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Cytotoxic triterpene saponins from the mangrove *Aegiceras corniculatum*

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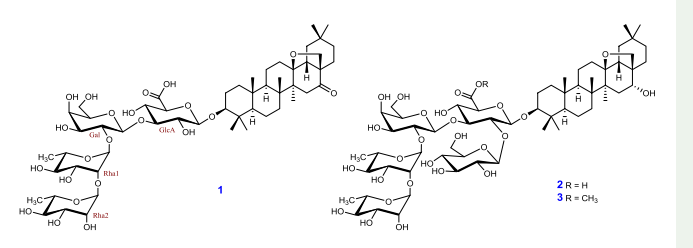
ABSTRACT

Using various chromatographic separations, sixteen compounds, including one new triterpene saponin named aegicoroside A (**1**), were isolated from the leaves of the Vietnamese mangrove *Aegiceras corniculatum*. Their structures were determined by spectroscopic methods such as 1D and 2D NMR and HR-ESI-MS. The cytotoxic activities of the isolated compounds against MCF7 (breast), HCT116 (colon), B16F10 (melanoma), and A549 (adenocarcinoma) cancer cell lines were also evaluated. Strong cytotoxicity was observed for sakurasosaponin (**2**) against all four cancer cell lines and for sakurasosaponin methyl ester (**3**) against MCF7, A549, and HCT116 cell lines with IC_{50} values ranging from 2.89 ± 0.02 to 9.86 ± 0.21 μM.



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1. Introduction

Aegiceras corniculatum (L.) Blanco (Myrsinaceae) is a shrub or small tree that grows up to 4 m high and is mainly distributed in Vietnam, China, Cambodia, Malaysia, Singapore, and Australia (Chi 2012). This plant has been traditionally used as an antiasthamatic, antidiabetic, and antirheumatic agent (Bandaranayake 2002). The major chemical constituents of *A. corniculatum* are terpenoids, alkaloids, fatty acids, and flavonoids (Chandrasekaran et al. 2010; Rajeswari and Rao 2015). The plant and its constituents have also been found to

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have various pharmacological effects such as antibacterial, analgesic, antidiabetic, anti-inflammatory, cytotoxic, and antioxidant activities (Rajeswari and Rao 2015). As part of our recent studies on the chemical constituents and biological activities of Vietnamese mangroves (Huong et al. 2014; Dat et al. 2015; Thao et al. 2015; Vinh et al. 2017), we report herein the isolation and structural determination of one new triterpene saponin, aegicoroside A (**1**), and 15 known compounds from the methanol extract of *A. corniculatum*, as well as evaluation of their cytotoxic activity.

2. Results and discussion

Fractionation and purification of the ethyl acetate (EtOAc) fraction from *A. corniculatum* led to isolation of one new saponin termed aegicoroside A (**1**) and 15 known compounds (**2**–**16**, see Figure 1), namely sakurasosaponin (**2**) (Ohtani et al. 1993; Lavaud et al. 1999), sakurasosaponin methyl ester (**3**) (Ohtani et al. 1993), (3*β*, 16*α*, 20*α*)-3,16,28-trihydroxyolean-12-en-29-oic acid 3-{*O*-*β*-D-glucopyranosyl (1→2)-*O*-[*β*-D-glucopyranosyl (1→4)]-*α*-L-arabinopyranoside} (**4**) (Zou et al. 2008), rutin (**5**) (Li et al. 2008), nicotiflorin (**6**) (Han et al. 2004), oleanolic acid *β*-D-glucopyranosyl ester (**7**) (Lee et al. 2006), isoquecitrin (**8**) (Guo et al. 2017), quercitrin (**9**) (Fossen et al. 1998), isomyricitrin (**10**) (Mansour et al. 2017), hyperoside (**11**) (Zhang et al. 2014), myricitroside (**12**) (Chung et al. 2004), astragalin (**13**) (Park et al. 2008), quercetin-3-D-xyloside (**14**) (Kalegari et al. 2011), chondrillasterol (**15**) (Akjhisa et al. 1987), and stigmasterol (**16**) (Habib et al. 2007). The known compounds were identified by detailed analysis of their spectroscopic data and comparison with previously reported values.

