Ester Derivatives from Tannase-treated Prunioside A and Their Anti-inflammatory Activities

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Prunioside A, isolated from the methanol extract of *Spiraea prunifolia* var. *Simpliciflora*'s root, is composed of coumaroyl, monoterpene-type, and glucosyl units. The esterase activity of tannase was used to remove the *p*-coumaroyl and glucopyranosyl groups. The enzymatically hydrolyzed compound was reacted with various acyl chlorides to synthesize its ester derivatives, which showed the inhibitory effects on NO production in murine machrophage–like RAW 264.7 cells stimulated with lipopolysaccharide and interferon-γ.

Key Words : *Spiraea prunifolia*, Prunioside A, Nitric oxide, NO production, Inhibitory effects

Introduction

A new terpene glucoside, prunioside A (**1**), has been recently isolated from the roots of *Spiraea prunifolia* var. *simpliciflora* (Rosaceae), a deciduous and latifoliate shrub, which have been traditionally used for the treatment of fever and emetic conditions.[1,2] The new compound has been determined to consist of *p*-coumaroyl, monoterpene-type and glucosyl units. Although this naturally occurring glucoside did not show significant biological activity of anti-inflammatory effect, its derivatives have been of much interest since the acetylated derivative had been reported to show the inhibitory effect on nitric oxide (NO) production in murine macrophage-like RAW 264.7 cells stimulated with interferon-γ (INF-γ) and lipopolysaccharide (LPS).[3]

NO along with prostaglandin E_2 (PGE_2) and cytokines such as interlukin-1 beta (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α), is well known for the involvement in the development of inflammation.[4,5] The production of NO as an inflammatory mediator has been found in macrophages exposed by immune stimulant such as LPS and INF-γ.[6,7] Two distinct types of NO synthases (NOS) have been identified as constitutive NOS (cNOS) and inducible NOS (iNOS). The inducible enzyme (iNOS) responsible for the overproduction of NO plays important roles in macrophage-mediated cytotoxicity. Although NO is involved in the host defence mechanism, the prolonged NO production has been known to contribute to the pathogenesis of various inflammatory and autoimmune diseases.[8,9] Therefore, the natural or synthetic compounds having the inhibitory effect on NO production by iNOS may be promising therapeutic agents for various inflammatory diseases.

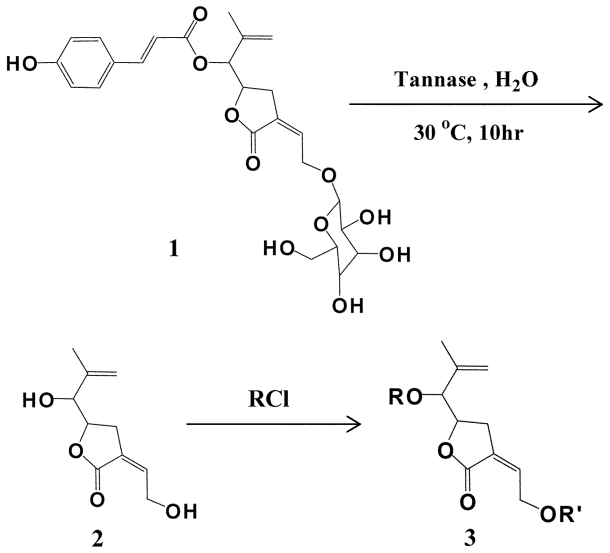
In the previous result, we report a series of prunioside A derivatives synthesized from 3-(4-Hydroxy-phenyl)-acrylic acid 1-[4-(2-hydroxy-ethylidine)-5-oxo-tetrahydro-furan-2-yl]-2-methyl-allyl ester which was prepared by the enzyme reaction of prunioside A. with β-Glucosidase. It was a surprise that those derivatives with various substituents revealed substantial inhibitory effects on NO production in murine cells respectively, whereas the prunioside A itself did not show much effects. This result implies that glucose group has blocked the potential activity of the molecule for the NO inhibition effect. The moderate NO inhibition effects reported for those prunioside A derivatives would also indicate that further removal of hydroxy-phenyl group would give enhanced potency for NO inhibition effect.

In the present work, further chemical modification of prunioside A was carried out by tannase followed by esterification with various acyl halides, and the biological activities of the ester derivatives on NO generation in murine macrophage-like RAW 264.7 cells stimulated with LPS and INF-γ were investigated.

