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Chemical constituents from *Kandelia candel* with their inhibitory effects on pro-inflammatory cytokines production in LPS-stimulated bone marrow-derived dendritic cells (BMDCs)

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ABSTRACT

Chemical investigation of *Kandelia candel* resulted in the isolation of 19 compounds (**1**–**19**), including one new sesquiterpene glycoside, kandelside (**1**), three megastigman glycoside compounds (**7**–**9**), 16 known phenolic compounds (**2**–**6** and **10**–**19**). Structures of the isolated compounds were elucidated based on spectral data comparison with reported values. Isolated compounds were also evaluated for their inhibitory effects on the production of pro-inflammatory cytokines interleukin (IL)-12 p40, IL-6, and tumor necrosis factor α (TNF-α) in lipopolysaccharide (LPS)-stimulated bone marrow-derived dendritic cells. Among these compounds, compound **9** exhibited strong inhibitory activity against IL-6 production (IC_{50} = 0.07 ± 0.05 μM) and moderate inhibitory activity against TNF-α production (IC_{50} = 49.86 ± 1.02 μM), but exhibited no activity on IL-12 p40 production. Compounds **5** and **6** significantly inhibited IL-12 p40, IL-6, and TNF-α production with IC_{50} values of 11.68 ± 0.38, 44.52 ± 1.08, and 28.73 ± 0.96 μM, respectively.

Mangroves are a diverse group of trees that grow in intertidal tropical and subtropical forests. In mangrove species, phenolics are abundant components that prevent damage from herbivores[1,2] and exhibit a diversity of other biological activities of historic and potential importance to humans.[3] Mangrove extracts have been used for diverse medicinal purposes and are known to exhibit antibacterial, antiherpetic, and antihelminthic activities.[4]

Kandelia candel (Rhizophoraceae) is most widely distributed in the Asian coastline. According to previous study, the hypocotyls of *K. candel* have high levels of phenolic compounds.[5] Phenolics are also important components in the leaf extract of *K. candel*. The bioactivity of phenolic compounds were screened for their antioxidant activities. Total phenolic content in the leaves of *K. candel* was about 130.32 mg/g, evaluated with the pharmacological effect for anti-oxidant activity.[6] While the anti-inflammatory activity was not investigated at the moment.

Many studies have shown that inflammation is part of a complex biological response of vascular tissue toward harmful exogenous stimuli[7] and is mediated by a variety of soluble factors, including a group of secreted polypeptides known as cytokines, which play a key role in the modulation of immune responses.

BMDCs play a key role in the interface between the innate and acquired immune systems.[8] Activated BMDCs perform crucial functions in immune and inflammatory responses via the pathogen-associated molecular patterns (PAMPs)-stimulated production of pro-inflammatory cytokines such as IL-12 p40, IL-6 and TNF-α. This study describes the isolation and structure elucidation of 19 compounds (see Fig. 1) were isolated from *K. candel*, as well as an evaluation of their in vitro anti-inflammatory effects.

The methanolic extract of *K. candel* were partitioned into fractions and isolated by multiple chromatographic steps over silica gel, Sephadex LH-20, and YMC RP-18 column chromatography (CC)[9] to yield compounds **1**–**19**.[10]

Kandelside (**1**)[11] was obtained as a white amorphous powder. According to high-resolution electron spray ionization mass spectroscopy (HR-ESI-MS), a basic ion peak at *m*/*z* 439.2315 $[M+Na]^+$

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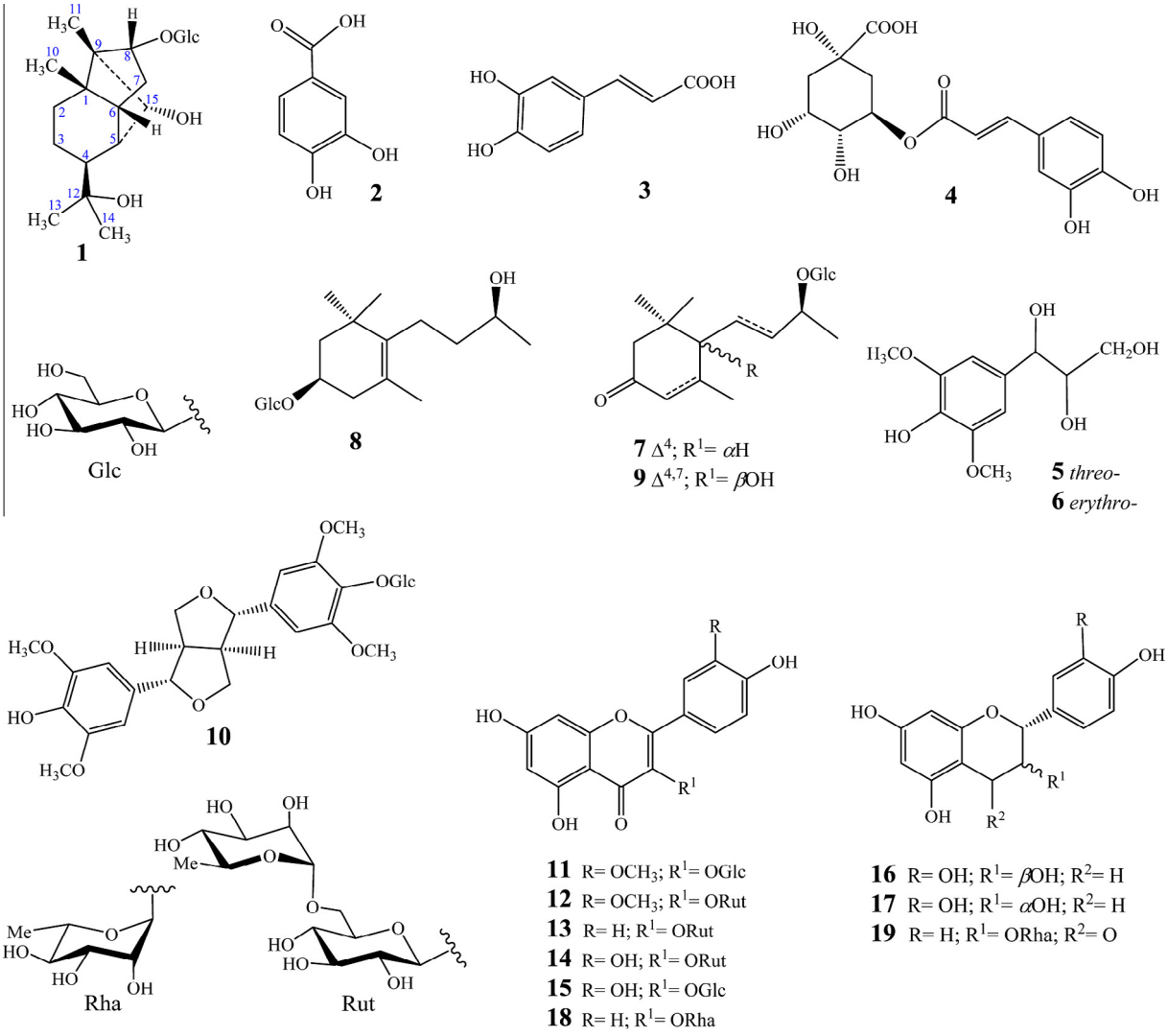

