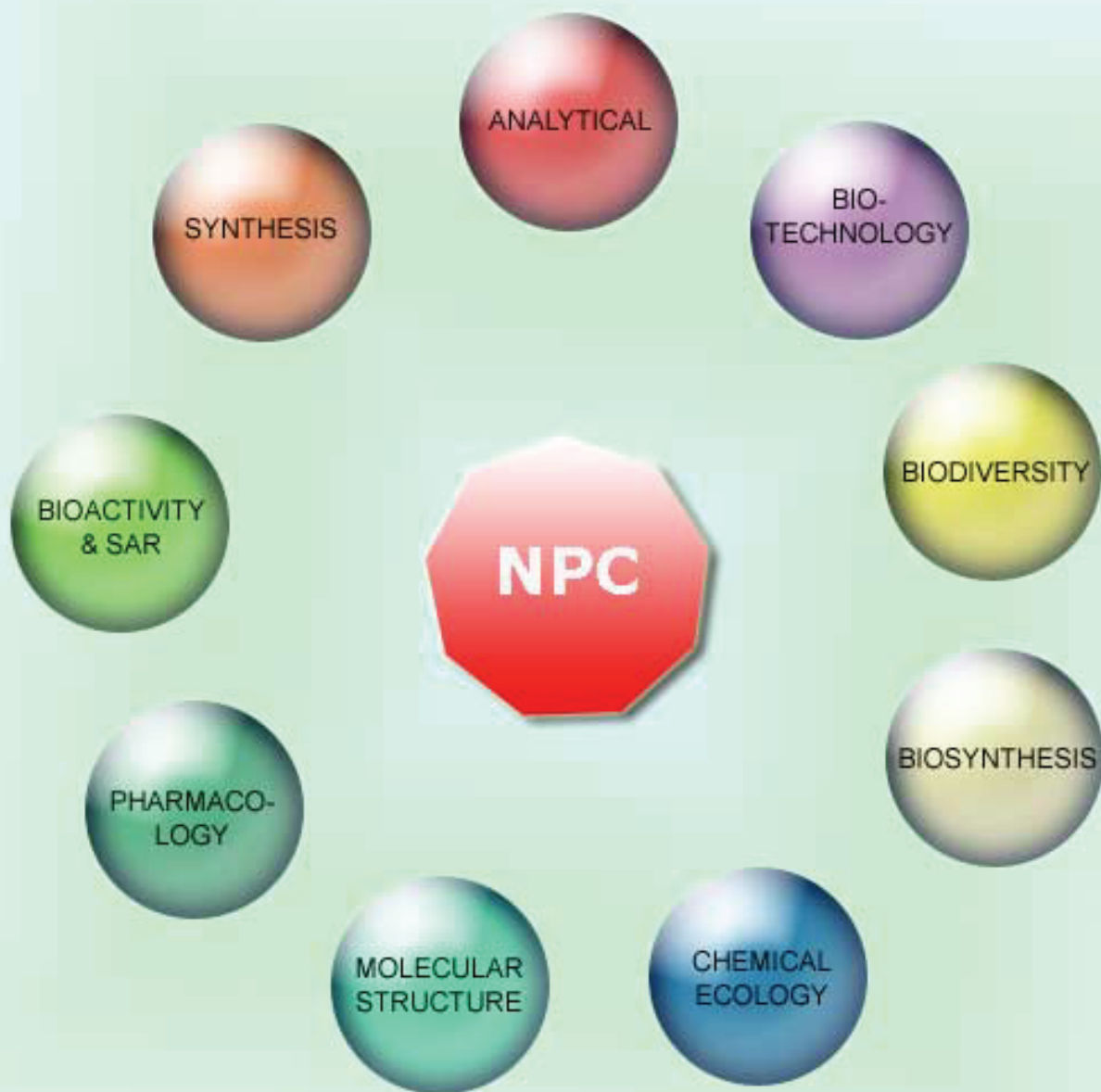


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Chemical Constituents of *Aglaia odorata* Leaves and Their Anti-inflammatory Effects

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Aglaia odorata Lour. is a traditional herbal medicine belonging to the *Meliaceae* family. The aim of this study was to identify useful compounds for human health from *A. odorata*. Our phytochemical investigation resulted in the isolation of four constituents hesperetin-7,3'-*O*-dimethylether, 5 α -dammar-20-ene-3 β ,24,25-triol, odorine, and odorinol. All compounds suppressed LPS-induced TNF- α expression in rat immortalized microglia HAPI cells; especially, hesperetin-7,3'-*O*-dimethylether showed most potent inhibitory effect. In addition, molecular docking analysis demonstrated that hesperetin-7,3'-*O*-dimethylether could be accommodated within hot spots of TNF- α dimeric protein.

