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Original article

Phenolic constituents from the roots of *Alangium chinense*

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ABSTRACT

Three new phenolics (**1**–**3**) and twenty-eight known compounds (**4**–**31**) were isolated from an ethanolic extract of roots of *Alangium chinense*. Compound **11** exhibited antiviral activity against Coxsackie virus B3 with IC_{50} values of 16.89 μmol/L. Compounds **1**, **10**–**17**, **19**–**21**, and **23** showed strong antioxidant activity against Fe^{2+}-cysteine-induced rat liver microsomal lipid peroxidation, with IC_{50} values of 0.14–8.18 μmol/L.

1. Introduction

Alangium chinense (Lour.) Harms is a deciduous shrub belonging to family Alangiaceae and distributes mainly in China. The roots, flowers, and leaves of this plant have historically been applied as a traditional Chinese medicine for the treatment of rheumatoid arthritis, traumatic injury, fracture, and pain [1]. Alkaloids, terpenoids and phenolics have been previously reported from this plant [2–4]. As part of a program to study the bioactive substances from medicinal plants, an ethanolic extract of dried roots of *A. chinense* was investigated. Three new (**1**–**3**) and twenty-eight known phenolics (**4**–**31**) [5–25] were identified (the names of the known compounds were deposited in Supporting information), and their antiviral/antioxidant bioactivities were also evaluated.

2. Experimental

2.1. General experimental

Optical rotations were recorded on a JASCO P-2000 automatic digital polarimeter. UV spectra were measured on a JASCO V650 spectrophotometer. CD spectra were recorded on a JASCO J-815 spectropolarimeter. IR spectra were recorded on a Nicolet 5700 FT-IR spectrometer. NMR spectra were recorded on INOVA-500 and SX-600 spectrometers. ESI-MS spectra were measured on an Agilent 1100 Series LC/MSD ion trap mass spectrometer. HR-ESI-MS data were recorded on an Agilent Technologies 6250 Accurate-Mass Q-TOF LC/MS spectrometer. EIMS and HREIMS data were recorded on an AutoSpec Ultima-TOF MS spectrometer. Preparative HPLC was performed on a Shimadzu LC-6AD instrument with an SPD-10A detector, using a YMC-Pack ODS-A column (250 mm × 20 mm, 5 μm). Sephadex LH-20 (Amersham Pharmacia Biotech AB, Sweden), ODS (45–70 μm, Merck), macroporous adsorptive resins (XAD-D101, Tianjin Nankai Chemical Inc., China), polyamide resin (30–60 mesh, Jiangsu Linjiang Chemical Inc., China), and silica gel (200–300 mesh, Qingdao Marine Chemical Inc., China) were used for column chromatography (CC). TLC was conducted with glass precoated with silica gel GF_{254} (Qingdao Marine Chemical Inc., China).

2.2. Plant material

The roots of *A. chinense* were collected from Guangxi Province, China in July 2009 and identified by Prof. Peng-Fei Tu (Peking University, School of Pharmaceutical Sciences). A voucher specimen (ID-S-2356) has been deposited in the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Chinese Academy of Medical Sciences, China.

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2.3. Extraction and isolation

Air-dried, powdered roots of *A. chinense* (200 kg) were macerated for 12 h with 800 L of aqueous 95% EtOH and refluxed for 6 h (800 L × 3). After removal of the solvent under vacuum, the resultant residue (8 kg) was suspended in acidic H_2O (100 L) and acidified to pH 2 with HCl to afford acidic H_2O-soluble and acidic H_2O-insoluble fractions. The acidic mixture was then filtered and partitioned with petroleum ether. The acidic H_2O phase was basified to pH 10 with NaOH and then partitioned with $CHCl_3$ to yield the $CHCl_3$ extract (90 g). The alkaline H_2O phase was then acidified to pH 7 with HCl and partitioned with *n*-BuOH to yield the *n*-BuOH extract (210 g). The crude $CHCl_3$ extract (90 g) was fractionated using a basified silica gel column (pH 8–9, 200–300 mesh, 1.6 kg), eluting with petroleum ether containing increasing amounts of EtOAc (1:0, 50:1, 20:1, 10:1, 5:1, 1:1), and then eluted with CH_2Cl_2:MeOH (10:1–0:100) to afford eight fractions (A–H). Fraction F (7.2 g) was fractionated *via* an ODS column (45–70 μm, 400 g) by eluting with a gradient of MeOH (5–100%) in H_2O to yield six major fractions (F1–F5). Fraction F5 (1.2 g) was chromatographed over a Sephadex LH-20 column with CH_2Cl_2:MeOH (5:1) and was further purified by reversed-phase preparative HPLC (MeOH–H_2O–TFA 40:60:0.03) to afford compound **1** (8 mg, Fig. 1). Fraction G (7.2 g) was fractionated *via* an ODS column (45–70 μm, 400 g) by eluting with a gradient of MeOH (5–100%) in H_2O to yield five major fractions (G1–G5). Fraction G3 (1.1 g) was chromatographed over a Sephadex LH-20 column with CH_2Cl_2:MeOH (5:1) and was further purified by reversed-phase preparative HPLC (MeOH–H_2O–TFA 30:70:0.03) to afford compounds **3** (17 mg, Fig. 1).