Aegicoroside A (**1**) was obtained as a white amorphous powder. The molecular formula ($C_{54}H_{86}O_{22}$) was determined by HR-ESI-MS with a protonated molecular ion peak at *m/z* 1109.5496 $[M + Na]^+$ (calcd for $C_{54}H_{86}NaO_{22}^+$, 1109.5503). The IR spectrum of compound **1** showed absorption due to hydroxyl (3349.8 cm^{-1}) and ketone (1740.5 cm^{-1}) groups. The NMR spectra (see Supplementary material) are indicative of a triterpene saponin with seven *tert*-methyl proton signals at δ_H 0.76, 0.86, 0.92, 0.93, 1.16, 1.19, and 1.28 (each, 3H, s) as well as four anomeric carbon signals at δ_C 100.8, 104.5, 104.7, and 107.3. The ^1H and ^{13}C NMR spectra for

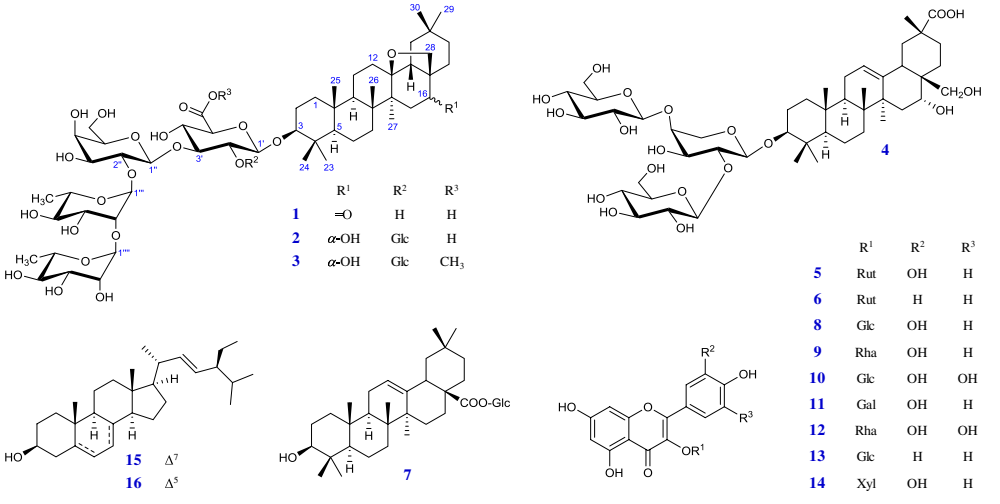

Figure 1. The structures of compounds **1**–**16**.

the aglycon exhibited signals of one oxymethylene [δ_C 75.7/δ_H 3.56 and 3.94 (each, 1H, d, J = 8.4 Hz)], one oxygenated quaternary carbon [δ_H 86.9], one oxymethine [δ_C 89.6/δ_H 3.28 (1H, dd, J = 4.2 and 12.0 Hz)] and one ketone group [δ_C 213.7]. The aglycon of **1** was identified as 13,28-epoxy-3*β*-hydroxy-16-oleanaone (aegicerin) previously reported from *A. corniculatum* (Zhang et al. 2005) by good agreement of its ^{1}H and ^{13}C NMR data with those of aegicerin (Machocho et al. 2003) and clethroidoside C (Liang et al. 2011) as well as further confirmation by 2D NMR spectra (see Supplementary material). The relative configurations for the aglycon of **1** were also identified by NOESY experiment. Proton H-3 (δ_H 3.28) had a NOESY correlation with H-5 (δ_H 0.65) indicating *α*-orientation of H-3. In addition, NOESY correlations of H_b-15 (δ_H 2.86) with H-26 (δ_H 1.28) and H_b-28 (δ_H 3.94) as well as H-18 (δ_H 2.06) with H_a-28 (δ_H 3.56) and H-30 (δ_H 0.86) confirmed *β*-orientation of the epoxy bridge between C-13 and C-28 (see Figure S8). Detailed analysis of HMQC, HMBC, and ^{1}H-^{1}H COSY correlations led to assignment of the ^{1}H and ^{13}C NMR data for all four sugar moieties (see section 3.3.1 and Table S1). Comparison of the ^{13}C NMR data for sugar moieties of **1** (Table S1) with those of sakurasosaponin (**2**) (Ohtani et al. 1993) and caryocaroside III-7 (Alabdul et al. 2006) in combination with 2D NMR data indicated that the tetrasaccharide chain was α-L-rhamnopyranosyl-(1→2)-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-galactopyranosyl-(1→3)-*β*-D-glucuronopyranoside. Furthermore, absolute configurations of the sugar moieties were identified as D-glucuronic acid, D-galactose, and L-rhamnose by acid hydrolysis of **1** followed by TLC and HPLC analysis in comparison with the authentic samples (Supplementary material). Attachment of the tetrasaccharide chain at C-3 of the aglycon was confirmed by HMBC correlation of the anomeric proton H-1′ (δ_H 4.88) with C-3 (δ_C 89.6). Consequently, the structure of **1** was identified as 3-*O*-[α-L-rhamnopyranosyl-(1→2)-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-galactopyranosyl-(1→3)-*β*-D-glucuronopyranosyl]-13*β*,28-epoxy-3*β*-hydroxy-olean-16-one.