Keywords: *Aglaia odorata*, Anti-inflammatory effect, Hesperetin-7,3'-*O*-dimethylether, TNF- α , Molecular docking.

Phytochemicals have continued to provide innovative therapeutic agents for various conditions over a period of years [1]. Exploration of natural bioactive molecules from medicinal plants becomes paramount for treatment options.

The genus *Aglaia* is the largest genus of the family *Meliaceae* comprising nearly 120 species with a wide distribution in tropical rainforest of South Asia. Previous reports revealed that chemical constituents of the genus *Aglaia* exert potent pharmacological efficacy including cytotoxicity on human cancer cells [2–5], anti-inflammatory [6], antibacterial [7], and antiviral properties [8,9]. One of the species is *Aglaia odorata*, which grows as high as 2–5 meters. The leaves of this plant are green throughout the year and are used as herbal remedy for treatment of human cough, vomiting, and inflammatory injuries in Indonesia. Several studies found in the literature concerning bioactive compounds in *A. odorata* [10,11]. Bisamides isolated from *A. odorata* inhibited both the initiation and promotion stages of two-stage skin carcinogenesis [12]. Diterpenes and triterpenes isolated from the leaves possessed potent inhibitory effects towards lipopolysaccharide (LPS)-induced NO production in RAW264.7 cells [13]. Essential oil of the stem exhibited antibacterial activity against Gram-positive pathogens [14]. Within the scope of our ongoing program aimed at the chemical study of Indonesian medicinal system 'Jamu' with a biologically interesting profile [15–17], we herein report great potential of constituents as anti-inflammatory agents from *A. odorata* leaves.

Using chromatographic techniques, four constituents were isolated from EtOAc extract of *A. odorata* leaves. Compound 1 was

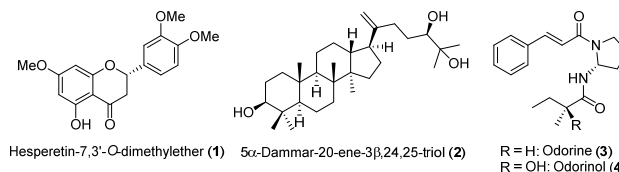


Figure 1: Chemical structures of isolated constituents.

obtained as a yellow powder, and its molecular formula was established as C₁₈H₁₈O₆ from HRESITOFMS for the peak at m/z 331.1182 [M + H]⁺ (calcd. for C₁₈H₁₈O₆, 331.1182). By 1D and 2D NMR analysis, the chemical structure of 1 was determined to be hesperetin-7,3'-*O*-dimethylether. Compound 2 was isolated as a white powder, and its HRESITOFMS showed the pseudomolecular ion peak at m/z 483.3828 [M + Na]⁺ (calcd. for C₃₀H₅₂O₃Na, 483.3814) corresponding to a molecular formula C₃₀H₅₂O₃. Furthermore, the HRESITOFMS exhibited the dehydrated molecular ions peak at m/z 443.3896 [M + H – H₂O]⁺ (calcd. for C₃₀H₅₁O₂, 443.3889) and 425.3776 [M + H – 2H₂O]⁺ (calcd. for C₃₀H₄₉O, 425.3783). Detailed spectroscopic analyses including COSY and HMBC, and comparison with the reported data previously [13] determined 2 as 5 α -dammar-20-ene-3 β ,24,25-triol. By NMR and MS analysis, the structures of compounds 3 and 4 were determined to be odorine and odorinol, respectively [18]. Their structures were illustrated in Figure 1.

