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Two new compounds with anti-inflammatory activity from *Alangium chinense*

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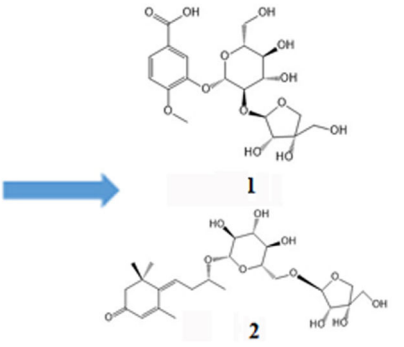
ABSTRACT

A new phenolic glycoside, chinenside A (**1**), and a new megastigmane glycoside, chinenionside A (**2**), together with twelve known compounds (**3-14**), were isolated from the roots of *Alangium chinense*. Their structures were deduced on the basis of extensive spectroscopic analyses and comparison with data reported in the literature. The anti-inflammatory activity in vitro of all 13 phenolic glycosides was evaluated against lipopolysaccharide-induced mouse macrophage RAW264.7 cells. The compounds **1**, **9**, and **10** potentially inhibited the productions of nitric oxide (NO), prostaglandin (PEG_2), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6). Compound **1** (50 μM) showed stronger anti-inflammatory activity than Triptolide (TPL, 20 nm).

Alangium chinese



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Alangium chinense; phenolic glycoside; megastigmane glycoside; anti-inflammatory activity

1. Introduction

Alangium chinense (Lour.) Harms (Alangiaceae) is a deciduous shrub indigenous to China (Sun et al. 2000). The roots of this plant, popularly known as 'Bai-Long-Xu', have been used historically in traditional Chinese medicine for the treatment of arthritis and

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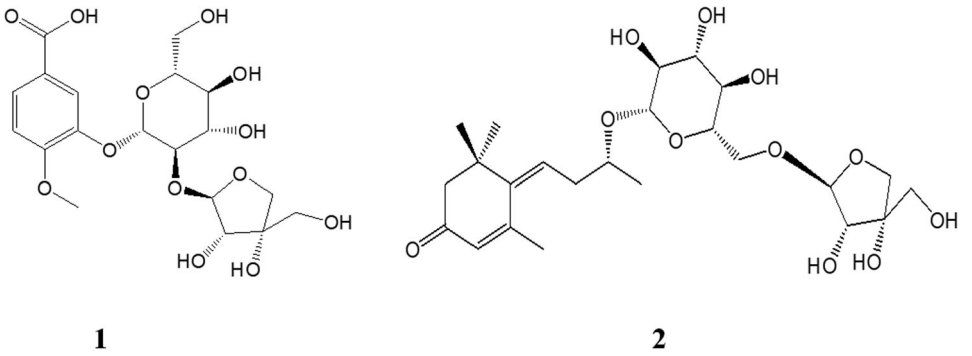

1 **2**

Figure 1. Chemical structures of compounds **1–2**.

heart failure (Sharma et al. 2011). This plant is well known as rich natural sources of alkaloids, phenolic glycosides, megastigmane glycosides and terpenoids. Yet, more than 50 constituents were isolated from the roots and leaves of this plant (Ma et al. 2015; Zhang et al. 2013). But the anti-inflammatory activitiy of this plant has not been researched. As part of a program to study bioactive substances, the n-butanol fraction of dried roots of *A. chinense* was investigated. As shown in Figure 1, we reported the isolation of a new phenolic glycoside, chinenside A (**1**), and a new megastigmane glycoside, chinenionside A (**2**), together with twelve known compounds (**3–14**). The anti-inflammatory activity of 13 phenolic glycosides was evaluated against lipopoly-saccharide-induced mouse macrophage RAW264.7 cells.

