

A new neolignan and lignans from the stems of *Lindera obtusiloba* Blume and their anti-allergic inflammatory effects

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Abstract A new neolignan, linderin A (**1**), together with six known lignans, (+)-xanthoxyol (**2**), pluviatilol (**3**), actifolin (**4**), (+)-syringaresinol (**5**), (+)-(7*S*,8*R*,8'*R*)-acuminatolide (**6**), and (+)-9'-*O*-trans-feruloyl-5,5'-dimethoxyariciresinol (**7**) were isolated from the stems of *Lindera obtusiloba* Blume (Lauraceae). Their chemical structures were elucidated by a combination of spectroscopic analysis and chemical reaction, and the absolute configuration of **1** was determined by Mosher's esterification. The effect of compounds **1–7** on tumor necrosis factor (TNF)- α , interleukin(IL)-6, and their inhibitory activity of histamine release were examined using human mast cells. Among the lignans tested, compounds **1**, **3**, **4**, **6**, and **7** inhibited release of histamine from mast cells. Especially, compounds **1** and **4** suppressed the gene expressions of pro-inflammatory

cytokines, TNF- α , and IL-6 in human mast cells. Our findings suggest that the lignan constituents in *L. obtusiloba* may contribute to its anti-allergic inflammatory effects.

Keywords: *Lindera obtusiloba* · Lignan · Linderin A · Anti-allergic effect

Introduction

Lindera obtusiloba Blume, which belongs to the family of Lauraceae, is widely distributed in Japan, China, and Korea. This plant has been used as a traditional medicine for the treatment of fever, abdominal pain, extravasation, inflammation and improvement of blood circulation (Yook 1989). Previous phytochemical studies revealed that this medicinal plant contains several secondary metabolites such as lignans (Kwon et al. 1999), neolignans, flavonoids (Park et al. 1996), and butanolides (Kwon et al. 2000). Furthermore, the lignans which have tetrahydrofuran moiety such as actifolin, pluviatilol, 5,6-dihydroxymatairesinol, (+)-syringaresinol, and (+)-9'-*O*-trans-feruloyl-5,5'-dimethoxyariciresinol were isolated from the methylene chloride soluble fraction of this plant (Kwon et al. 1999). These tetrahydrofuranoid lignans from *L. obtusiloba* have been reported to have cytotoxic activity against a few panels of human tumor cell lines. Moreover, lignans which have tetrahydrofuran moiety isolated from the flower buds of *Magnolia fargesii* showed significant superoxide radical scavenging activity. In a recent study, we demonstrated that an extract of *L. obtusiloba* had anti-allergic inflammatory effects (Choi et al. 2011). To verify the active principles in the plant, we isolated a series of lignans including a new neolignan (**1**) and evaluated their anti-

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allergic activity. In this paper, we describe the isolation and structure determination of a new neolignan, linderin A (**1**), as well as the anti-allergic effect of isolates (**1–7**) in human mast cells. Of the six known lignans (**2–7**), (+)-xanthoxyl (**2**) and (+)-(7*S*,8*R*,8'*R*)-acuminatolide (**6**) were isolated for the first time from this species.

Materials and methods

General experimental procedures

The NMR spectra were recorded on Bruker 250 MHz (DMX 250) and JEOL ECA-500 MHz spectrometers, and chemical shifts were recorded in ppm downfield from TMS as the internal standard. The HR-EI-MS spectra were performed on JMS-700 mass spectrometer (JEOL, Japan). Optical rotations were measured using a JASCO DIP-1000 (Jasco, Japan). Column chromatography was carried out on Merck Silica gel (70–230 mesh) and Merck Lichroprep RP-18 gel (40–63 μ m). Flash chromatography was conducted using a RediSep[®] *R_f* Column (120 g, NE, USA). TLC was performed on aluminum plates precoated with Kieselgel 60 F₂₅₄ (Merck). For preparative HPLC, LC-10AD pump (Shimadzu, Japan), SPD-10A detector (Shimadzu) and Shim-Pack Prep-ODS (20 $\times$ 250 mm) column were used.

Plant material

Stems of *L. obtusiloba* purchased from Yak-Ryung-Si Market in Daegu, Korea and were identified by Dr. Seung Ho Lee at the College of Pharmacy, Yeungnam University. A voucher specimen (YU00190) has been deposited in the Natural Product Laboratory at the College of Pharmacy, Yeungnam University, Korea.