Experimental Section

General experimental procedures. ESIMS data were recorded on a MicroMass Quatro LC with electro-spray ionization. NMR spectra were measured in acetone-d_6 using a JEOL Eclipse-500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), and chemical shifts were referenced relative to the corresponding residual solvent signals (acetone-d_6: δ 2.04/29.9). HPLC separations were performed on a Symmetry Prep C_{18} column (1.9 × 30 cm; 7-mm particle size; flow rate of 4 mL/min). Compounds were monitored by measuring UV absorption at 210 and 254 nm on a Hewlett-Packard HP 8453 spectrophotometer.

Extraction and purification of prunioside A (1). The roots of *S. prunifolia* were collected from Iksan City, Chonbuk Province, Korea in May 2002 and dried as previously described.[3] Prunioside A was purified from the methanol extract of the air-dried roots (1 kg) of *S. prunifolia* according to the previous method.[10]



Scheme 1

Enzymatic hydrolysis of prunioside A (1) with tannase. A solution of **1** (80 mg) in H_2O (5 mL) was incubated with 80 mg of tannase (49 units/mg, *Aspergillus oryzae*, Wako) at 30 °C for 12 h. The reaction mixture was extracted with EtOAc (3 × 5 mL). Compound **2** (19 mg), 3-(2-Hydroxy-ethylidene)-5-(1-hydroxy-2-methyl-allyl)-dihydro-furan-2-one, was obtained by reversed-phase HPLC from the dried organic residue (Scheme 1); ^{1}H NMR (500 MHz, acetone-d_6): δ 1.77 (3H, *s*, H-10), 2.81 (1H, *m*, H-4), 2.91 (1H, *m*, H-4), 4.08 (1H, *m*, H-6), 4.59 (2H, *m*, H-1), 4.65 (1H, *ddd*, *J* = 8.3, 5.1, 5.1 Hz, H-5), 4.91 (1H, *br s*, H-8), 5.05 (1H, *br s*, H-8), 6.27 (1H, *m*, H-2); ^{13}C NMR: δ 17.8, 30.8, 58.1, 76.6, 78.8, 112.5, 125.2, 142.4, 144.6, 169.3; ESI-MS: *m/z* 221 (100%, M + Na^+).

Acylation of compound 2. To a solution of compound **2** (3 mg, 1.52 × 10^{-5} mol) and 4-*N*,*N*-dimethylamino-pyridine (0.3 mg) in acetonitrile (2 mL) was added acid chloride (8-10 μL), and the resulting solution was stirred for 10-15 min at room temperature. The residue was redissolved in EtOAc after evaporation of the reaction solvent under N_2 and extracted with H_2O (2 × 2 mL). The organic phase was evaporated again, and the dried organic residue was subjected to reversed-phase HPLC to afford the derivatives (**3**).

Benzoic acid 2-[5-(1-benzoyloxy-2-methyl-allyl)-2-oxo-dihydro-furan-3-ylidene]-ethyl ester (4). Benzoyl chloride (10 μL, 7.1 × 10^{-5} mol) was used and the reaction was allowed in acetonitrile for 15 min at room temperature. The residue was purified to afford 4.5 mg (yield 73%) of compound **4**; ^{1}H NMR (500 MHz, acetone-d_6): δ 1.88 (3H, *s*), 2.93 (1H, *m*), 3.10 (1H, *m*), 5.08 (1H, *br, s*), 5.15 (1H, *br, s*), 5.08-5.15 (2H, *m*), 5.33 (2H, *m*), 5.59 (1H, *d*, *J* = 4.6), 6.36 (1H, *m*), 7.48 (4H, *m*), 7.59 (2H, *m*), 7.96 (4H, *m*); ^{13}C NMR: δ 17.8, 24.9, 63, 80.7, 85.3, 107.6, 128.4, 128.4, 129.7, 129.7, 130.5, 130.5, 132.8, 132.8, 135.6, 136.2, 147.9, 165.8, 167, 167; ESI-MS: *m/z* 429 (100%, M + Na^+).