The cytotoxic activities of compounds **1**–**15** against human cancer cell lines such as MCF7 (breast), HCT116 (colon), B16F10 (melanoma), and A549 (adenocarcinoma) were evaluated by MTT assays following previously reported protocols (Vinh et al. 2017) as described in the Supplementary materials. The results (Table 1) show that sakurasosaponin (**2**) exhibited strong cytotoxicity against all the four tested cancer cell lines (MCF7, A549, B16F10, and HCT116) with IC_{50} values of 9.85 ± 0.14, 2.89 ± 0.02, 4.96 ± 0.67, and 3.40 ± 0.48 μM, respectively, relative to the positive control, mitomycin C (Table 1). Sakurasosaponin methyl ester (**3**) also exhibited strong cytotoxicity on MCF7, A549, and HCT116 cell lines with IC_{50} values of 9.86 ± 0.21, 5.45 ± 0.13, and 2.21 ± 0.05 μM, respectively. Significant cytotoxicity was observed for aegicoroside A (**1**) against all the cancer cell lines (IC_{50} ranging from 20.75 ± 0.06 to 41.84 ± 0.64 μM) and for **3** against the B16F10 cell line (IC_{50} = 18.27 ± 0.04 μM). The other compounds showed no (IC_{50} > 100 μM) or weak cytotoxicity (IC_{50} from 62.30 ± 0.13 to 90.50 ± 0.60 μM) against the tested cancer cell lines. Given the potential cytotoxicity of **2** and **3**, these two compounds might be potential candidates for further investigation on the molecular mechanisms of action on specific anticancer targets.

3. Experimental

3.1. Biological material

The leaves of *A. corniculatum* were collected at Bai Tu Long bay, Quang Ninh Province, Vietnam in July 2016, and were identified by Dr Nguyen The Cuong (Institute of Ecology and

Table 1. Cytotoxic effect of compounds **1**–**15**.

Compounds	IC_{50} values (μM)			
	MCF7	A549	B16F10	HCT116
1	41.84 ± 0.64	37.71 ± 0.43	20.75 ± 0.64	31.61 ± 1.20
2	9.85 ± 0.14	2.89 ± 0.02	4.96 ± 0.67	3.40 ± 0.48
3	9.86 ± 0.21	5.45 ± 0.13	18.27 ± 0.04	2.21 ± 0.05
4	>100	>100	>100	>100
5	>100	>100	>100	>100
6	>100	>100	>100	>100
7	>100	>100	>100	77.08 ± 5.90
8	>100	>100	>100	>100
9	>100	>100	>100	>100
10	>100	>100	>100	78.38 ± 3.18
11	>100	>100	>100	>100
12	>100	>100	>100	>100
13	66.37 ± 2.41	>100	>100	>100
14	>100	>100	>100	>100
15	>100	90.50 ± 0.60	>100	62.30 ± 0.13
Mitomicin C[a]	2.73 ± 1.37	0.74 ± 0.05	5.67 ± 0.70	2.82 ± 0.08

[a]Positive control. Values are presented as mean ± SD ($n = 3$).

