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Araliachinoside A: A New Triterpene Glycoside From *Aralia chinensis* Leaves

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Abstract

From the leaves of *Aralia chinensis*, 3 oleanane-type triterpene glycosides have been isolated, including 1 new glycoside, 3β,23-dihydroxyolean-12-ene-28-oic acid 3-*O*-β-D-glucopyranosyl-(1→3)-*α*-L-arabinopyranosyl-(1→3)-β-D-glucuronopyranoside 28-*O*-β-D-glucopyranosyl ester (named as araliachinoside A, **1**), and 2 known ones, 3β,23-dihydroxyolean-12-ene-28-oic acid 3-*O*-*α*-L-arabinopyranosyl-(1→3)-*β*-D-glucuronopyranoside 28-*O*-β-D-glucopyronosyl ester (**2**) and 3β-hydroxyolean-12-ene-28-oic acid 3-*O*-β-D-glucuronopyranoside 28-*O*-β-D-glucopyronosyl ester (**3**). Their chemical structures were elucidated by using a combination of high-resolution electrospray ionization-mass spectrometry, 1-dimensional and 2-dimensional nuclear magnetic resonance spectral data, and by comparison with previous literature. Compounds **1-3** displayed cytotoxic activity toward KB and HepG2 cell lines with half-maximal inhibitory concentration values ranging from 8.1 ± 0.1 to 15.7 ± 0.3 μM in in vitro assay.

Keywords

araliaceae, *Aralia chinensis*, araliachinoside A, triterpene glycoside, cytotoxic activity

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Introduction

The genus *Aralia* contains about 70 species used medicinally in Asia and the Americas.[1] Some of these species have been used in traditional medicine, such as *A. armata*,[2,3] *A. elata*,[4] and *A. chinensis*.[5] Phytochemical study of *Aralia* plants has led to the isolation of oleanane-type triterpenoid saponins, diterpenoids, phenolics, and acetylenic lipids.[1]

Aralia chinensis L. is endemic to China and Vietnam and has been used as a traditional medicine to cure rheumatism, hepatitis, nephritis, and diabetes.[6] Twenty-seven oleanane-type saponins have been isolated from the root bark of *A. chinensis*.[7,8] However, there has been no report on the chemical composition of this plant growing in Vietnam. As part of our continuing research to find bioactive components from the genus *Aralia*,[9] we report herein the identification of 1 new (**1**) and 2 known oleanane-type triterpene saponins (**2** and **3**) from the leaves of *A. chinensis*. Cytotoxic activity of the isolated compounds on some cell lines was also evaluated.

Results and Discussion

Compounds **1-3** were obtained as white amorphous powder. Compounds **2** and **3** were identified as 3*β*,23-dihydroxy olean-12-ene-28-oic acid 3-*O*-*α*-L-arabinopyranosyl-(1→3)-*β*-D-glucuronopyranoside 28-*O*-*β*-D-glucopyronosyl ester (**2**)[10] and 3*β*-hydroxyolean-12-ene-28-oic acid 3-*O*-*β*-D-glucuronopyranoside 28-*O*-*β*-D-glucopyronosyl ester (**3**)[11] (Figure 1) by comparing their spectroscopic data (high-resolution electrospray ionization-mass spectrometry [HR-ESI-MS], ^{1}H nuclear magnetic resonance [NMR], ^{13}C NMR, distortionless enhancement by polarization transfer, heteronuclear single quantum correlation [HSQC], heteronuclear multiple quantum correlation [HMBC]) with the corresponding data in the literature (Table 1, Supplemental Figures S9-S19).