The crude *n*-BuOH extract (210 g) was fractionated using a macroporous adsorptive resins column (XAD-D101, 3.9 kg), eluting with D_2O and then eluted with ethanol/D_2O (95/5) to afford ethanol/D_2O (95/5) fraction (135 g). The ethanol/D_2O (95/5) fraction (135 g) was fractionated using a polyamide resins column (30–60 mesh, 2.0 kg), and eluted with D_2O containing increasing amounts of ethanol (88:12, 75:25, 60:40, 5:95) to afford D_2O fraction (86 g). The D_2O fraction (86 g) was fractionated using a silica gel column (200–300 mesh, 1.5 kg), and eluted with petroleum ether containing increasing amounts of acetone (25:1, 10:1, 5:1, 3:1) and then with CH_2Cl_2:MeOH (20:1–0:100) to afford seven fractions (A–G). Fraction D (22.7 g) was fractionated *via* an ODS column (45–70 μm, 400 g) by eluting with a gradient of MeOH (5–100%) in H_2O to yield five major fractions (D1–D5). Fraction D1 (3.4 g) was chromatographed over a Sephadex LH-20 column with MeOH:H_2O (4:1) and was further purified by reversed-phase preparative HPLC (MeOH–H_2O 22:78) to afford compound **2** (15 mg, Fig. 1).

Twenty-eight known compounds (**4**–**31**) were also isolated and identified from the roots of *A. chinense*, the detail were deposited in Supporting information.

(7*R*,8*R*)-Threo-4,7,9,9′-tetrahydroxy-3,5,2′-trimethoxy-8-*O*-4′-neolignan (**1**): White amorphous powder; $[\alpha]_D^{20}$ +55.2 (*c* 0.3, MeOH); UV (MeOH) λ_{max} (log ε) 207 (4.73), 233 (4.08), 280 (3.57) nm; CD (MeOH) 234 (Δε −5.48), 253.5 (Δε +2.26), 313 (Δε +0.89) nm. IR (KBr) ν_{max} 3399, 2940, 1678, 1613, 1513, 1462, 1426, 1327, 1262, 1220, 1118, 1032, 835, 802, 722 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) and ^{13}C NMR (150 MHz, CD_3OD) data, see Table 1; ESI-MS *m/z* 431 $[M+Na]^+$, 407 $[M-H]^-$; HR ESI-MS *m/z* 431.1676 $[M+Na]^+$ (calcd. for $C_{21}H_{28}O_8Na$, 431.1676).

2-(Hydroxymethyl)phenol 1-*O*-β-D-glucopyranose-(1 → 6)-*O*-α-L-rhamno-pyrano side (**2**): White amorphous powder; $[\alpha]_D^{20}$ +75.1 (*c* 0.6, MeOH); IR (KBr) ν_{max} 3382, 2923, 1604, 1493, 1455, 1234, 1071, 761 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see Table 1; ESIMS *m/z* 455 $[M+Na]^+$, 431$[M-H]^-$; HR ESI-MS *m/z* 455.1525 $[M+Na]^+$ (calcd. for $C_{19}H_{28}O_{11}Na$, 455.1524).