Cyclopentanecarboxylic acid 2-[5-(1-cyclopentane-carbonyloxy-2-methyl-allyl)-2-oxo-dihydro-furan-3-yl-idene]-ethyl ester (5). Cyclopentanecarbonyl chloride (10 μL, 7.0 × 10^{-5} mol) was allowed to react with compound **2** in acetonitrile (2 mL) for 15 min at room temperature. The amount of coumpound **5** after the separation was 3.8 mg (yield 64%); ^{1}H NMR (500 MHz, acetone-d_6): δ 1.56-1.91 (18H, *m*), 1.79 (3H, *s*), 2.77 (1H, *m*), 3.11(1H, *m*), 4.89 (1H, *ddd*, *J* = 5.0, 5.0, 8.3), 5.01 (1H, *br, s*), 5.04 (1H, *br, s*), 5.14 (2H, *m*), 5.30 (1H, *d*, *J* = 4.1), 6.24 (1H, *m*); ^{13}C NMR: δ 17.8, 22.8, 22.8, 24.9, 25.4, 25.4, 41.3, 41.6, 63.7, 80.7, 85, 107.6, 135.6, 136.2, 147.9, 165.5, 176, 176; ESI-MS: *m/z* 413 (100%, M + Na^+).

3-Methyl-but-2-enoic acid 2-{5-[2-methyl-1-(3-methyl-but-2-enoyloxy)-allyl]-2-oxo-dihydro-furan-3-ylidene}-ethyl ester (6). The reaction was performed with dimethyl-acryloyl chloride (10 μL, 8.4 × 10^{-5} mol) for 15 min at room temperature. Compound **6** (4.2 mg, yield 76%) was isolated after the separation procedures; ^{1}H NMR (500 MHz, acetone-d_6): δ 1.79 (3H, *s*), 1.91 (6H, *dd*, *J* = 1.4, 1.4), 2.14 (6H, *dd*, *J* = 1.4,1.4), 2.78 (1H, *m*), 3.08 (1H, *m*), 3.12 (1H, *m*), 4.90 (1H, *ddd*, *J* = 5.1, 5.1, 8.3), 5.02 (1H, *br, s*), 5.05 (1H, *br, s*), 5.15 (2H, *m*), 5.34 (1H, *d*, *J* = 5.1), 5.69 (1H, *m*), 5.71 (1H, *m*), 6.23 (1H, *m*); ^{13}C NMR: δ 17.8, 18.7, 18.7, 24.7, 24.7, 24.9, 63.5, 80.7, 85.8, 107.6, 113.8, 115.6, 135.6, 136.2, 147.6, 147.9, 149.1, 165.5, 171, 171; ESI-MS: *m/z* 385 (100%, M + Na^+).

Butyric acid 2-[5-(1-butyryloxy-2-methyl-allyl)-2-oxo-dihydro-furan-3-ylidene]-ethyl ester (7). Compound **7** (2.5 mg, yield 49%) was obtained from the reaction of butyryl chloride (10 μL, 9.4 × 10^{-5} mol) and compound **2** for 15 min at room temperature; ^{1}H NMR (500 MHz, acetone-d_6): δ 0.92 (6H, *m*), 1.61 (4H, *m*), 1.79 (3H, s), 2.31 (4H, *m*), 2.76 (1H, *m*), 3.11 (1H, *m*), 4.89 (1H, *ddd*, *J* = 5.1, 5.1, 8.7), 5.02 (1H, *br, s*), 5.05 (1H, *br, s*), 5.14 (2H, *m*) , 5.32 (1H, *d*, *J* = 4.6), 6.24 (1H, *m*); ^{13}C NMR: δ 13.4, 13.4, 17.8, 18.2, 18.2, 24.9, 35.9, 36.2, 63.4, 80.7, 85.7, 107.6, 135.6, 136.2, 147.9, 165.5, 172, 172; ESI-MS: *m/z* 361 (100%, M + Na^+).