Biological Resources, VAST, Vietnam). The voucher specimens (ĐTCB-HSB 15) have been deposited at the herbarium of Institute of Marine Biochemistry, VAST, Vietnam.

3.2. Extraction and isolation

The dried leaves of *A. corniculatum* (2 kg) were extracted three times (each 5 L) with MeOH by sonication for 1 h. The MeOH extract was concentrated under reduced pressure to obtain a residue (200 g). This residue was suspended in water (3 L) and successively partitioned with *n*-hexane (4 × 3 L) and EtOAc (3 × 3 L) to give: *n*-hexane (H, 15 g), EtOAc (E, 25 g) and a water layer after removal of the solvents.

The EtOAC fraction (E, 25 g) was separated by VLC using gradient concentrations of MeOH in CH_2Cl_2 (from 0 to 100%) to give six fractions (E1 to E6). Fraction E4 (9 g) was separated into four subfractions (E4.1–E4.4) using silica gel column chromatography (CC) with CH_2Cl_2-MeOH-H_2O (3.5:1:0.07, v/v). Subfraction E4.3 (3 g) was separated by YMC RP-18 and Sephadex LH-20 CC using solvent acetone-H_2O (1:1, v/v) and further purified by silica gel CC with CH_2Cl_2-MeOH-H_2O (2.5:1:0.1, v/v) to afford compounds **1** (30 mg) and **4** (39 mg). Repeating the same steps as for subfraction E4.3, compounds **2** (200 mg) and **3** (47 mg) were obtained from subfraction E4.4 (2 g). Subfraction E4.2 (2 g) was separated by YMC RP-18 and Sephadex LH-20 CC using solvent acetone-water (1:1, v/v) to give compounds **9** (9 mg), **10** (15.7 mg), and **11** (4.3 mg). Similarly, fraction E3 (7 g) was separated into five subfractions (E3.1–E3.5) using silica gel CC with EtOAc–MeOH (7:1, v/v). Subfraction E3.4 (3 g) was isolated and purified by silica gel CC using EtOAc–MeOH (5:1, v/v), followed by Sephadex LH-20 CC to give compounds **5** (20 mg), **6** (3.7 mg), **7** (3.2 mg), and **8** (25 mg). Subfraction E3.3 (2 g) was purified by YMC CC using an eluent of MeOH-H_2O (1.3:1, v/v), followed by Sephadex LH-20 CC to obtain compounds **12** (17 mg), **13** (18 mg), and **14** (11 mg). Fraction E1 (3 g) was separated by silica gel CC using gradient elution of *n*-hexane-acetone (20:1–3:1, v/v) to give compounds **15** (20 mg) and **16** (3.0 mg).

3.2.1. *Aegicoroside A* (1)