2-(Ethoxymethyl)phenol 1-*O*-β-D-glucopyranoside (**3**): White amorphous powder; $[\alpha]_D^{20}$ +92.3 (*c* 0.8, MeOH); IR (KBr) ν_{max} 3461, 3268, 2874, 1677, 1604, 1492, 1454, 1391, 1235, 1197, 1104, 1071, 893, 856, 754 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) data, see Table 1; ESI-MS *m/z* 337 $[M+Na]^+$; HR ESI-MS *m/z* 337.1276 $[M+Na]^+$ (calcd. for $C_{15}H_{22}O_7Na$, 337.1258).

2.4. Acid hydrolysis of **2**

Compound **2** (3 mg) was dissolved in 2 mol/L HCl (aq) (2 mL) and heated at 90 °C for 10 h under constant stirring. After extraction with EtOAc (3× 2 mL), the aqueous layer was evaporated and cryodesiccated. Each residue was dissolved in dry pyridine (1 mL), and then L-cysteine methyl ester hydrochloride (4 mg) was added. Each mixture was stirred at 60 °C for 2 h, and then 0.4 mL of *N*-trimethylsilylimidazole was added, followed by heating to dryness at 60 °C for 2 h. Each dried reactant was partitioned between *n*-hexane and H_2O (4 mL), and the *n*-hexane fraction was subjected to gas chromatography (GC) (column: DM-5, 0.25 mm × 30 m × 25 μmol/L; detector: FID; temperature: 280 °C; injector temperature: 260 °C; carrier: N_2 gas). The sugars from each reactant were identified by comparison of their retention times with those for authentic standards [t_R: 24.77 min for D-glucose, 24.34 min for L-rhamnose].

2.5. Acid hydrolysis of **3**

Following the same method used for acid hydrolysis of **2**, compound **3** (2 mg) was hydrolyzed to afford the sugar moieties. The sugars from each reactant were then identified by comparison of their retention times with those for authentic standards [t_R: 19.84 min for D-glucose].

2.6. In vitro *anti-Coxsackie virus B3 activity assay*

The anti-coxsackie virus B3 activity assay was determined using the same method as previously described [2]. Briefly, confluent Vero cells grown in 96-well microplates were infected with 100 median tissue culture infective doses (100TCID50) of Cox B3 virus. After 1 h of adsorption at 37 °C, the monolayers were

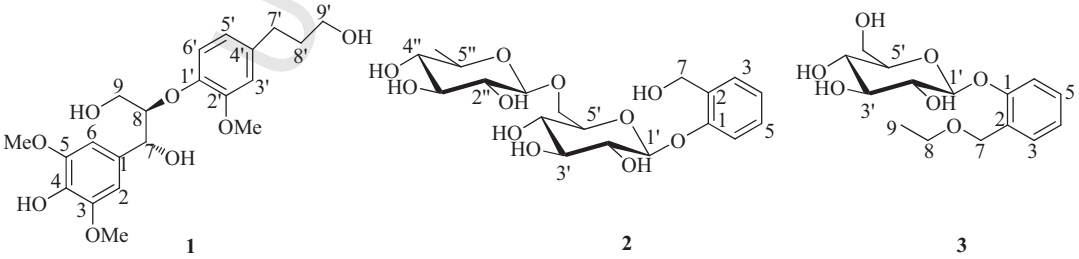

Fig. 1. Structures of compounds **1**–**3** from *A. chinense*.

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Table 1
^{1}H NMR and ^{13}C NMR data of compounds **1**–**3** in CD_3OD.[a]