Benzoic acid 2-[5-(1-hydroxy-2-methyl-allyl)-2-oxo-dihydro-furan-3-ylidene]-ethyl ester (8). The reaction of compound **2** with benzoyl chloride (8 μL, 5.7 × 10^{-5} mol) was performed for 10 min to afford 3.2 mg (yield 70%) of compound **8**; ^{1}H NMR (500 MHz, acetone-d_6): δ 1.78 (3H, *s*), 2.94 (1H, *m*), 3.02 (1H, *m*), 4.12 (1H, *br, s*), 4.74 (1H, *m*), 5.08 (1H, *br, s*), 4.93 (1H, *br, s*), 5.07 (1H, *br, s*), 5.40 (2H, *m*), 6.38 (1H, *m*), 7.52 (2H, *t*, *J* = 7.8), 7.63 (2H, *t*, *J* = 7.3), 8.02 (1H, *d*, *J* = 8.3); ^{13}C NMR: δ 17.6, 24.7, 63, 82, 84, 107.6, 128.4, 129.7, 130.5, 132.8, 135.6, 136.2, 147.9, 165.5, 167; ESI-MS: *m/z* 325 (100%, M + Na^+).

Cyclopentanecarboxylic acid 2-[5-(1-hydroxy-2-methyl-allyl)-2-oxo-dihydro-furan-3-ylidene]-ethyl ester (9). Cyclopentanecarbonyl chloride (8 μL, 6 × 10^{-5} mol) was reacted with compound **2** for 10 min. Compound **9** (3.2 mg, yield 72%) was obtained after the separation; ^{1}H NMR (500 MHz, acetone-d_6): δ 1.54-1.87 (9H, *m*), 1.77 (3H, *s*), 2.85 (1H, *m*), 2.98 (1H, *m*), 4.09 (1H, t), 4.69 (1H, *m*), 4.91 (1H, *br, s*), 5.05 (1H, *br, s*), 5.13 (2H, *m*), 6.19 (1H, *m*); ^{13}C NMR: δ 17.6, 22.8, 24.7, 25.4, 41.3, 63.7, 82, 84, 107.6, 135.6, 136.2, 147.9, 165.5, 176; ESI-MS: *m/z* 317 (100%, M + Na^+).

3-Methyl-but-2-enoic acid 2-[5-(1-hydroxy-2-methyl-

allyl)-2-oxo-dihydro-furan-3-ylidene]-ethyl ester (10). The acylation of compound **2** with dimethylacryloyl chloride (8 μL, 6.7×10^{-5} mol) was carried out for 10 min to yield 3.2 mg (75%) of compound **10**; ^{1}H NMR (500 MHz, acetone-d_6): δ 1.77 (3H, *s*), 1.78 (3H, *br, s*), 2.90 (1H, *m*), 2.97 (1H, *m*), 3.08 (2H, *s*), 4.10 (1H, *t, J* = 5.5), 4.71 (1H, *m*), 4.82 (1H, *br, s*), 4.86 (1H, *br, s*), 4.92 (1H, *br, s*), 5.05 (1H, *br, s*), 5.15 (2H, *m*), 6.20 (1H, *m*); ^{13}C NMR: δ 17.6, 18.7, 24.7, 24.7, 63.5, 82, 84, 107.6, 115.6, 135.6, 136.2, 147.6, 147.9, 165.5, 171; ESI-MS: *m/z* 303 (100%, M + Na^+).

Butyric acid 2-[5-(1-hydroxy-2-methyl-allyl)-2-oxo-dihydro-furan-3-ylidene]-ethyl ester (11). Compound **11** (3.3 mg, yield 83%) was gained from the reaction of compound **2** with butyryl chloride (8 μL, 7.5×10^{-5} mol) for 10 min; ^{1}H NMR (500 MHz, acetone-d_6): δ 0.92 (3H, *t, J* = 7.3), 1.61 (2H, *m*), 1.77 (3H, s), 2.30 (2H, t, *J* = 7.3), 2.88 (1H, *m*), 2.90 (1H, *m*), 4.09 (1H, d, *J* = 4.6), 4.70 (1H, *m*), 4.92 (1H, *br, s*), 5.05 (1H, *br, s*), 5.13 (2H, *m*), 6.24 (1H, *m*); ^{13}C NMR: δ 13.4, 17.6, 18.2, 24.7, 35.9, 63.4, 82, 84, 107.6, 135.6, 136.2, 147.9, 165.5, 172; ESI-MS: *m/z* 291 (100%, M + Na^+).