Reagents and cell culture

Compound 48/80, anti-dinitrophenyl (DNP) IgE, DNP human serum albumin (HSA), pyrrolidine dithiocarbamate (PDTC), phorbol 12-myristate 13-acetate and calcium ionophore.

A23187 (PMACI) were purchased from the Sigma Chemical Co. (St. Louis, MO, USA). Anti-TNF- α and IL-6 antibodies were purchased from R&D Systems Inc. (Minneapolis, MN, USA). The human mast cell line (HMC-1) was grown in Iscove's media (Life Technologies, Grand Island, NY, USA) supplemented with 10 % fetal bovine serum (FBS) and 2 mmol/L glutamine at 37.8 °C in 5 % CO₂.

Extraction and isolation

Dried stems of *L. obtusiloba* (10 kg) were extracted with MeOH (50 L $\times$ 3) at room temperature. The extract was

concentrated in vacuo to afford a black gum (282 g), which was dissolved in water and continuously partitioned with solvents, then concentrated to give extracts of *n*-hexane (56.2 g), EtOAc (58.7 g), *n*-BuOH (60.4 g), and water (107.1 g), respectively. The EtOAc-soluble extract (50.1 g) was chromatographed on a silica gel column eluted with a gradient mixture of 100 % MC to 50 % MeOH to afford nine fractions (LOET1–LOET9). Fraction 2 (5.9 g) was chromatographed on a MPLC normal phase column (RediSep[®] *R_f* Column, 120 g) with *n*-hexane and MeOH gradient mixture (10:0 to 0:10) to afford nine subfractions (LOET2-1–LOET2-9). LOET2-6 (263.3 mg) was chromatographed over Silica gel column using a gradient of MC-acetone (1:19 to 1:1) to obtain five subfractions (LOET2-6-1–LOET2-6-5). LOET2-6-2 (5.6 mg) was purified by preparative HPLC with a gradient of MeOH–H₂O (1:2 to 1:0) to afford compound **1** (3.2 mg). LOET2-4 (652.6 mg) was separated by using preparative HPLC with a gradient of MeOH–H₂O (3:2 to 1:5), resulting in the isolation of compounds **2** (19.2 mg), **3** (31.7 mg), **4** (19.2 mg), and **5** (2.6 mg). LOET2-3 (39.3 mg) was also purified using HPLC with a gradient of MeOH–H₂O (1:2 to 1:0) to afford compound **6** (18.9 mg). LOET2-8 (211.4 mg) was subjected to a normal phase MPLC using a gradient of CHCl₃–EtOAc (1:0 to 0:1) to yield four subfractions (LOET2-8-1–LOET2-8-4). LOET2-8-2 (22.2 mg) was purified by preparative HPLC with a gradient of MeOH–H₂O (1:2 to 1:0) to afford compound **7** (6.2 mg).

Linderin A (**1**)

Yellowish wax, $[\alpha]_D^{20} +53.3$ (*c* 0.023, MeOH); HR-EI-MS at *m/z*: 386.1045 [*M*]⁺ (Calcd for C₂₀H₁₈O₈, 386.1002); ¹H and ¹³C NMR: see Table 1.

Preparation of (S)- and (R)-MPTA ester derivatives of **1** by Mosher's esterification method

(*R*)-MTPA (α -methoxy- α -(trifluoromethyl)phenyl-acetyl) esters of compound **1** was prepared using Mosher's esterification method performed in NMR tubes. Compound **1** (1.0 mg) and 4-(dimethylamino)-pyridine (0.2 mg) were transferred into an NMR tube, and this mixture was dried under vacuum. Deuterated pyridine (0.5 mL) and (*S*)-(+)- α -methoxy- α -(trifluoromethyl)phenyl-acetyl chloride (6.0 μ L) were added into the NMR tube immediately under a N₂ gas stream, then the NMR tube was sealed and shaken to mix the sample and MTPA chloride evenly. The reaction NMR tube was permitted to stand at room temperature and monitored every 2 h by ¹H NMR. The derivatives of compound **1** were afforded completely after 6 h, and then the reaction was stopped by shaking the unsealed NMR tube under air (Su et al.