2. Results and discussion

Compound **1** was isolated as white amorphous powder. Its molecular formula was determined to be $C_{19}H_{26}O_{13}$ on the basis of HRESIMS (m/z 485.1269 $[M+Na]^+$, calcd. for $C_{19}H_{26}NaO_{13}$ 485.1266). The ^{1}H NMR data of **1** (Table S1) showed signals for a 1,3,4-trisubstituted [δ_H 7.50 (1H, d, $J=0.8$ Hz, H-2), 7.40 (1H, dd, $J=8.4$, 0.8 Hz, H-5), 6.95 (1H, d, $J=8.4$ Hz, H-6)] phenyl ring and two anomeric protons [δ_H 4.96 (1H, d, $J=7.2$ Hz, H-1′), 5.44 (1H, s, H-1′′)] for the diglycosidic moiety (Wang et al. 2011). The ^{13} C NMR data of **1** (Table S1) exhibited 19 carbon signals, including 11 carbon signals, which was ascribed to a diglycosidic moiety (δ_C 98.3, 74.9, 77.4, 70.0, 77.0, 60.6, 108.4, 76.1, 79.5, 74.1, 64.6), one methoxy group (δ_C 55.3), and a carbonyl group (δ_C 170.1). Moreover, the remaining six carbons (δ_C 147.5, 147.3, 133.4, 121.7, 113.4, 113.0) indicated that there was a phenyl unit. All proton and carbon signals were accurately determined by 2D NMR experiments, including HSQC and HMBC. The HMBC correlations (Figure S1) of the methoxy protons (δ_H 3.74, 3H, s) to C-3 (δ_C 147.3), C-4 (δ_C 147.5), and C-5(δ_C 121.7) indicated that the existence of methoxy group at C-4. After acid hydrolysis, compound **1** gave D-apiose and D-glucose (see Acid hydrolysis and sugar analysis in the supplementary material). The glucosyl group was deduced to be at C-1 by an HMBC correlation from H-1′ (δ_H 4.97, $J=7.2$ Hz) to C-3 (δ_C 147.3). In the HMBC spectrum, the correlation of H-1′′ (δ_H 5.44, s) with C-2′ (δ_C 74.9) indicated that the apiose moiety was attached to C-2′ of the glucosyl group. The relative configurations of two glucose residues were determined to be β by the coupling constants (J)

of 7.2 and 0 Hz. Therefore, the structure of compound **1** was elucidated as 3-*O*-[β-D-apiofuranosyl (1→2)-β-D-glucopyranosyl]-4-methoxy-benzoic acid, and given the trivial name chinenside A.

Compound **2** was isolated as white amorphous powder. Its molecular formula was established as $C_{24}H_{38}O_{11}$ on the basis of HRESIMS (m/z 525.2293 $[M+Na]^+$, calcd. for $C_{24}H_{38}NaO_{11}$ 525.2306). The IR spectrum indicated the hydroxyl and ketone carbonyl stretching bands at 3382 and 1647 cm^{-1}. The ^1H NMR data of **2** (Table S2) showed signals of two anomeric protons [δ_H 4.33 (1H, d, $J=7.6$ Hz, H-1′), 5.00 (1H, d, $J=2.4$ Hz, H-1′′)] for the diglycosidic moiety. The ^{13}C NMR data of **2** (Table S2) exhibited 24 carbon signals, including 11 carbon signals, which was assigned to a diglycosidic moiety (δ_C 102.5, 75.1, 78.1, 71.9, 77.0, 69.1, 111.0, 78.0, 80.5, 74.9, 65.5). The ^{13} C NMR spectra data were similar to those of (Z)-6-[9-(β-D-glucopyranosyloxy)butylidene]-l,1,5-trimethyl-4-cyclohexen-3-one (Khan et al. 2003), except for five carbon signals (δ_C 111.0, 78.0, 80.5, 74.9, 65.5) attributed to a apiose moiety. After acid hydrolysis, compound **2** gave D-apiose and D-glucose. The glucosyl group was deduced to be at C-9 by an HMBC correlation from H-1′ (δ_H 4.33, $J=7.6$ Hz) to C-9 (δ_C 75.9). In the HMBC (Figure S1) spectrum, the correlation of H-1′ ′ (δ_H 5.00, $J=2.4$ Hz) with C-6′ (δ_C 69.1) indicated that the apiose moiety was attached to C-6′ of the glucosyl group. The relative configurations of two glucose residues were determined to be β by the coupling constants (*J*) of 7.6 and 2.4 Hz (Yue et al. 2014). It was reported that the chemical shifts of C-9, C-10, and C-1′ were indicative for 9*R* (δ_9 75.7-76.8, δ_{10} 19.7-20.4, $\delta_{1'}$ 102.0-102.9), and 9*S* (δ_9 77.7-78.1, δ_{10} 21.8-22.0, $\delta_{1'}$ 103.7-103.9) configurations in 9-hydroxy megastigmane 9-*O*-β-D-glucopyranosides (Matsunam et al. 2010). Thus, the absolute configuration of compound **2** at C-9 was assigned as R on the basis of the diagnostic chemical shifts of C-9 (δ_C 75.9), C-10 (δ_C 20.1), and C-1′ (δ_C 102.5) in the ^{13}C NMR data. Therefore, the structure of compound **2** was elucidated as (9 R)-(Z)-6-[9-(β-D-apiofuranosyl (1→6)-β-D-glucopyranosyl)butylidene]-l,1,5-trimethyl-4-cyclohexen-3-one, and given the trivial name chinenionside A.