Macrophage cell line culture. The murine macrophage cell line RAW264.7 was purchased from the American Tissue Culture Collection (Rockville, MD). The cells were maintained as the procedure described previously.[3]

Measurement of nitrite concentration. Experiments were performed on cells grown in the presence of various concentrations of test compounds dissolved in DMSO with LPS (1 μg/mL) for 18 h. Nitrite concentration was determined according to the method described previously.[3] Sodium nitrite was used as a standard.

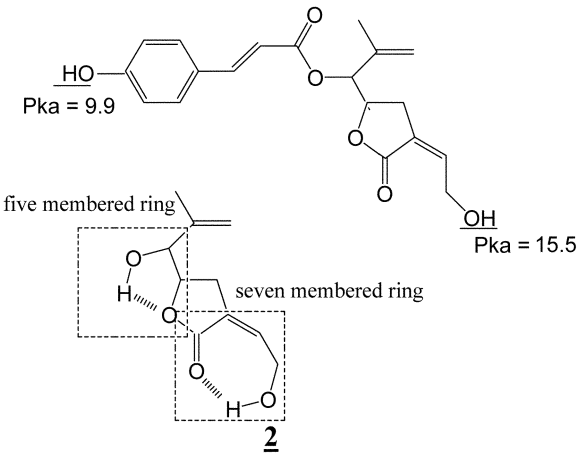
Analysis of mRNA levels for iNOS. RAW 264.7 cells grown were treated with various concentrations of the ester derivatives prepared in this study, and stimulated with LPS for 6 h. The total RNA was isolated from the cells by the acid-guanidium isothiocyanate phenol chloroform (AGPC) method. The reverse transcription reactions were performed in the PCR buffer containing 5 mM $MgCl_2$, 5 mM KCl, 1 mM Tris-HCl, 1 mM dNTPs, 1.75 units/μL M-MLV reverse transcriptase. The complementary DNA (cDNA) of iNOS was amplified using the primers, 5'-CAT GGC TTG CCC CTG GAA GTT TCT CTT CAA AG-3' and 5'-GCA GCA TCC CCT CTG ATG GTG CCA TCG-3'. cDNA of β-Actin was also amplified as a control. RT-PCR was basically carried out according to the method described previously.[10]

Results and Discussion

Prunioside A has been isolated from the roots of *S. pruniofolia* which is a plant of great interest for its traditional usage as an herbal medicine in Oriental countries and identified as a unique terpene glucoside having a coumaroyl group.[3,10] Based on the observation that its acetylated derivatives showed the inhibitory effect on the production of NO, known as an inflammatory mediator, prunioside A was enzymatically modified using tannase (Scheme 1). The enzyme has been successfully applied for removing the glucosyl group from tannic acid to synthesize propyl gallate.[11] The incubation of prunioside A with tannase at 30 °C for 12 h in the present study yielded compound **2**, in which both the coumaroyl and glucosyl moieties were removed. The tannase-treated compound was further reacted with acyl chlorides to synthesize its various ester derivatives (Scheme 1).

In the acylation reaction, introduction of less of 1 equivalent amount of acyl chlorides to compound **2** resulted in monosubstituted derivatives in which the primary allylic hydrogen was reacted first. The product distribution of the monosubstituted products in the tannase treated compound for acylation is well contrasted with those of β-glucosidase treated ones.[12] That is, in the latter, the phenolic hydrogen is favored for the substitution due to its lower *p*Ka value whereas the primary hydrogen was attacked first. in the former. Although the hydrogen of the primary alcohol is also allylic that allow facile substitution, it is a surprise that the product distribution was so biased to the monosubstituted ones that allowed facile isolations. As compared to the tannase treated compounds, there is an additional intra-hydrogen bonding that might restrict the reactivity of the reactant further. This interaction would be explained as shown in Scheme 2. The formation of a five member ring as a result of intra-hydrogen bonding would raise the *p*Ka value of the secondary alcohol. It is interesting to note that the primary alcohol part would also form a localized 7-membered ring so that the *p*Ka of it was 15.5, but the substitution of phenolic hydrogen (*p*Ka 9.9) took placed first. Thus, the formation of intra molecular hydrogen bonding affects the rate of acylation reaction in our reactions, which controls the distribution between mono- and bis-substituted products, depending their stoichiometry, with various acyl substituents (Table 1).