As with compounds **2** and **3**, the NMR data of **1** suggested that this compound was an oleanane-type

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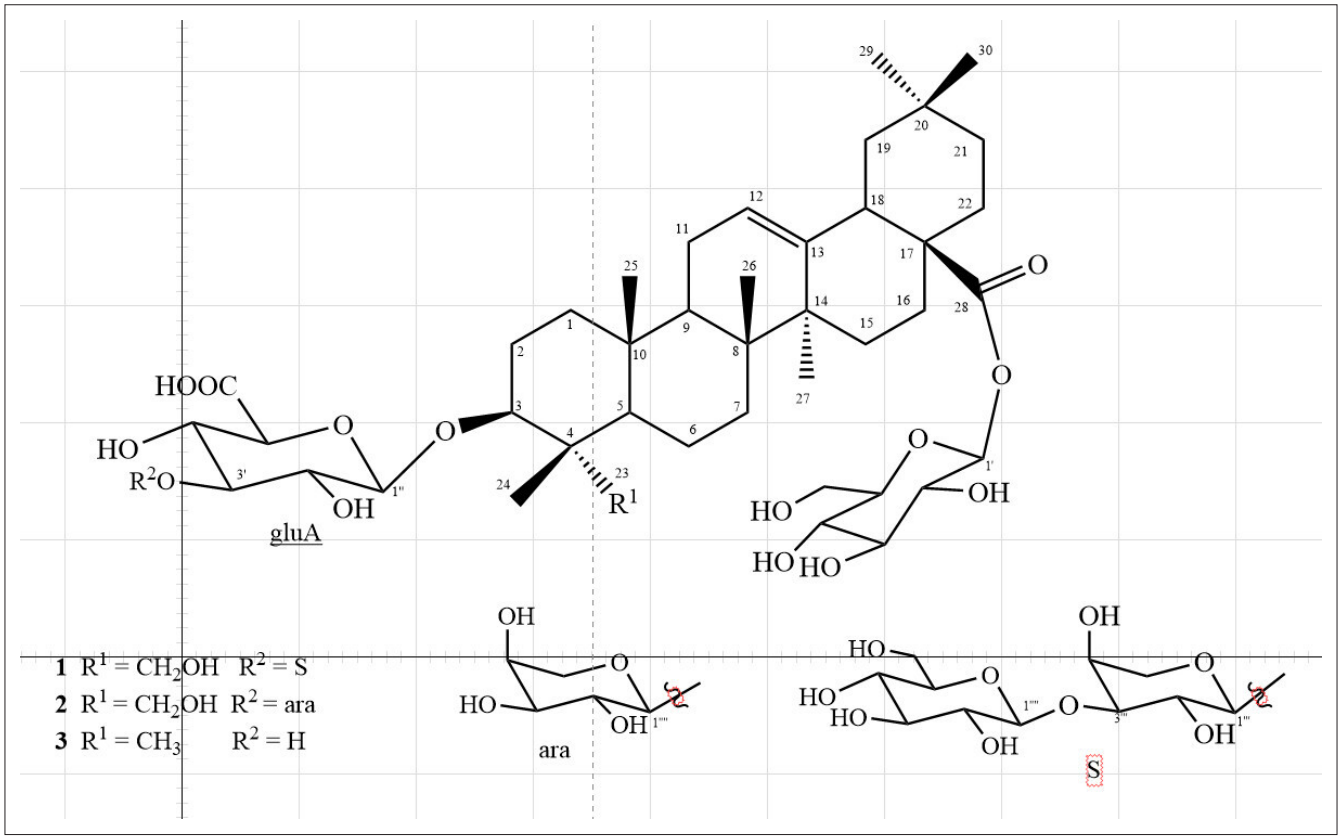

Figure 1. Chemical structures of compounds **1-3**.