Position	**1**		**2**		**3**	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	133.0		157.2		157.4	
2	105.3	6.72 s	132.5		129.3	
3	149.1		130.2	7.27 d (7.5)	130.7	7.28 d (7.5)
4	136.0		124.1	6.97 t	123.7	6.96 t
5	149.1		130.0	7.22 t	130.4	7.20 t
6	105.3	6.72 s	117.4	7.12 d (7.5)	117.1	7.15 d (7.5)
7	74.2	4.87 d (5.4)	61.2	4.73 d (13.0), 4.54 d (13.0)	69.0	4.67 d (12.0), 4.48 d (12.0)
8	87.4	4.23 dd (5.4, 9.6)			67.0	3.51 q
9	61.9	3.47 dd (5.4, 12.0), 3.72 overlap			15.6	1.15 t
1′	147.6		103.6	4.78 d (8.4)	103.5	4.82 d (7.5)
2′	151.6		74.3	3.29 m	75.3	3.42 m
3′	113.9	6.84 d (1.8)	78.3	3.39 m	78.5	3.36 overlap
4′	138.1		72.4	3.77 m	71.6	3.35 overlap
5′	122.0	6.68 overlap	75.3	3.42 m	78.2	3.36 overlap
6′	119.4	6.95 d (7.8)	68.1	3.96 dd (11.0, 1.75), 3.54 m	62.8	3.84 d (12.0,1.7), 3.65 dd (5.0, 12.0)
7′	32.7	2.61 t (7.8)				
8′	35.6	1.80 m				
9′	62.2	3.55 t				
1″			102.5	4.64 d (1.35)		
2″			71.8	3.31 m		
3″			72.6	3.61 m		
4″			77.2	3.50 m		
5″			70.1	3.56 m		
6″			18.2	1.14 d (6.25)		
$-OCH_3$	56.7 × 2	3.84 (6H)				
$-OCH_3$	56.5	3.84 (3H)				

[a] ^{13}C 150 MHz, ^{1}H 600 MHz for **1**. ^{13}C 125 MHz, ^{1}H 500 MHz for **2** and **3**. Proton coupling constants (*J*) in Hz were given in parentheses.

washed with phosphate buffered saline (PBS) and incubated at 37 °C in maintenance media (MEM plus 2% fetal bovine serum (FBS)) with or without different concentrations of test compounds. The viral cytopathic effect (CPE) was observed when the viral control group reached 4+, and the antiviral activity of the tested compounds was determined by Reed and Muench analyses.

2.7. Antioxidant assay

The antioxidant assays were conducted according to methods previously described [2]. Briefly, 1.0 mg of microsomal protein in 1 mL of 0.1 mol/L PBS buffer (pH 7.4) was incubated with 0.2 μmol/L cysteine and the test samples at 37 °C for 15 min. Lipid peroxidation was initiated by the addition of 0.05 mmol/L $FeSO_4$. After incubation, 1 mL of 20% trichloroacetic acid was added to terminate the reaction. The mixture was centrifuged for 10 min at 3000 rpm. The supernatant was removed and reacted with 0.67% TBA for 10 min at 100 °C. After cooling, the MDA (malondialdehyde, a compound produced during microsomal lipid peroxidation induced by Fe^{2+}-cysteine, was detected using the thiobarbituric acid (TBA) method) was quantified by UV/vis (absorbance at 532 nm), from which the inhibition rate (*IR*) was calculated as $IR\ [\%] = 100\% - A_t/(A_p - A_c) \times 100$, where A_p, A_t, and A_c refer to the absorbance of Fe^{2+}-cysteine, test compound, and control (solvent only), respectively. Vitamin E was selected as the positive control.

3. Results and discussion

Compound **1**, a white amorphous powder, displayed a molecular formula of $C_{21}H_{28}O_8$ with 8 degrees of unsaturation, as established by HR-ESI-MS (*m/z* 431.1676 $[M+Na]^+$, calcd. 431.1676). The IR spectrum showed the absorptions of hydroxyl group (3399 cm^{-1}) and aromatic ring (1513 and 1462 cm^{-1}). The NMR data of **1** (Table 1) indicated the presence of a symmetric 1,3,4,5-tetrasubstituted phenyl, an 1′,2′,4′-trisubstituted phenyl, three methoxyls, four methylenes (two oxygenated), and seven methine (two oxygenated) groups. Analysis of the 1D and 2D NMR data (including ^{1}H–^{1}H COSY, HSQC, HMBC spectra) allowed for the establishment of two C6-C3 units (A: C1-C9 and B: C1′-C9′) of lignan in **1**. The HMBC correlations (Fig. 2) from H-2/6 to C-7/C-4, from H-7 to C-2/6/9 and from H-9 to C-7, from H-8 to C-1, from OMe-3 to C-3 and from OMe-5 to C-5, together with their chemical shifts, led to the determination of unit C1-C9. Similarly, based on the HMBC correlations from H-3′ to C-1′/C-5′/C-7′, from H-5′ to C-1′/C-3′/C-7′, from H-6′ to C-2′/C4′, from H-7′ to C-3′/C-5′, from H-8′ to C-4′, from H-9′ to C-7′, from OMe-2′ to C-2′, the unit C1′-C9′ was determined. The HMBC correlation from H-8 to C-1′, together with the chemical shifts of C-8 and C-1′, suggested that units A and B were connected through C8-O-C1′ bond to form the planar structure, 4,7,9,9′-tetrahydroxy-3,5,2′-trimethoxy-8-O-4′-neolignan.