Figure 1. The structures of isolated compounds (**1**–**19**) from *K. candel*.

(calcd. for $C_{21}H_{36}O_8Na$, 439.2410) confirmed its molecular structure of $C_{21}H_{36}O_8$. The infrared (IR) spectrum of compound **1** showed absorption due to a hydroxyl group (3373 cm^{-1}). The ^{13}C-nuclear magnetic resonance (NMR) spectra of **1** illustrated signals of 21 carbon atoms, including four methyls, four methylenes, ten methines, and three quaternary carbons, which were identified by DEPT-135 experiments (see Table 1). Signals representing one anomeric carbon (δ_C 102.4, C-1′), six oxymethines (δ_C 88.0, 78.5, 78.5, 78.4, 75.0, and 71.9), one oxygenated quaternary (δ_C 73.9, C-12), and one oxymethylene (δ_C 63.1, C-6′) were also observed. The ^1H NMR spectrum of **1** showed an anomeric proton signal at δ_H 4.20 (1H, d, J = 7.8 Hz, H-1′). Therefore, the glucose unit was suggested to be connected to aglycon in a β-glycosidic linkage. Moreover, the ^1H NMR spectrum showed four methyl groups at δ_H 0.95 (3H, s, H-11), δ_H 1.05 (3H, s, H-10), δ_H 1.10 (3H, s, H-14), and δ_H 1.12 (3H, s, H-13). The ^1H and ^{13}C NMR of compound **1** were similar to those of 2α,12-dihydroxycopacamphan-15-one 2-O-β-D-glucopyranoside,[12] except for the replacement of a carbonyl group in 2α,12-dihydroxycopacamphan-15-one 2-O-β-D-glucopyranoside by oxymethine, and a glucose moiety attach to C-8 in **1**. The structure of **1** was further confirmed by heteronuclear multiple bond correlation (HMBC) and heteronuclear single quantum coherence (HSQC) experiments. The placement of the oxymethine carbon at C-15 (δ_C 88.0) was determined by HMBC correlation signals between H-4 (δ_H 1.52), H-5 (δ_H 1.39), H-6 (δ_H 1.76), H-11 (δ_H 0.95), and C-15 (δ_C 88.0), confirmed with HSQC correlation between H-15 (δ_H 3.44, br s) and C-15 (δ_C 88.0). The correlations between H-4 (δ_H 1.52), H-13 (δ_H 1.12), H-14 (δ_H 1.10) and C-12 (δ_C 73.9), as well as H-11 (δ_H 0.95), H-6 (δ_H 1.76) and C-8 (δ_C 78.5), were also observed in HMBC spectra, which was confirmed with HSQC correlation between H-8 (δ_H 4.28, dd, J = 3.0, 7.8 Hz) and C-8 (δ_C 78.5). According to the signal correlation between $H_{glc\text{-}1'}$ (δ_H, d, J = 7.8 Hz) and C-8 (δ_C 78.5), the glucose moiety was determined to connect to C-8 of aglycon. In addition, the hydrolysis of **1** was determined as D-glucoside.[13] Detailed analyses of other HMBC correlations (see Fig. 2) clearly identified the planar structure of compound **1** as 8,12,15-trihydroxycopacamphan-8-O-β-D-glucopyranoside.

The relative configuration of three chiral centers (C-1, C-4, and C-9) in **1** were assigned to the same as those of 2α,12-dihydroxycopacamphan-15-one 2-O-β-D-glucopyranoside,[12] which was elucidated by X-ray diffraction analysis, and showed that CH_3-10,