Table 1 NMR data of compound **1** (CD₃OD)

	δ_C^a	δ_H^b	HMBC	NOESY
1	136.1	—	—	
2	108.3	6.98, d (1.7)	C-1, 4, 6, 7	
3	149.2	—		
4	148.9	—		
5	108.9	6.74, d (7.9)	C-1, 3, 6	
6	121.8	6.88, dd (7.9, 1.7)	C-2, 4, 7	
7	85.9	4.55, d (8.6)	C-1, 2, 6, 8, 9, 10	H-8, 9, 10, 11
OCH ₂ O	102.4	5.93, s	C-4	
8	56.9	2.47, m	C-1, 7, 9, 10	H-7, 9, 10
9	64.8	4.37, m	C-7, 8, 10, 7'	H-7, 8, 10, 11
		4.51, dd (11.3, 5.3) ^c		
10	75.3	4.37, m ^c	C-7, 8, 11	H-7, 8, 9, 11
11	75.5	3.94, dd (9.5, 3.6)	C-7, 8, 10	H-7, 9, 10
		4.00, dd (9.5, 5.8)		
1'	124.9	—	—	
2'	110.1	7.16, d (1.7)	C-3', 4', 7'	
3'	149.3	—	—	
4'	153.4	—	—	
5'	108.9	6.85, d (8.2)	C-1', 3', 4'	
6'	126.4	7.45, dd (8.2, 1.7)	C-2', 4', 7'	
7'	167.1	—	—	
OCH ₂ O	103.4	6.05, s	C-4'	

^a Assignment based on HMQC and HMBC NMR data (125 MHz)

^b Assignment based on COSY and HMBC (500 MHz)

^c Signals partially overlapped

2002). In the manner described for (*R*)-MTPA ester of compound **1**, (*S*)-MTPA ester of compound **1** (1.0 mg) was reacted in a second NMR tube with (*R*)-MTPA chloride (6.0 μ L), and 4-(dimethylamino)-pyridine (0.2 mg) at room temperature for 6 h using deuterated pyridine (0.5 mL) as solvent, to afford the (*S*)-MTPA derivative of **1**.

(*S*)-MTPA ester of **1** (**1a**)

¹H NMR (500 MHz, pyridine-*d*₅): 5.8330 (1H, m, H-10), 4.8047 (1H, d, *J* = 7.6, H-7), 4.3278 (1H, br. d, *J* = 11.3 Hz, H-11), 4.1679 (1H, dd, *J* = 11.3, 4.6 Hz, H-11), 4.7138 (2H, d, *J* = 6.2 Hz, H-9).

(*R*)-MTPA ester of **1** (**1b**)

¹H NMR (500 MHz, pyridine-*d*₅): 5.8407 (1H, m, H-10), 4.8125 (1H, d, *J* = 7.6, H-7), 4.3385 (1H, br. d, *J* = 11.2 Hz, H-11), 4.1597 (1H, dd, *J* = 11.2, 4.7, H-11), 4.7279 (2H, d, *J* = 6.2 Hz, H-9).

(+)-xanthoxyl (**2**)

White wax, $[\alpha]_D^{20}$ +84.9 (*c* 0.1, CHCl₃); ¹H NMR (250 MHz, CDCl₃): δ 6.77–6.88 (6H, m, Ar–H), 5.93 (2H, s, OCH₂O), 4.71 (1H, d, *J* = 4.6 Hz, H-2), 4.70 (1H, d,

J = 4.6 Hz, H-6), 4.14–4.27 (2H, m, H-4), 3.87 (3H, s, OMe), 3.71–3.92 (2H, m, H-8), 2.97–3.11 (2H, m, H-1); ¹³C NMR (63 MHz, CDCl₃): δ 147.9 (C-3'), 147.1 (C-4'), 146.7 (C-3'), 145.2 (C-4'), 135.0 (C-1'), 132.8 (C-1'), 119.3 (C-6'), 118.9 (C-6'), 114.3 (C-5'), 108.6 (C-5'), 108.1 (C-2'), 106.5 (C-2'), 101.0 (OCH₂O), 85.8 (C-2), 85.8 (C-6), 71.7 (C-8), 71.6 (C-4), 55.9 (C-1), 54.3 (C-5), 54.1 (OMe).