In the ^{1}H NMR spectrum, the coupling constant ($J_{7,8}$ = 5.4 Hz) indicated the 7,8-*threo* relative configuration [26]. A negative Cotton effect at 234 nm ($\Delta\varepsilon$ −5.48) in the CD spectrum suggested the 8*R* configuration for **1** [27–31]. Based on the relative configuration assigned above, the absolute configuration was determined to be 7*R* and 8*R*. Thus, **1** was characterized as shown in Fig. 1 and named to be (7*R*,8*R*)-*threo*-4,7,9,9′-tetrahydroxy-3,5,2′-trimethoxy-8-O-4′-neolignan.

Compound **2** was obtained as white amorphous powder, and its molecular formula was established as $C_{19}H_{28}O_{11}$ by HR-ESIMS at *m/z* 455.1525 $[M+Na]^+$ (calcd. for 455.1524), with 6 degrees of unsaturation. The IR spectrum showed the absorptions of hydroxyl and aromatic groups at 3382 and 1493 cm^{-1}, respectively. The ^{13}C NMR and DEPT spectra of **2** showed the presence of 19 carbon signals, including one methyl, two methylenes, fourteen methines, and two quaternary carbons in the structure. One 1,2-disubstituted phenyl unit was assigned based on the chemical shifts and splitting pattern of four aromatic protons at δ_H 6.97–7.27 in the ^{1}H NMR of **2** (Table 1), which were confirmed by the six ^{13}C resonances at δ_C 117–157. The HMBC correlations (Fig. 2) from H-7 to C-1 (δ_C 157.2)/C-2

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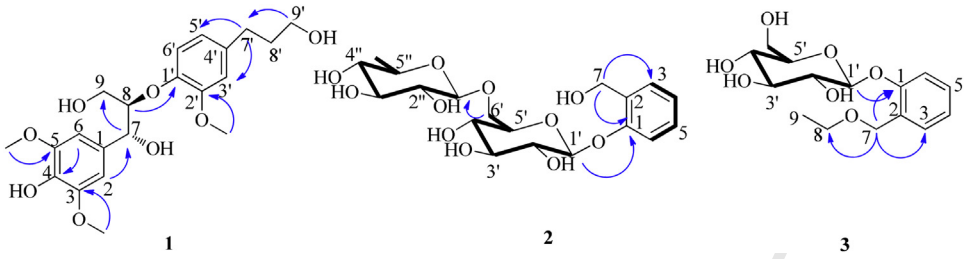

Fig. 2. Key ^{1}H–^{1}H COSY (—) and HMBC (H→C) correlations of **1**–**3**.

(δ_C 132.5)/C-3 (δ_C 130.2) demonstrated that one methylene group C-7 (δ_C 61.2) was attached at the C-2 to form the 2-(hydroxymethyl)phenol aglycone. The ^{1}H NMR data displayed the signals of two anomeric protons at δ_H 4.78 (1H, d, 8.4 Hz) and 4.64 (1H, d, 1.35 Hz), indicating the existence of two mono-sugar moieties. Analysis of the ^{1}H–^{1}H COSY, HSQC, and acidic hydrolysis experiments allowed for the establishment of the two sugar moieties to be rhamnopyranosyl (C1″-C6″) and glucopyranosyl (C1′-C6′), respectively. The HMBC correlation (Fig. 2) from H-1′ to C-1 revealed that the glucopyranosyl moiety was connected at C-1 of the 2-(hydroxymethyl)phenol aglycone. Based on the HMBC correlations between H-6′ and C-1″ and between H-1″ to C-6′, the rhamnopyranosyl was determined to be linked at C-6′ of the glucopyranosyl moiety. Thus, the planar structure of **2** was established to be 2-(hydroxymethyl)phenol 1-O-glucopyranose-(1 → 6)-rhamnopyranoside.