triterpene glycoside.[7,8] Its molecular formula was determined as $C_{53}H_{84}O_{24}$ from the HR-ESI-MS (negative mode) quasi-molecular ion peaks at *m/z* 1103.5277 $[M - H]^-$ (calcd. for $C_{53}H_{83}O_{24}$: 1103.5280), *m/z* 1139.5004 $[M + {}^{35}Cl]^-$ (calcd. for $C_{53}H_{84}O_{24}{}^{35}Cl$: 1139.5041), and *m/z* 1141.5041 $[M + {}^{37}Cl]^-$ (calcd. for $C_{53}H_{84}O_{24}{}^{37}Cl$: 1141.5012) (Supplemental Figure S1). Comparing these results with those of compound **2** found that compound **1** has 1 more glycosylic unit. The ^1H NMR and ^{13}C NMR spectra of **1** (Supplemental Figures S2, S3) showed typical signals of the 3*β*,23-dihydroxyolean-12-ene-28-oic acid aglycone for the C-12/C-13 double bond (δ_H 5.27/δ_C 123.8 and δ_C 144.9), 1 oxygenated methylene group at C-23 (δ_H 3.27 and 3.64/ δ_C 65.0), 1 oxygenated methine group at C-3 (δ_H 3.70/δ_C 82.3), 1 carboxylate group at C-28 (δ_C 178.2), and 6 singlet methyl signals at δ_H 0.72, 0,82, 0.93, 0.95, 1.09, and 1.19, which had HSQC cross-peaks with carbon signals at δ_C 13.1, 17.8, 33.5, 23.9, 16.5, and 26.3, respectively.[10,11] Based on the biosynthesis of the oleanane skeleton, the 2 methyl groups at C-25 and C-26, and the proton H-18 had β-orientations, while H-5 and H-9 and the methyl group at C-27 had *a*-orientations. Thus, the NOESY correlations between H-5 (δ_H 1.25) and H-3 (δ_H 3.70) and H-5 and H_2-23 (δ_H 3.64/3.27) confirmed the β-orientation of the oxygenated group at C-3 and the oxygenated methylene group at C-23 (Figure 2). The 28-*O*-β-D-glucopyronosyl ester moiety was confirmed by NMR signals at δ_C 95.7/δ_H 5.40, δ_C 73.9/δ_H 3.34, δ_C 78.3/δ_H 3.44, δ_C 71.2/δ_H 3.37, δ_C 78.7/δ_H 3.32, and δ_C 62.5/δ_H 3.70 and 3.84,[8] which were further confirmed by the ^1H-^1H COSY and HMBC spectra, as shown in Figure 2. Comparing the NMR data of the other sugar moiety of **1** with those of **2** (Table 1) found that these 2 compounds have the same 3-*O*-*a*-L-arabinopyranosyl-(1→3)-β-D-glucuronopyranoside moiety, which was further confirmed by ^1H-^1H COSY, HSQC and HMBC spectra (Supplemental Figures S5-S7). The HMBC correlation from gluA H-1″ (δ_H 4.52) to C-3 of the aglycone (δ_C 82.3) and from ara H-1‴ (δ_H 4.66) to C-3″ (δ_C 86.8) confirmed that the ara unit linked to C-3″ of the gluA unit, and gluA unit attached to C-3 of the aglycone, as in compound **2**. The last sugar was attached to ara C-3‴, which was confirmed by the drastically changed carbon and proton chemical shifts at ara C-3‴ between compounds **1** and **2**, and by the observation of an HMBC correlation from H-1⁗ (δ_H 4.58) to C-3‴ (δ_C 84.4). All the NMR assignments of **1** were made by comparing its data with that of compound **2** and further elucidated by HSQC, ^1H-^1H COSY, and HMBC spectra, as shown in Table 1. The chemical shifts, multiplicity of signals, absolute values of the anomeric proton coupling constants (J_{H1-H2} = 7.5-8.0 Hz), and their magnitudes in the NMR spectrum (Table 1) indicated the *β*

Table 1. ^{1}H and ^{13}C NMR Spectroscopic Data for Compounds **1-3** in Deuterated Methanol.