(+)-(7*S*,8*R*,8'*R*)-acuminatolide (**6**)

Brown wax, $[\alpha]_D^{20}$ +22.3 (*c* 0.1, MeOH); ¹H NMR (500 MHz, CD₃OD): δ 6.89 (1H, d, *J* = 1.8, H-2), 6.85 (1H, dd, *J* = 8.0, 1.8 Hz, H-5), 6.79 (1H, d, *J* = 8.0 Hz, H-6), 5.93 (2H, s, H-3) 4.67 (1H, d, *J* = 6.5 Hz, H-7), 4.52 (1H, dd, *J* = 9.7, 6.9 Hz, H-9), 4.36 (1H, dd, *J* = 9.7, 2.1, H-9'), 4.28 (1H, dd, *J* = 9.0, 9.0 Hz, H-9), 4.08 (1H, dd, *J* = 9.7, 2.1 Hz, H-9'), 3.54 (1H, m, H-8), 3.16 (1H, m, H-8'); ¹³C NMR (63 MHz, CD₃OD): δ 180.9 (C-7'), 149.5 (C-3), 148.9 (C-4), 135.0 (C-1), 120.8 (C-6), 109.1 (C-5), 107.5 (C-2), 102.5 (OCH₂O), 87.5 (C-7), 71.7 (C-9'), 71.0 (C-9), 49.5 (C-8'), 47.5 (C-8).

Real-time polymerase chain reaction (PCR)

Quantitative real-time PCR was carried out using the Thermal Cycler Dice TP850 (Takara Bio Inc., Shiga, Japan)

according to the manufacturer's protocol. Total RNA was isolated from ear tissues of each group. The conditions for PCR were similar to ones previously described (Kim et al. 2007). Briefly, 2 μ L of cDNA (100 ng), 1 μ L of sense and antisense primer solution (0.4 μ M), 12.5 μ L of SYBR Premix Ex Taq (Takara Bio Inc.), and 9.5 μ L of H₂O were mixed together to obtain a final 25 μ L reaction mixture in each reaction tube. The primers used for PCR were (IL-4 F 5'-ACAGGAGAAGGGACGCCAT, R 5'-GAAGCCGTA-CAGA CGAGCTCA; IL-13 F 5'-GCAACATCAACAG GACCAGA, R 5'-GTCAGGGAATCCAGGGCTAC; IL-31 F 5'-TCGGTCATCATAGCACATCTGGAG, R 5'-GC ACAGTCCCTTTGGAGTTAAGTC; TNF- α F 5'-CCTGT AGCCACGTCGTAGC, R 5'-TTGACCTCAGCGCT-GAGTTG). The amplification conditions were 10 s at 95 °C, 40 cycles of 5 s at 95 °C and 30 s at 60 °C, 15 s at 95 °C, 30 s at 60 °C, and 15 s at 95 °C. The normalization and quantification of mRNA expression was performed using the TP850 software supplied by the manufacturer.

Histamine assay

The histamine content was measured by the *o*-phthalaldehyde spectrofluorometric procedure as previously described (Kim et al. 2006). The serum was separated from the released histamine by centrifugation at 400 $\times$ g for 5 min at 4 °C. The fluorescent intensity was measured at an excitation 355 nm and emission 450 nm using a Perkin-Elmer Fluorescence Spectrometer LS-50B (Norwalk, CT, USA).

Statistical analysis

Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC, USA). Treatment effects were analyzed using ANOVA followed by Dunnett's multiple range tests. Significance was set at $P < 0.05$.

Results and discussion

We isolated a new neolignan, linderin A (**1**), together with six known lignans, (+)-xanthoxylol (**2**) (Takanu et al. 2001), pluviatilol (**3**) (Kwon et al. 1999), actiforin (**4**) (Kwon et al. 1999), (+) syringaresinol (**5**) (Kwon et al. 1999), (+)-(7*S*,8*R*,8'*R*)-acuminatolide (**6**) (Kuo et al. 2011), and (+)-9'-*O*-trans-feruloyl-5,5'-dimethoxylaric-iresinol (**7**) (Kwon et al. 1999) from the stems of *L. obtusiloba* (Fig. 1). Their chemical structures were elucidated by a combination of spectroscopic analysis and chemical reaction. The absolute configuration of **1** was determined by Mosher's esterification.