White amorphous powder, $[\alpha]_C^{20}$ –34.8 (*c* 0.1, MeOH); IR (KBr) ν_{max}: 3349, 2931, 1740, 1306 and 1079 cm^{-1}; ^1H NMR (pyridine-d_5, 600 MHz): δ_H 0.72 (1H, m, H_a-1), 1.46 (1H, m, H_b-1), 1.80 (1H, m, H_a-2), 2.24 (1H, m, H_b-2), 3.28 (1H, dd, *J* = 4.2, 12.0 Hz, H-3), 0.65 (1H, d, *J* = 10.8 Hz, H-5), 1.30 (1H, m, H_a-6), 1.34 (1H, m, H_b-6), 1.22 (1H, m, H_a-7), 1.34 (1H, m, H_b-7), 1.13 (1H, d, *J* = 13.0 Hz, H-9), 1.48 (1H, m, H_a-11), 1.75 (1H, m, H_b-11), 1.58 (1H, br d, *J* = 12.0 Hz, H_a-12), 2.00 (1H, m, H_b-12), 2.02 (1H, d, *J* = 15.6 Hz, H_a-15), 2.86 (1H, d, *J* = 15.6 Hz, H_b-15), 2.06 (1H, dd, *J* = 5.0, 11.5 Hz, H-18), 1.50 (2H, m, H-19), 1.24 (1H, m, H_a-21), 1.84 (1H, m, H_b-21), 1.22 (1H, m, H_a-22), 2.29 (1H, m, H_b-22), 1.19 (3H, s, H-23), 0.92 (3H, s, H-24), 0.76 (3H, s, H-25), 1.28 (3H, s, H-26), 1.16 (3H, s, H-27), 3.56 (1H, d, *J* = 8.4 Hz, H_a-28), 3.94 (1H, d, *J* = 8.4 Hz, H_b-28), 0.93 (3H, s, H-29), 0.86 (3H, s, H-30), 4.88 (1H, d, *J* = 8.0, H-1′), 4.15 (1H, H-0032′), 4.23 (1H, t, *J* = 9.0 Hz, H-3′), 4.41 (1H, t, *J* = 9.0 Hz, H-4′), 4.50 (1H, H-5′), 5.20 (1H, d, *J* = 8.0 Hz, H-1″), 4.66 (1H, dd, *J* = 8.0, 9.0 Hz, H-2″), 4.20 (1H, dd, *J* = 2.5, 9.0 Hz, H-3″), 4.37 (1H, br d, *J* = 2.5 Hz, H-4″), 4.12 (1H, m, H-5″), 4.50 (1H, H_a-6″), 4.30 (1H, H_b-6″), 6.25 (1H, br s, H-1‴), 4.76 (1H, br d, *J* = 2.5 Hz, H-2‴), 4.88 (1H, dd, *J* = 2.0, 9.0 Hz, H-3‴), 4.16 (1H, H-4‴), 5.04 (1H, m, H-5‴), 1.45 (3H, d, *J* = 6.0 Hz, H-6‴), 5.96 (1H, br s, H-1⁗), 4.84 (1H, dd, *J* = 0.5, 3.0 Hz, H-2⁗), 4.58 (1H, dd, *J* = 3.0, 9.0 Hz, H-3⁗), 4.30 (1H, H-4⁗), 4.55 (1H, dd, *J* = 6.0, 9.0 Hz, H-5⁗) and 1.68 (3H, d, *J* = 6.0 Hz, H-6⁗); ^{13}C NMR (pyridine-d_5, 150 MHz): δ_C 39.5 (C-1), 27.2 (C-2), 89.6 (C-3), 40.2 (C-4), 56.0 (C-5), 18.3 (C-6), 34.5 (C-7), 43.5 (C-8), 50.7 (C-9), 37.3 (C-10), 19.5 (C-11), 32.4 (C-12), 86.9 (C-13), 50.5 (C-14), 46.4 (C-15), 213.7 (C-16), 56.8 (C-17), 55.3 (C-18), 40.7 (C-19), 32.5 (C-20), 36.3 (C-21), 25.7 (C-22), 28.7 (C-23), 17.3 (C-24), 16.7 (C-25), 19.4 (C-26), 22.5 (C-27), 75.7 (C-28), 34.0 (C-29), 24.1 (C-30), 107.3 (C-1′), 74.3 (C-2′), 88.7 (C-3′), 72.7 (C-4′), 77.7 (C-5′), 174.5 (C-6′), 104.7 (C-1″), 75.8 (C-2″), 76.7 (C-3″), 71.2 (C-4″), 77.6 (C-5″), 62.6 (C-6″), 100.8 (C-1‴), 79.2 (C-2‴), 71.9 (C-3‴), 75.2 (C-4‴), 68.9 (C-5‴), 19.0 (C-6‴), 104.5 (C-1⁗), 72.6 (C-2⁗), 73.2 (C-3⁗), 74.6 (C-4⁗), 70.9 (C-5⁗) and 19.0 (C-6⁗); HR-ESI-MS *m/z* 1109.5496 $[M + Na]^+$ (calcd for $C_{54}H_{86}NaO_{22}^+$, 1109.5503).

Supplementary material

General experimental procedures, acid hydrolysis and sugar identification, cytotoxicity MTT assay, 1D and 2D NMR spectra, and table of ^1H and ^{13}C NMR data for the new compound **1**.

Disclosure statement

No potential conflict of interest was reported by the author.

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