	1		**2**		**3**	
C	δ_C	δ_H (mult., *J*, Hz)	δ_C	δ_H (mult., *J*, Hz)	δ_C	δ_H (mult., *J*, Hz)
1	39.5	0.98 (m)/1.60 (m)	39.5	0.98 (m)/1.62 (m)	39.9	1.02 (m)/1.62 (m)
2	26.1	1.78 (m)/1.95 (m)	26.1	1.78 (m)/1.96 (m)	26.9	1.71 (m)/2.01 (m)
3	82.2	3.69 (dd, 3.5, 12.0)	82.2	3.69 (m)	90.7	3.20 (m)
4	43.8	-	43.8	-	40.2	-
5	48.0	1.25 (m)	49.0	1.63 (m)	57.1	0.80 (m)
6	18.9	1.38 (m)/1.49 (m)	18.9	1.38 (m)/1.49 (m)	19.3	1.40 (m)/1.56 (m)
7	33.1	1.61 (m)/1.73 (m)	33.4	1.29 (m)	34.0	1.35 (m)/1.50 (m)
8	40.6	-	40.6	-	40.7	-
9	49.0	1.62 (m)	48.1	1.25 (m)	49.0	1.60 (m)
10	37.6	-	37.6	-	37.9	-
11	24.5	1.90 (m)	24.5	1.87 (m)	24.6	1.90 (m)
12	123.7	5.27 (br s)	123.7	5.27 (br s)	123.9	5.27 (t, 3.5)
13	144.9	-	144.9	-	144.8	-
14	43.0	-	43.0	-	42.9	-
15	28.8	1.10 (m)/1.80 (m)	28.8	1.10 (m)/1.80 (m)	28.9	1.10 (m)/1.81 (m)
16	23.9	1.71 (m)/2.07 (m)	24.2	1.90 (m)/2.07 (m)	24.0	1.73 (m)/2.07 (m)
17	48.2	-	49.0	-	48.0	-
18	42.6	2.88 (dd, 13.5, 3.5)	42.6	2.87 (dd, 14.0, 4.0)	42.6	2.88 (dd, 14.0, 4.0)
19	47.2	1.18 (m)/1.71 (m)	47.2	1.16 (m)/1.73 (m)	47.2	1.18 (m)/1.73 (m)
20	31.5	-	31.5	-	31.5	-
21	34.9	1.21 (m)/1.40 (m)	34.9	1.22 (m)/1.40 (m)	34.9	1.23 (m)/1.42 (m)
22	33.4	1.30 (m)/1.61 (m)	33.1	1.62 (m)/1.72 (m)	33.2	1.62 (m)/1.75 (m)
23	65.0	3.27 (m)/3.64 (m)	64.9	3.27 (m)/3.64 (m)	28.5	1.07 (s)
24	13.1	0.72 (s)	13.3	0.71 (s)	17.3	0.87 (s)
25	16.5	1.00 (s)	16.5	0.99 (s)	16.0	0.97 (s)
26	17.8	0.82 (s)	17.7	0.82 (s)	17.8	0.82 (s)
27	26.3	1.19 (s)	26.3	1.18 (s)	26.3	1.17 (s)
28	178.2	-	178.1	-	178.1	-
29	33.5	0.93 (s)	33.2	0.93 (s)	33.5	0.93 (s)
30	23.9	0.95 (s)	23.9	0.95 (s)	24.0	0.95 (s)
28-*O*-*β*-D-glucopyranosyl						
1′	95.7	5.40 (d, 8.0)	95.7	5.40 (d, 8.0)	95.7	5.40 (d, 7.5)
2′	73.9	3.34 (m)	73.9	3.34 (m)	73.9	3.30 (m)
3′	78.3	3.43 (m)	78.2	3.42 (m)	78.7	3.36 (m)
4′	71.1	3.39 (m)	71.9	3.54 (m)	71.2	3.38 (m)
5′	78.6	3.37 (m)	78.6	3.36 (m)	78.3	3.43 (m)
6′	62.4	3.70 (m) 3.84 (m)	62.4	3.70 (dd, 11.5, 4.5) 3.83 (dd, 11.5, 2.0)	62.5	3.70 (dd, 11.5, 4.5) 3.83 (dd, 11.5, 2.0)
3-*O*-*β*-D-glucuronopyranosyl						
1″	104.6	4.52 (d, 7.5)	104.7	4.50 (d, 8.0)	106.7	4.35 (d, 7.5)
2″	74.5	3.47 (m)	74.5	3.45 (m)	75.6	3.25 (m)
3″	86.8	3.66 (m)	86.1	3.61 (m)	78.0	3.38 (m)
4″	72.1	3.60 (m)	71.1	3.38 (m)	73.8	3.46 (m)
5″	76.9	3.70 (d, 9.0)	77.5	3.67 (d, 9.0)	76.5	3.55 (d, 9.0)
6″	176.6	-	176.6	-	177.0	-
3″-*O*-*a*-L-arabinopyranosyl						
1‴	105.1	4.66 (d, 7.5)	105.2	4.59 (d, 7.0)		
2‴	71.9	3.84 (m)	72.5	3.68 (m)		
3‴	84.4	3.70 (m)	74.2	3.57 (m)		
4‴	69.7	4.11 (br s)	69.7	3.83 (m)		
5‴	67.0	3.65 (m)/4.00 (m)	67.4	3.62 (m)/3.96 (m)		