Compound **1** was isolated as a yellowish wax, $[\alpha]_D^{20} +53.3$ (c 0.023, MeOH). The molecular formula was determined as C₂₀H₁₈O₈ from the HR-EI-MS at m/z : 386.1045 [M]⁺ (Calcd for C₂₀H₁₈O₈, 386.1002). The presence of a tetrahydrofuran and two benzodioxol groups were suggested by ¹H NMR spectrum, which showed seven tetrahydrofuran protons at δ_H 4.55 (1H, d, J = 8.6 Hz),

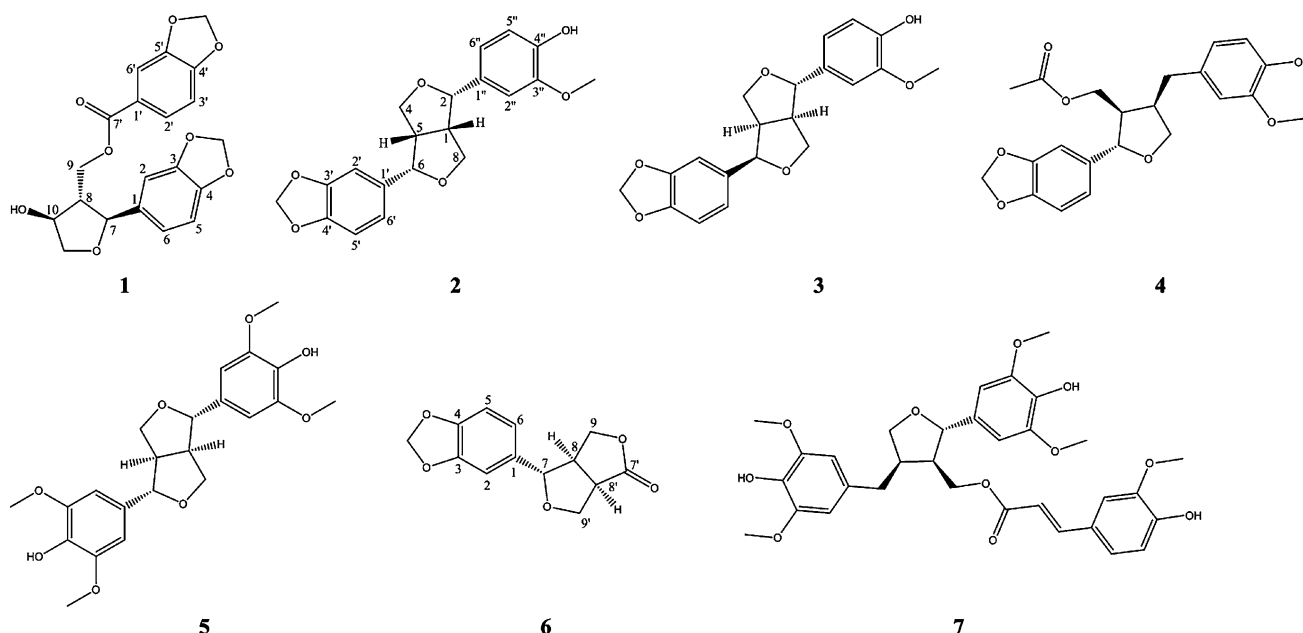


Fig. 1 Structures of compounds **1–7** isolated from *L. obtusiloba*

4.51 (1H, dd, $J = 11.3, 5.3$ Hz), 4.37 (1H, m), 4.37 (1H, m), 4.00 (1H, dd, $J = 9.5, 5.8$ Hz), 3.94 (1H, dd, $J = 9.5, 3.6$ Hz), and 2.47 (1H, m) together with dioxymethylene peaks shown at δ_{H} 6.05 (2H, s) and 5.93 (2H, s), and six aromatic protons including a couple of ABX system signals at δ_{H} 7.45 (1H, dd, $J = 8.2, 1.7$ Hz), 7.16 (1H, d, $J = 1.7$ Hz), 6.85 (1H, d, $J = 8.2$ Hz), 6.98 (1H, d, $J = 1.7$ Hz), 6.88 (1H, dd, $J = 7.9, 1.7$ Hz), and 6.74 (1H, d, $J = 7.9$ Hz). A tetrahydrofuran, two benzodioxol, two dioxymethylene, and a carboxyl groups were confirmed by ^{13}C NMR data, where the tetrahydrofuran moiety was observed at δ_{C} 85.9, 75.5, 75.3, 64.8, 56.9, the benzodioxol groups were detected at δ_{C} 153.4, 149.3, 149.2, 148.9, 136.1, 126.4, 124.9, 121.8, 110.1, 108.9, 108.9, 108.3, the dioxymethylenes were displayed at δ_{C} 103.4, 102.4, and the carboxyl group was shown at δ_{C} 167.1. The position of carboxyl group was demonstrated