We then examined anti-inflammatory effects of four isolated compounds. In this paper, we determine whether these compounds suppress LPS-induced expression of the pro-inflammatory cytokine

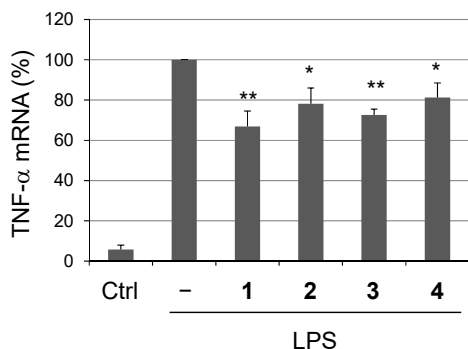


Figure 2: Effect of isolated compounds on LPS-induced TNF- α mRNA expression. HAPI cells were treated with LPS for 6 h in the presence or absence of each compound. The levels of TNF- α mRNA were determined by RT-PCR. Values (mean \pm SEM, n=3) are expressed as a percentage relative to the mRNA expression level in cells treated with LPS alone. * $p < 0.05$, ** $p < 0.01$ (vs. LPS alone). – is not exposed to the compound treatment. Ctrl is a negative control (without LPS and compound treatment).

TNF- α in microglia, resident immune cells in the central nervous system. HAPI cells were treated with LPS (100 ng/mL) for 6 h in the presence of compounds (50 μ M). After the treatment, the expression levels of TNF- α mRNA were detected using RT-PCR. As shown in Figure 2, LPS markedly induced expression of TNF- α mRNA, and all compounds suppressed LPS-induced TNF- α mRNA expression. Hesperetin-7,3'-*O*-dimethylether (**1**) had most potent inhibitory effect among them. Next, we examined the effects of **1** on LPS-induced expression of TNF- α protein. Hesperetin-7,3'-*O*-dimethylether (**1**) also suppressed TNF- α at the protein level (Figure 3). Diterpenes and triterpenes isolated from the leaves of *A. odorata* have previously been shown to inhibit LPS-induced NO production [13]. These findings indicate that several compounds contained in *A. odorata* leaves possess anti-inflammatory effects.

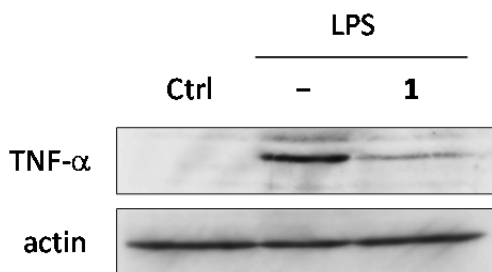


Figure 3: Effect of hesperetin-7,3'-*O*-dimethylether (**1**) on LPS-induced TNF- α protein expression. HAPI cells were treated with LPS for 6 h in the presence or absence of **1**. After treatment, whole cell extracts were prepared from the cells and subjected to Western blot analysis. A representative blot from three independent experiments is shown.

Therefore, we analyzed the detailed intermolecular interactions and probable binding mode of hesperetin-7,3'-*O*-dimethylether (**1**) with TNF- α dimeric protein (PDB ID: 2AZ5 [19]). Computational molecular simulations demonstrated that **1** favorably docked to the SPD304 (a TNF- α antagonist) binding hot spots (Figure 4A). Free binding energy of the best pose of **1** in TNF- α was ΔG -12.06 kcal/mol. The B-ring was accommodated within the hydrophobic pocket formed by the subunit-A residues Ile58, Tyr59, Gly121, Gly122, and Val123, and the non-classical hydrogen bonding between the 3'-OMe group and Tyr59 was observed (Figure 4B).

Furthermore, the A-ring interacted with the subunit-B Tyr119 (π -interaction) and the 7-OMe group formed the non-classical hydrogen bonding with the same Tyr119. The SPD304 has a 4-chromanone unit, which is similar to the 4-chromanone structure of