(Continued)

Table 1. Continued

	1		2		3	
C	δ_C	δ_H (mult., *J*, Hz)	δ_C	δ_H (mult., *J*, Hz)	δ_C	δ_H (mult., *J*, Hz)
3‴-*O*-*β*-D-glucopyranosyl						
1⁗	105.6	4.58 (d, 8.0)				
2⁗	75.3	3.33 (m)				
3⁗	77.7	3.40 (m)				
4⁗	71.1	3.41 (m)				
5⁗	77.8	3.32 (m)				
6⁗	62.6	3.70 (m)/3.84 (m)				

Abbreviations: NMR, nuclear magnetic resonance; NOESY, nuclear Overhauser effect spectroscopy.
NMR data were assigned by heteronuclear single quantum correlation, heteronuclear multiple quantum correlation, ^{1}H-^{1}H correlation spectroscopy, nuclear Overhauser effect spectroscopy spectra.

configuration at the anomeric positions for glucopyranosyl and glucuronopyranosyl units.[10-12] Furthermore, an NOE correlation between ara H-3‴ (δ_H 3.70) and ara H-4‴ (δ_H 4.11) was observed in the NOESY spectrum of **1** (Supplemental Figure S8). This evidence was consistent with an *a* configuration for the arabinopyranosyl sugar.[12] The monosaccharides in the sugar residue were further confirmed to be D-glucuronic acid, D-glucose, and L-arabinose by hydrolysis, conversion to thiazolidine derivatives, high-performance liquid chromatography (HPLC) analysis and comparison of the retention times with those of standard monosaccharide derivatives prepared in the same procedure.[13] Consequently, compound **1** was determined to be 3*β*,23-dihydroxyolean-12-ene-28-oic acid 3-*O*