by the HMBC spectrum showing correlation peaks of H-9 and H-6' resonating at each δ_{H} 7.45, 4.37 with C-7' (Fig. 2). The relative stereochemistry of **1** was proposed by coupling constant value, and nuclear overhauser effect (NOE) correlation. The *trans* configuration of C-7 and C-8 was determined by its large coupling constant ($J_{7,8} = 8.6$ Hz) (Lee et al. 2009), and also verified by correlation peaks between H-7 and H-10 in NOESY spectrum (Table 1). Mosher's esterification (Su et al. 2002) was used to determine the stereochemistry on C-10 of **1**, and to calculate the difference between the (*S*)-MTPA ester and (*R*)-MTPA ester, as shown in Fig. 3. However, the $\Delta\delta$ ($\delta_{\text{S}} - \delta_{\text{R}}$) values has a shade differences, these small values can be explained by anisotropy effect of the aromatic ring on the tetrahydrofuran (Kubo et al. 1996; Lee et al. 2009). Therefore, the absolute configuration of

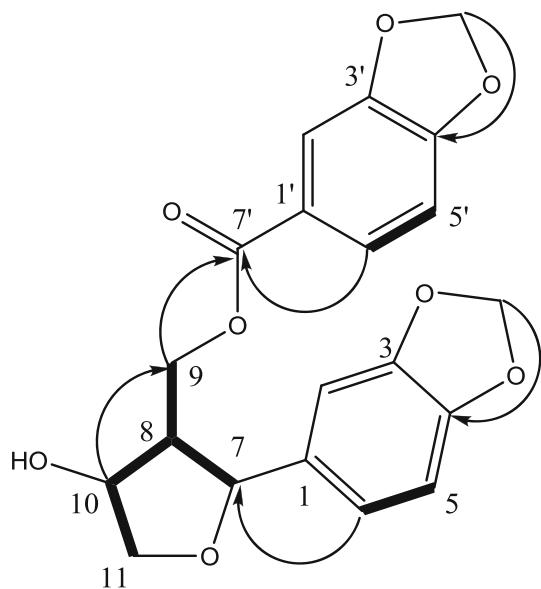


Fig. 2 ^1H - ^1H COSY (—) and Key HMBC (→) correlations of **1**

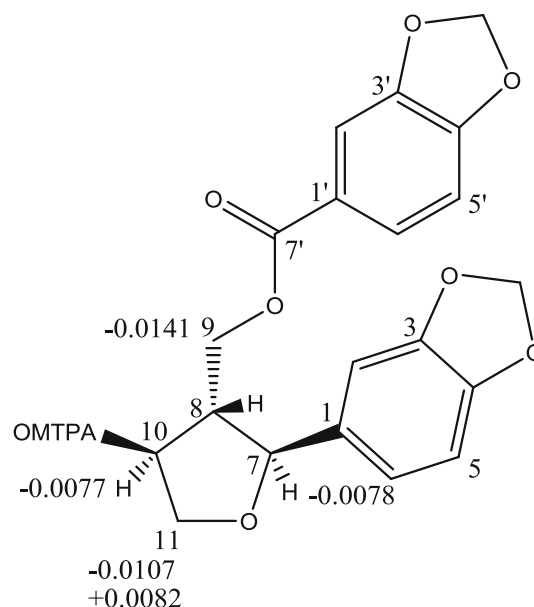


Fig. 3 $\Delta\delta$ ($\delta_{\text{S}} - \delta_{\text{R}}$) Values of MPTA esters of **1** by Mosher's esterification method

C-10 was determined to be *S*. Consequently, the structure of **1** was determined to be ((*7S,8S,10S*)-2-(benzo[d][1,3]dioxol-5-yl)-4-hydroxytetrahydrofuran-3-yl)methylbenzo[d][1,3]dioxole-5-carboxylate (**1**), and was named linderin A.