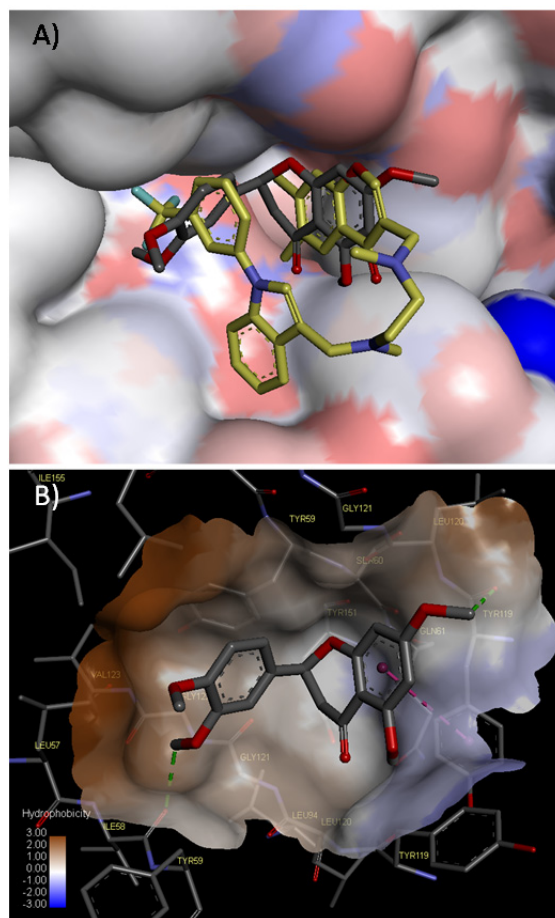


Figure 4: Molecular docking analysis of hesperetin-7,3'-*O*-dimethylether (**1**) to TNF- α dimeric protein. A) Surface view of TNF- α binding **1** and SPD304 (carbon atoms colored yellow); B) 3D-Orientation of **1** in SPD304 binding site of TNF- α (non-classical hydrogen bond: green dotted line; π -interaction: pink dotted line).

1. It was presumed that **1** is an appropriate form for docking to TNF- α dimeric protein.

In conclusion, our chemical investigation of *A. odorata* leaves resulted in the isolation of four chemical constituents. Among them, hesperetin-7,3'-*O*-dimethylether displayed potent anti-inflammatory effect *in vitro* and *in silico*. These results provide the scientific information and enhance the ethnopharmacological value of *A. odorata* leaves.

Experimental

General: All solvents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. MS spectra were obtained using a JEOL JMS-700/GI spectrometer and the Waters UPLC-MS system (Aquity UPLC XevoQToF). ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded with a JEOL ECX 400 spectrometer with tetramethylsilane as an internal standard. Silica gel column chromatography (CC) was performed on silica gel N-60 (40–50 μ m, Kanto Chemical Co., Inc.). TLC spots on plates pre-coated with silica gel 60 F₂₅₄ (TLC, Wako Pure Chemical Industries, Ltd.) were detected with a UV lamp (254 nm). Fractionations for all CCs were based on TLC analyses.

Extraction and isolation: *Aglaia odorata* Lour. leaves were collected from Lubuk Minturun Padang, West Sumatera Indonesia, Padang in October, 2014. A voucher specimen (no.290/K-

ID/ANDA/XII/2014) has been deposited at Andalas University Herbarium (ANDA), Padang. Dried leaves (2.6 kg) were macerated successively with *n*-hexane (9 × 3 L) and EtOAc (7 × 3 L) at room temperature. The *n*-hexane and EtOAc extracts were filtered and concentrated *in vacuo*, to yield *n*-hexane extract (120 g) and EtOAc extract (105 g). A portion of EtOAc extract (30 g) was separated by silica gel column chromatography (CC) eluted with *n*-hexane/EtOAc in a stepwise manner (10/0 to 0/10; v/v) to give 10 fractions (Fr. A – Fr. J). Recrystallization of Fr. E (764 mg) in *n*-hexane/EtOAc afforded compound **1** (41 mg). Using the same techniques, compound **2** (150 mg) was recrystallized from Fr. B (402 mg). The Fr. H (504 mg) was further purified upon PTLC (silica gel 70 F₂₅₄, 1 mm, CHCl₃/MeOH = 10/1) to give compound **3** (12 mg) and compound **4** (11 mg).

Hesperetin-7,3'-O-dimethylether (**1**)

IR (film): 3380, 2919, 1636, 1304, 1210 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 12.0 (1H, s, 5-OH), 6.99 (1H, s, H-2'), 6.98 (1H, dd, *J* = 8.3 and 1.8 Hz, H-6'), 6.90 (1H, d, *J* = 9.2 Hz, H-5'), 6.08 (1H, d, *J* = 2.8 Hz, H-8), 6.06 (1H, d, *J* = 2.3 Hz, H-6), 5.37 (1H, dd, *J* = 13.3 and 2.8 Hz, H-2), 3.92 (3H, s, 3'-OMe), 3.91 (3H, s, 4'-OMe), 3.81 (3H, s, 7'-OMe), 3.12 (1H, dd, *J* = 17.4 and 13.3 Hz, H-3), 2.80 (1H, dd, *J* = 17.4 and 3.2 Hz, H-3).