Compounds **3–14** were isolated from the roots of *A. chinense*. They were identified as chinenside B (**3**), henryoside (**4**) (Jensen et al. 1979), henryoside-6′-*O*-β-D-glucoside (**5**) (Kikuchi et al. 2011**)**, salicin(**6**) (Kanho et al. 2005), vanilloloside (**7**) (Pan et al. 2012), 2-hydroxy-3-*O*-β-D-glucopyranosylbenzoic acid (**8**) (Sunghwa and Koketsu 2009), gentisic acid-5-*O*-β-D-glucoside (**9**) (Yeon et al. 2013), isotachioside (**10**) (Inoshiri et al. 1987), tachioside (**11**) (Inoshiri et al. 1987), gallic acid-3-*O*-β-D-glucoside (**12**) (Lu and Foo 1999), methyl salicylate-6-*O*-β-D-glucopyranosylbenzoic acid (**13**) (Xu et al. 2011), glucosyringic acid (**14**) (Geng et al. 2006).

All isolated phenolic glycosides (**1, 3–14**) were evaluated for anti-inflammatory activities by measuring the NO, PGE_2, TNF-α, IL-1β, and IL-6 levels in LPS-stimulated RAW264.7 cells. Macrophages produce inflammatory cytokines such as NO, PGE_2, TNF-α, IL-1β, and IL-6 when exposed to stimuli (Hung et al. 2009). Triptolide (TPL) was used as a positive control. None of the 13 compounds (50 μM) exhibited detectable cytotoxic activity towards RAW264.7 cells in the MTT assay. As shown in Figures S10–S14, the low levels of NO (17.2 ± 1.9), PGE_2 (585 ± 26), TNF-α (272 ± 100), IL-1β (13.3 ± 1.1) and IL-6 (0.73 ± 0.06) were observed in unstimulated RAW264.7 cells. However, the levels of NO (46.2 ± 1.8), PGE_2 (1148 ± 35), TNF-α (25234 ± 404), IL-1β

(27.3 ± 1.1) and IL-6 (14.95 ± 0.60) production markedly increased after LPS treatment. Our results, as shown in the **Figures S10–S14**, confirmed that compounds **1**, **9**, and **10** potentially inhibited the expressions of NO, PGE_2, TNF-α, IL-1β, and IL-6 at concentrations (52,050 μM) in LPS-stimulated RAW264.7 cells. Among them, compound **1** (50 μM) showed the highest inhibition rate which inhibited the levels of NO (20.8 ± 1.9), PGE_2 (654 ± 44), TNF-α (376 ± 39), IL-1β (14.6 ± 0.8) and IL-6 (0.69 ± 0.10). And the anti-inflammatory activities of compound **1** (50 μM) were stronger than the positive control (TPL) which inhibited the levels of NO (28.2 ± 2.2), PGE_2 (701 ± 19), TNF-α (13344 ± 227), IL-1β (16.2 ± 0.8) and IL-6 (4.34 ± 0.42).

3. Experimental

See supplementary data.

4. Conclusions

Fourteen compounds (**1–14**), including a new phenolic glycoside (**1**) and a new megastigmane glycoside (**2**), were isolated from the roots of *A. chinense*. The anti-inflammatory activity of 13 phenolic glycosides (**1**, **3–14**) was evaluated on RAW264.7 cells, and the results indicated that compound **1** showed the strongest anti-inflammatory activity. Therefore, it is possible to demonstrate that the phenolic glycosides might be important anti-inflammatory constituents of *A. chinense*.

Disclosure statement

No potential conflict of interest was reported by the authors.

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