Compound **6** was isolated as brown wax, $[\alpha]_{\text{D}}^{20} +22.3$ (c 0.1, MeOH). The ^1H NMR spectrum of **6** showed a typical ABX spin system at δ_{H} 6.89 (1H, d, $J = 1.8$ Hz), 6.85 (1H, dd, $J = 8.0, 1.8$ Hz), 6.79 (1H, d, $J = 8.0$ Hz), and an oxygenated methylene group at δ_{H} 5.93 (2H, s) together with five oxygenated protons at δ_{H} 4.67 (1H, d, $J = 6.5$ Hz), 4.50 (1H, dd, $J = 9.7, 6.9$ Hz), 4.36 (1H, dd, $J = 9.7, 2.1$ Hz), 4.28 (1H, dd, $J = 9.0, 9.0$ Hz), 4.08 (1H, dd, $J = 9.7, 2.1$ Hz), and two methin signals at δ_{H} 3.54 (1H, m), and 3.16 (1H, m) were also confirmed by the ^1H NMR data. The ^{13}C NMR and HMQC spectra showed carbon signals for six methines, three methines, and four quaternary carbons. The position of dioxymethylene was determined by HMBC correlation peak at δ_{H} 5.93 (2H, s) with C-3. The absolute configuration of this compound was elucidated by the comparison of the optical rotation and coupling constants with reported values (Kuo et al. 2011). Thus, the structure of **6** was determined as (+)-(*7S, 8R, 8'R*)-acuminatolide, which was isolated for the first time from this plant.

Of the seven lignans, compounds **2** and **6** were isolated for the first time from this species. Lignans from *Lindera* genus have been reported to have superoxide radical scavenging activity (Hironobu et al. 2002; Kwon et al. 1999). In our recent study, an extract of *L. obtusiloba* has

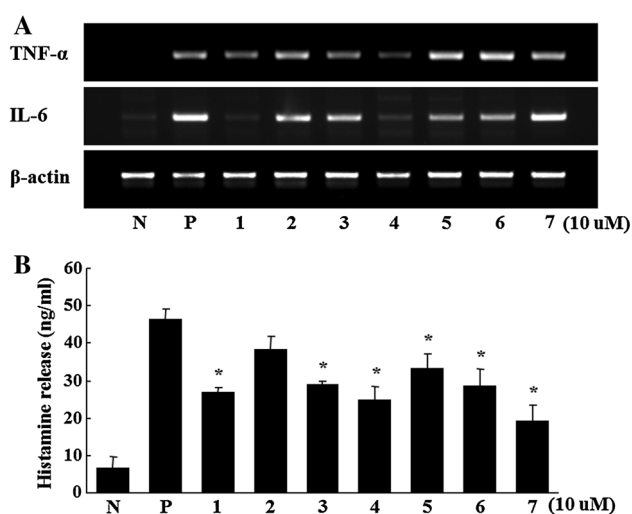


Fig. 4 Anti-allergic inflammatory effects of compounds **1–7** isolated from *L. obtusiloba* on human mast cells. HMC-1 cells were pre-incubated with compounds **1–7** for 30 min prior to incubation with PMA (20 nM) and calcium ionophore A23187 (1 μ M). **a** Effect of compounds **1–7** on the expression of pro-inflammatory cytokines. Extraction and analysis of mRNA was performed as described in “Materials and methods” section. **b** Effect of compounds **1–7** on histamine release in mast cells. Histamine content was measured by spectrofluorometer. Each bar represents the mean $\pm$ SEM of three independent experiments. *Significant difference at $P < 0.05$

shown to exert anti-allergic inflammatory effect by inhibiting histamine release and pro-inflammatory cytokine production (Choi et al. 2011). To verify the anti-allergic effect, we evaluated the inhibitory effects of compounds **1–7** on histamine release and gene expression of IL-6 and TNF- α in human mast cells. As shown in Fig. 4a, linderin A (**1**) and actiforin (**4**) significantly inhibited the production of IL-6 and TNF- α . In addition, the lignans **1** and **4** suppressed histamine release from mast cells (Fig. 4b). These results suggest that the lignan constituents may be responsible for the anti-allergic inflammatory effect of *L. obtusiloba*.

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