¹³C NMR (100 MHz, CDCl₃): δ 196.0 (C-4), 168.1 (C-7), 164.2 (C-9), 162.9 (C-5), 149.6 (C-3'), 149.4 (C-4'), 130.9 (C-1'), 118.9 (C-6'), 111.2 (C-5'), 109.5 (C-2'), 103.2 (C-10), 95.2 (C-8), 94.4 (C-6), 79.3 (C-2), 56.08 (3'-OMe), 56.06 (4'-OMe), 55.8 (7'-OMe), 43.4 (C-3).

HRMS-ESI: *m/z* [M + H]⁺ calcd for C₁₈H₁₉O₆: 331.1182; found: 331.1182.

Cell culture and treatment: Rat immortalized microglia HAPI cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% heat-inactivated fetal calf serum (FCS), 4 mM glutamine, 100 units/mL penicillin G, and 0.1 mg/mL streptomycin in a humidified 5% CO₂/95% air incubator at 37°C. HAPI cells (2 × 10⁵ cells/dish) were seeded in a 35-mm-diameter dish and cultured in DMEM containing 1% heat-inactivated FCS. Next day, cells were pretreated with each compound (50 μM) for 30 min and then add lipopolysaccharide from *E. coli* (LPS, 100 ng/mL) for 6 h.

Reverse transcription-polymerase chain reaction (RT-PCR): After the treatment, the cells were washed with phosphate-buffered saline (PBS) and total RNA was extracted with trizol reagent (Invitrogen, Carlsbad, CA, USA). First-strand cDNA was synthesized from 1 μg of total RNA. Target genes were amplified using primers specific for rat TNF-α (forward primer, 5'-AAAGCATGATCCGAGATGTG-3'; reverse primer, 5'-ATCTGCTGGTACCACCAGTT-3') and rat glyceraldehyde-3-phosphate dehydrogenase (GAPDH; forward primer, 5'-ACCACAGTCCATGCCATCAC-3'; reverse primer, 5'-

TCCACCACCCTGTTGCTGTA-3'). PCR amplification of TNF-α was conducted using EX Taq polymerase (Takara Bio, Otsu, Japan) as follows: 2 min at 94°C, 1 cycle; 40 s at 94°C, 40 s at 58°C, and 1 min at 72°C, 35 cycles. PCR amplification of GAPDH was conducted using Taq DNA polymerase (Invitrogen) as follows: 2 min at 94°C, 1 cycle; 40 s at 94°C, 40 s at 58°C, and 1 min at 72°C, 18 cycles. Aliquots of the PCR mixtures were separated on a 2% agarose gel and stained with ethidium bromide. Densitometric analyses were performed using the Multi Gauge software (Fuji Film, Tokyo, Japan). The mRNA levels were normalized relative to the GAPDH mRNA level of each sample.

Western blotting analysis: After the treatment, cells were washed twice with ice-cold PBS. The cells were collected using 150 μL of lysis buffer (20 mM Tris-HCl, pH 7.4, containing 1 mM EDTA, 1 mM EGTA, 1% Triton X-100, 10 mM NaF, 1 mM Na₃VO₄, 20 mM β-glycerophosphate, 5 μg/mL leupeptin, 1 mM phenylmethylsulfonyl fluoride, and 1 mM dithiothreitol), and lysed on ice for 30 min. The lysates were centrifuged at 18,000 × *g* for 10 min at 4°C to remove cellular debris. Whole-cell extracts (30 μg) were subjected to Western blot analysis. Western blotting was performed with SDS-PAGE as previously described [20]. Proteins were detected using ImmunoStar LD (Wako Pure Chemical) and imaged using an LAS-3000 (Fuji Film).

Statistical analysis: Data were analyzed using ANOVA followed by post hoc Bonferroni tests. A *P* value of less than 0.05 was considered to be significant.

Molecular modeling: The crystallographic coordinates of the 2.1 Å human TNF-α structure co-crystallized with SPD304 (PDB ID: 2AZ5 [19]) was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (<http://www.rcsb.org>). Initially, the 3D structure of TNF-α was cleaned and the binding sites were considered for further analysis. The conformation of **1** was optimized using Gaussian09 software. All simulations were performed using AutoDock version 4.2 [21]. The Lamarckian genetic algorithm of the AutoDock 4.2 package was performed for 100 iterations with a maximum of 27,000 generations per iteration, a population size of 150 individuals, and a maximum of 2.5 × 10⁶ energy evaluations per generation. The binding pattern and interactions of compound **1** were visualized using Discovery Studio version 4.5.

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