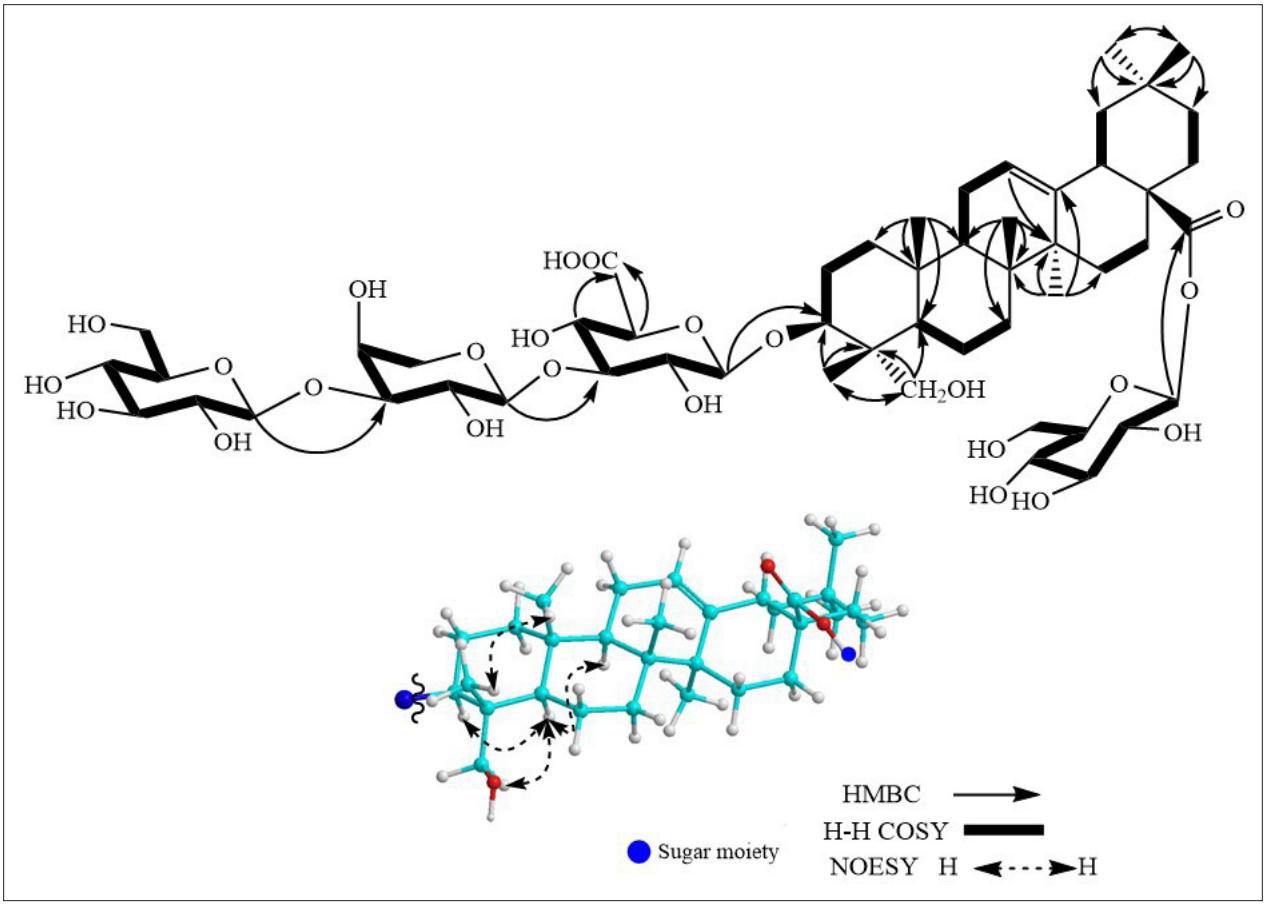

Figure 2. The ^{1}H-^{1}H correlation spectroscopy (COSY) and key heteronuclear multiple quantum correlation (HMBC) and nuclear Overhauser effect spectroscopy (NOESY) correlation of compound **1**.

Table 2. Cytotoxic Effects of Compounds **1-3** Toward KB and HepG2 Cell Lines.

Compounds	IC_{50} (μM) KB	IC_{50} (μM) HepG2
1	15.7 ± 0.3	12.5 ± 0.2
2	12.1 ± 0.3	10.5 ± 0.1
3	8.1 ± 0.1	9.5 ± 0.3
Ellipticine[a]	1.3 ± 0.1	1.5 ± 0.1

Abbreviation: IC_{50}, half-maximal inhibitory concentration.
[a]Positive control compound.

-β-D-glucopyranosyl-(1→3)-*a*-L-arabinopyranosyl-(1→3)-β-D-glucuronopyranoside 28-*O*-β-D-glucopyranosyl ester, a new compound, and named as araliachinoside A (Figure 1).

Compounds **1-3** were evaluated in vitro for their cytotoxic activity by using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetra zolium bromide (MTT) assay against 2 human cancer cell lines (KB and HepG2). Compounds **1-3** displayed cytotoxic activity toward KB and HepG2 cancer cell lines with half-maximal inhibitory concentration (IC_{50}) values from 8.1 ± 0.1 to 15.7 ± 0.3 μM (Table 2). For the structure and cytotoxicity relationship of these compounds, our results suggested that the longer the C-3 sugar moiety is, the lower its cytotoxic activity becomes.