The esters (compound **3**) derived from prunioside A were investigated for the effect on NO production in RAW 264.7 cells activated with LPS and IFN-γ. Table 1 shows the ester compounds and their concentrations of 50% inhibition (IC_{50}) on NO production in the stimulated RAW 264.7 cells. All the monoterpene-type esters (compound **4**-**11**) markedly inhibited the NO generation in IFN-γ and LPS- treated macrophage-like RAW 264.7 cells in a dose-dependent



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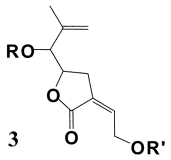
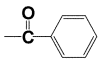
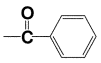
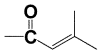
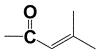
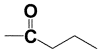
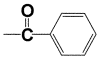
Scheme 2

Table 1. Biological activities of the monoterpene-type esters (**3**) derives from prunioside A



Entry	R	R'	Product	Yield (%)	IC_{50} Inhibition
1			4	73	2.5 μg/mL
2			5	64	3.0 μg/mL
3			6	76	2.0 μg/mL
4			7	76	15.0 μg/mL
5	H		8	70	10.0 μg/mL
6	H		9	72	7.5 μg/mL
7	H		10	75	6.5 μg/mL
8	H		11	83	5.0 μg/mL

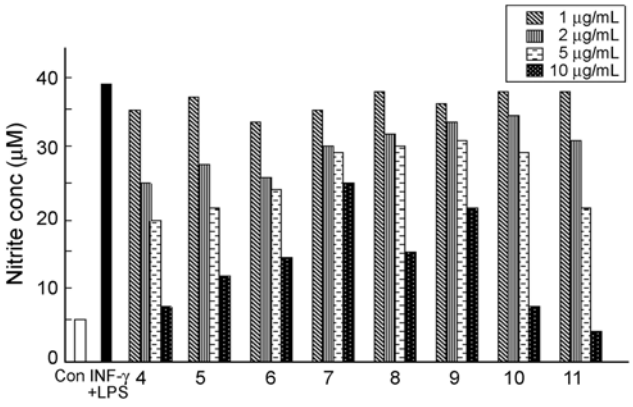


Figure 1. Effects of compounds **4**-**11** on NO production in LPS-stimulated RAW 264.7 cells. Cells were stimulated for 18 h with LPS (1 μg/mL) and IFN-γ (5 U/mL) in the presence or absence of test compounds at indicated concentrations.

manner (Fig. 1). Compound **11** has the most evident inhibitory effect with an IC50 value of 5.0 μg/mL of the derivatives examined. To further evaluate whether the inhibition of NO production by compound **11** was correlated with iNOS, the transcription level of iNOS was examined by RT-PCR (reverse transcriptase- polymerase chain reaction) analysis. As shown Figure 2, the reduction of iNOS mRNA was observed in RAW 264.7 cells treated with the immune stimulants in a concentration dependent manner. As compared with our previous report, removal of both coumaroyl and glucosyl resulted in much enhanced potency toward NO inhibitory activities. These results strongly indicate that the monoterpene-type ester unit derived originally from prunioside A produces a concentration-dependent inhibitory effect against NO production and iNOS expression in RAW 264.7 cells in response to LPS and IFN-γ.

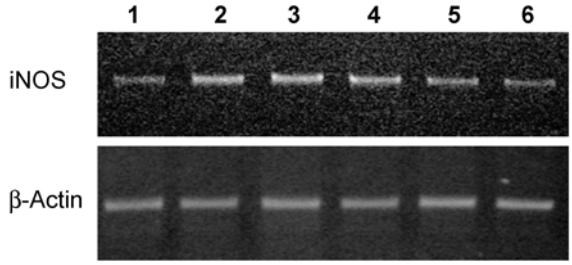


Figure 2. The agarose gel analysis of RT-PCR products for iNOS and β-actin as a control. The activated cells were cultured with various concentrations of compound **11** for 18 h: lane 1, control; lane 2, 3, 4, 5, and 6 are different in concentration of compound **11** (0, 1, 2, 5, 10 μg, respectively).

In summary, we have synthesized the biologically important esters from prunioside A by tannase treatment followed by acylation and demonstrated that the derivatives inhibited the production of NO and the expression level of iNOS in activated macrophages. Based on the present study, it may be expected that the monoterpene-type esters would be useful for the treatment of inflammatory diseases.

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