The splitting patterns of the anomeric proton H-1′ (d, J = 8.4 Hz) indicated that the glucopyranose was in β-configuration. The absolute configuration of β-glucopyranose was then confirmed to be D by acid hydrolysis and GC analysis. The relative configuration of H-1″ of rhamnopyranoside could not be assigned by the coupling constant of the anomeric proton. Therefore, the rhamnopyranoside was unambiguously determined to be α-L-rhamnopyranoside by acid hydrolysis and GC analysis. Thus, the structure of **2** was characterized to be 2-(hydroxymethyl)phenol 1-O-β-D-glucopyranose-(1 → 6)-O-α-L-rhamnopyranoside.

Compound **3** was obtained as white amorphous powder, and its molecular formula was established as $C_{15}H_{22}O_7$ based on the HR-ESIMS at m/z 337.1276 $[M+Na]^+$ (calcd. for 337.1258), with 5 degrees of unsaturation. Comparison the NMR data of **3** with **2** (Table 1) revealed that **3** was an analog of **2**, a glucoside of 2-(hydroxymethyl)phenol, except for the absence of rhamnopyranosyl and the presence of one ethanol group in **3**. Acid hydrolysis and GC experiment unambiguously confirmed the presence of β-D-glucose in the structure. The HMBC correlations (Fig. 2) from H-1′ (anomeric proton of glucosyl) to C-1 (δ_C 157.4), from H-7 to C-1 (δ_C 157.4)/C-3 (δ_C 130.7)/C-8 (δ_C 67.0), and from H-8 to C-7 established that the glucopyranosyl moiety was located at C-1 and the ethoxymethyl group was located at C-2 of the phenyl. The resonance of the anomeric proton at δ_H 4.82 (1H, d, J = 7.5 Hz, H-1′) indicated a β-glycosidic linkage. Thus, the structure of **3** was characterized as shown and named to be 2-(ethoxymethyl)phenol 1-O-β-D-glucopyranoside.

Twenty-eight known phenolics (**4**–**31**) were identified based on their spectroscopic profiles (NMR, UV, MS, and CD) and comparison to published data.

Two different assays (*in vitro* anti-coxsackie virus B3 activity assay, and antioxidant assay) were carried out to evaluate the bioactivities of **1**–**31**. Compounds **2**–**9**, **18**, and **22** showed no activity in the assay. Compound **11** exhibited antiviral activities against Coxsackie virus B3 with IC_{50} values of 16.89 μmol/L. Compounds **1**, **10**–**17**, **19**–**21**, and **23** showed strong antioxidant activities against Fe^{2+}-cysteine induced rat liver microsomal lipid peroxidation, with IC_{50} values of 0.14–8.18 μmol/L (Table 2). Among them, compound **11** inhibited the strongest antioxidant activity with the IC_{50} values of 0.14 μmol/L. In the same assay, the IC_{50} of the positive control, vitamin E, was 54.2 μmol/L, indicated that compounds **1**, **10**–**17**, **19**–**21**, and **23** showed much strong bioactivity than vitamin E and indicated that these compounds had potential health benefit.

Table 2
Antioxidant activity of compounds **1**, **10**–**17**, **19**–**21**, and **23**.[a]

Compound	IC_{50} (μmol/L)	Compound	IC_{50} (μmol/L)
1	8.18	**16**	1.14
10	0.65	**17**	0.50
11	0.14	**19**	5.25
12	0.23	**20**	0.50
13	0.97	**21**	7.29
14	0.41	**23**	4.29
15	5.69	Vitamin E	54.2

[a] Compounds **2**–**9**, **18** and **22** were inactive.

4. Conclusion

In summary, three new phenolics (**1**–**3**) and twenty-eight known compounds (**4**–**31**) were isolated from an ethanolic extract of roots of *A. chinense*. Compound **11** exhibited antiviral activity against Coxsackie virus B3 with IC_{50} values of 16.89 μmol/L. Compounds **1**, **10**–**17**, **19**–**21**, and **23** showed strong antioxidant activities against Fe^{2+}-cysteine-induced rat liver microsomal lipid peroxidation, with IC_{50} values of 0.14–8.18 μmol/L. This investigation could shed new light on the further understanding of the bioactive chemical constituents of *A. chinense*.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.05.012.

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