Experimental

General

The NMR spectra were recorded on a Bruker 500 MHz spectrometer and HR-ESI-MS on an Agilent 6530 Accurate Mass Q-TOF LC/MS. The QTOF instrument was set at 2 GHz extended dynamic range resolution mode, negative ESI capillary voltage of 3500 V, fragmentor voltage of 175 V, MS scan ranging from m/z 100-1700, and an MS acquisition rate of 1.0 spectra/s. Optical rotation was measured on a Jasco P2000 polarimeter. Column chromatography was performed using silica gel, reverse phase C-18, and Diaion HP-20 resins as a stationary phase. HPLC was carried out using an AGILENT 1100 HPLC system. For thin-layer chromatography, precoated silica gel 60 F_{254} and RP-18 F_{254S} plates were used. The compounds were visualized by spraying with a 5% solution of sulphuric acid in ethanol, followed by heating with a heat gun.

Plant Material

Aralia chinensis L. leaves were collected at Cao Loc, Lang Son, Vietnam, in May 2018, and identified by botanist Nguyen. The Cuong at the Institute of Ecology and Biological Resources, VAST. A voucher specimen (coded: NCCT-P71B) was deposited at the Institute of Marine Biochemistry, VAST.

Extraction and Isolation

Dried *A. chinensis* leaves (4.5 kg) were ultrasonically extracted with methanol (MeOH), 3 times (each 10 L of MeOH for 60 minutes). After filtration, the solvent was removed in vacuo to give 230 g of a dark methanolic residue. This crude extract was suspended in water and successively partitioned with dichloromethane and ethyl acetate to give organic soluble fractions and a water layer. The water layer was poured onto a Diaion (HP-20) column and washed with water to remove salts and oligosaccharides. Saponins were stepwise eluted by MeOH/water (25%, 50%, 75%, and 100% vol of MeOH) to give 4 fractions (ACW1-ACW4). Fraction ACW3 (12.5 g) was chromatographed on a silica gel column, eluting with dichloromethane/MeOH (8/1, v/v) to give 4 fractions, ACW3A-ACW3D. Fraction ACW3B (4.2 g) was further chromatographed on a reverse phase C18 column, eluting with MeOH/water (3/1, v/v) to give 4 fractions (ACW3B1- ACW3B4). Fraction ACW3B3 (76 mg) was subjected to HPLC (J'sphere H-80 column, length 250 mm × 20 mm ID, eluting with 18% acetonitrile in water, a flow rate of 3 mL/min) to yield compound **1** (8.7 mg). Fraction ACW3B2 (120 mg) was subjected to HPLC (J'sphere H-80 column, length 250 mm × 20 mm ID, eluting with 20% acetonitrile in water, flow rate of 3 mL/min) to yield compounds **2** (12.0 mg) and **3** (15.0 mg).

3β,23-Dihydroxyolean-12-ene-28-oic acid 3-O-β-D-glucopyranosyl-(1→3)-a-L-arabinopyranosyl-(1→3)-β-D-glucuronopyranoside 28-O-β-D-glucopyranosyl ester (araliachinoside A, **1***).* White amorphous powder. $[\alpha]_D^{25}$: −46.0° (*c* 0.1, MeOH); HR-ESI-MS m/z 1103.5277 $[M - H]^-$ (calcd. for $C_{53}H_{83}O_{24}$: 1103.5280), m/z 1139.5004 $[M + {}^{35}Cl]^-$ (calcd. for $C_{53}H_{84}O_{24}{}^{35}Cl$: 1139.5041), and m/z 1141.5041 $[M + {}^{37}Cl]^-$ (calcd. for $C_{53}H_{84}O_{24}{}^{37}Cl$: 1141.5012). ^1H NMR (deuterated methanol [CD_3OD], 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz) data, see Table 1.

*3β,23-Dihydroxyolean-12-ene-28-oic acid 3-O-a-L-arabinopyranosyl-(1→3)-β-D-glucuronopyranoside 28-O-β-D-glucopyronosyl ester (***2***).* White amorphous powder. $[\alpha]_D^{25}$: −55.0° (*c* 0.1, MeOH); HR-ESI-MS m/z 941.4707 $[M - H]^-$ (calcd. for $C_{47}H_{73}O_{19}$: 941.4746); ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz) data, see Table 1.

