1470 {$[M + Na]^+$, $C_{26}H_{28}NaO_{12}$; Calcd 555.1473}.

Firmiside B (**2**)

Colorless gum; $[\alpha]_D^{25}$ 19.0 (c = 0.02, MeOH); CD (MeOH): 226 (+1.5), 236 (−1.3), 344 (+0.6); UV λ_{max} (MeOH) nm (logε): 330 (1.2), 231 (1.9), 219 (3.1); IR (KBr): 3406, 2937, 1664, 1596, 1501, 1464, 1424, 1332, 1217, 1129, 1072, 1033, 826, 648; ^{1}H (700 MHz) NMR data (Table 1); ^{13}C (175 MHz) NMR data (Table 2); HR-FAB-MS: 571. 1785 ($[M + Na]^+$, $C_{27}H_{32}NaO_{12}$; Calcd 571.1786).

Firmiside C (**3**)

Colorless gum; $[\alpha]_D^{25}$ 19.6 (c = 0.03, MeOH); CD (MeOH) 232 (−2.0); UV λ_{max} (MeOH) nm (logε): 336 (1.6), 220 (2.0), 206 (3.4); IR (KBr): 3385, 3940, 2835, 1662, 1596, 1511, 1465, 1423, 1271, 1223, 1135, 1032, 636; ^{1}H (700 MHz) NMR data (Table 1); ^{13}C (175 MHz) NMR data (Table 2); HR-FAB-MS: 559.1785 {$[M + Na]^+$, $C_{26}H_{32}NaO_{12}$; Calcd 559.1786}.

Enzyme Hydrolysis of Compounds 2 and 3[32,33] Each compound (1.0 mg each) was hydrolyzed with hesperidinase (30 mg, from *Aspergillus niger*, Sigma-Aldrich, St. Louis, MO, U.S.A.) at 40°C for 60 h. The hydrolysate was extracted with $CHCl_3$, and each $CHCl_3$ extract was evaporated under reduced pressure. The reaction mixtures of **2** and **3** were purified on silica gel [Waters Sep-Pak Vac 6cc ($CHCl_3$–MeOH, 10 : 1)] to yield **2a** and **3a**, which were identified by comparing their ^{1}H-NMR data with those reported in the literatures. The each H_2O layer was identified as D-glucose by co-TLC with an authentic sample [silica gel, solvent: $CHCl_3$–MeOH–H_2O (2 : 1 : 0.2), *Rf* value: 0.20] and its optical rotation values: $[\alpha]_D^{25}$ +52.1 (c = 0.04, MeOH) from **2**; $[\alpha]_D^{25}$ +75.0 (c = 0.05, MeOH) from **3**.

Measurement of NO Production in LPS-Activated BV-2 Cells[31] The BV-2 cell line was originally developed by Dr. V. Bocchini at the University of Perugia (Perugia, Italy). BV-2 microglial cells were stimulated with 100 ng/mL LPS with or without samples for 24 h. Nitrite in the culture media, a soluble oxidation product of NO, was measured using the Griess reaction. The supernatant (50 μL) was harvested and mixed with an equal volume of Griess reagent (1% sulfanilamide, 0.1% *N*-1-napthylethylenediamine dihydrochloride in 5% phosphoric acid). After 10 min, the absorbance at 540 nm was measured using a microplate reader (Emax, Molecular Device, Sunnyvale, CA, U.S.A.). N^G-Monomethyl-L-arginine (L-NMMA, Sigma), a well-known nitric oxide synthase inhibitor served as a positive control. Cell viability was measured using a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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