3β-Hydroxyolean-12-ene-28-oic acid 3-O-β-D-glucuronopyranoside 28-O-β-D-glucopyronosyl ester (3). White amorphous powder. $[\alpha]_D^{25}$: −38.0° (*c* 0.1, MeOH); HR-ESI-MS m/z 793.4322 $[M - H]^-$ (calcd. for $C_{42}H_{66}O_{14}$: 793.4374), m/z 829.4100 $[M + {}^{35}Cl]^-$ (calcd. for $C_{42}H_{66}O_{14}{}^{35}Cl$: 829.4141), and m/z 831.4080 $[M + {}^{37}Cl]^-$ (calcd. for $C_{42}H_{66}O_{14}{}^{37}Cl$: 831.4112). ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz) data, see Table 1.

Cytotoxic Assay

Two human cancer cell lines (epidermoid carcinoma cell line KB-ATCC CCL-17 and hepatoma carcinoma cell line HepG2-ATCCHB-8065), obtained from the American Type Culture Collection (USA) ATCC, were used for cytotoxic evaluation. The cells were grown in Roswell Park Memorial Institute

Medium 1640 supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37 °C in a humidified atmosphere (95% air and 5% carbon dioxide). The exponentially growing cells were used throughout the experiments. The inhibitory effects of the compounds on the growth of the human cancer cell lines were determined by measuring the metabolic activity using an MTT assay. Briefly, human cancer cell lines (1×10^5 cells/mL) were treated for 3 days with a series of concentrations of the compounds (in dimethylsulfoxide): 0.125, 0.5, 2.0, 8.0, 32.0, and 128.0 μg/mL. After incubation, 0.1 mg MTT solution (50 μL of a 2 mg/mL solution) was added to each well, and the cells were then incubated at 37 °C for 4 hours. The plates were centrifuged at 1000 rpm for 10 minutes at room temperature, and the media were then carefully aspirated. Dimethylsulfoxide (150 μL) was added to each well to dissolve the formazan crystals. The plates were read immediately at 540 nm on a microplate reader (TECAN GENIOUS). All the experiments were performed 3 times, and the mean absorbance values were calculated. The results are expressed as the percentage of inhibition that produced a reduction in the absorbance by the treatment of the compounds compared with the untreated controls. A dose-response curve was generated, and the IC_{50} was determined for each compound as well as each cell line.

Conclusions

Three oleanane-type triterpene glycosides, including a new one, 3*β*,23-dihydroxyolean-12-ene-28-oic acid 3-*O*-*β*-D-glucopyranosyl-(1→3)-*a*-L-arabinopyranosyl-(1→3)-*β*-D-glucuronopyranoside 28-*O*-*β*-D-glucopyranosyl ester (named as araliachinoside A, **1**), and 2 known ones, 3*β*,23-dihydroxyolean-12-ene-28-oic acid 3-*O*-*a*-L-arabinopyranosyl-(1→3)-*β*-D-glucuronopyranoside 28-*O*-*β*-D-glucopyronosyl ester (**2**) and 3*β*-hydroxyolean-12-ene-28-oic acid 3-*O*-*β*-D-glucuronopyranoside 28-*O*-*β*-D-glucopyronosyl ester (**3**), were isolated from the leaves of *A. chinensis*. Their chemical structures were elucidated using a combination of HR-ESI-MS, 1D and 2D NMR spectra, as well as by comparison with literature data. Compounds **1-3** displayed cytotoxic activity toward KB and HepG2 cancer cell lines with IC_{50} values ranging from 8.1 ± 0.1 to 15.7 ± 0.3 μM in in vitro assay. The above results are completely in accordance with the previous literature that oleanane-type triterpene glycosides are typically present in the *Aralia* genus. In addition, the significant cytotoxic activity results suggest that either saponin compounds or enriched saponin fractions from *A. chinensis* could be useful as anticancer agents. Further research, such as induction of apoptosis of compounds **1-3** on KB and HepG2 cells, should be undertaken to clarify the cytotoxic mechanism of these compounds.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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