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PHENOLIC GLUCOSIDES FROM *ALANGIUM PLANTANIFOLIUM*

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A novel phenolic glucoside alangitanifoliside A (**1**) together with two known phenolic glucosides 4′,6′-*O*-(*S*)-hexahydroxydiphenylsalicin (**2**) and salicin (**3**), and gallic acid were isolated from stem barks of *Alangium plantanifolium*. Their structures were determined by spectroscopic and chemical methods. The structure of **1** was elucidated to be 1-*O*-[2-(1-hydroxy-6-oxocyclohex-2-ene-1-carboxymethyl)-phenyl]-4,6-*O*-[(*S*)-,4,4′,5,5′ 6,6′-hexahydroxydiphenoyl]-β-D-glucopyranose.

Keywords: *Alangium plantanifolium*; Alangiaceae; Alangitanifolisides A

INTRODUCTION

Alangium, the sole genus in the family Alangiaceae, is composed of about 22 species distributed in the tropics and subtropical area of the Eastern Hemisphere, eight species are known to occur in South China [1]. A variety of alkaloids [2–4] and glycosides [5–12] were reported as chemical constituents of species in this genus. *A. plantanifolium* and *A. chinense* are used in Chinese traditional medicine for the treatment of rheumatalgia, paralysis, cardianeuria, and wound [13]. Pharmacological studies of the extracts from these two species showed muscular relaxing activity, and anabasine was considered as the active component [14]. We report here the isolation and structural elucidation of a new phenolic glucoside named alangitanifoliside A (**1**).

RESULTS AND DISCUSSION

The ethanolic extract of the air-dried and ground stem barks of *A. plantanifolium* was subjected to column chromatography on silica gel to afford a fraction, which was further purified to give alangitanifolisides A (**1**). In addition, 4′,6′-*O*-(*S*)-hexahydroxydiphenylsa-

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licin (**2**), salicin (**3**), and gallic acid were obtained and identified from their spectral data and by comparison with literature values [11,12].

Alangitanifoliside A (**1**) was obtained as white powder, $[\alpha]_D^{18} + 6.0$ (c 0.30, MeOH). Its IR (KBr, cm^{-1}) spectrum showed a strong broadened absorption band for hydroxyl groups (3413), bands for conjugated carboxyl groups (1736, 1618), and aromatic rings (1602, 1503, and 1494). The positive FABMS spectrum exhibited quasi-molecular ion peaks at *m/z* 749 $[M+Na]^+$ and 727 $[M+H]^+$, its molecular formula was deduced to be $C_{34}H_{30}O_{18}$ by HRFABMS (found for $C_{34}H_{30}O_{18}Na$: 749.1328, calcd.: 749.1329; found for $C_{34}H_{31}O_{18}$: 727.1546, calcd.: 727.1510). The NMR data (Table I) revealed that **1** is a phenolic glycoside, this was confirmed by HMQC and HMBC experiments. The signals at δ_H 4.99 (d, 1H, $J = 7.5$ Hz) and δ_C 102.5, correlated to each other in the HMQC spectrum, were assignable to anomeric proton and carbon of the sugar moiety, and the β configuration at the anomeric carbon was suggested by the coupling constant. The chemical shifts and coupling patterns of

TABLE I ^1H and ^{13}C NMR data for alangitanifoliside A (**1**)

No.	**1***		**1†**	
	^1H	^{13}C	^1H	^{13}C
1	4.99 d (7.5)	102.5 d	4.98 d (7.8)	101.0 d
2	3.56 dd (7.5, 9.3)	76.0 d	3.39 dd (7.8, 9.6)	77.6 d
3	3.68 dd (9.3, 9.3)	76.0 d	3.60 dd (9.9, 9.6)	77.6 d
4	4.90 dd (9.3, 10.2)	73.5 d	4.60 dd (9.9, 9.9)	74.3 d
5	3.98 dd (10.2, 6.0)	73.3 d	4.05 dd (9.9, 6.0)	73.9 d
6a	3.76 br d (13.2)	64.9 t	3.70 brd (13.2)	63.2 t
6b	5.15 dd (13.2, 6.0)		4.93 dd (13.2, 6.0)	
1′		157.0		154.9 s
2′		126.6		124.7 s
3′	7.25 br d (7.5)	131.6	7.24 dd (1.5, 7.5)	129.1 d
4′	6.97 br dd (7.5, 7.5)	123.9	7.02 brdd (7.5, 7.5)	122.3 d
5′	7.28 br dd (7.5, 8.1)	131.6	7.31 brdd (7.5, 8.1)	129.9 d
6′	7.10 br d (8.1)	116.5	7.13 brd (8.1)	115.1 d
7′a	5.12 d (12.3)	64.6	5.11 d (12.6)	62.6 t
7′b	5.39 d (12.3)		5.28 d (12.6)	
1″		116.9 s		115.3 s
2″		126.6 s		124.5 s
3″	6.49 s	108.4 d	6.32 s	105.5 d
4″		146.0 s		144.4 s
5″		137.6 s		135.1 s
6″		145.0 s		144.3 s
7″		170.2 s		168.1 s
1‴		117.2 s		115.7 s
2‴		126.8 s		124.8 s
3‴	6.65 s	108.8 d	6.50 s	106.3 d
4‴		146.0 s		144.6 s
5‴		137.8 s		135.4 s
6‴		145.0 s		144.7 s
7‴		169.9 s		167.2 s
1⁗		79.5 s		77.6 d
2⁗	5.72 dt (9.6, 1.5)	129.6 d	5.72 dt (9.6, 1.5)	128.9 d
3⁗	6.11 dt (9.6, 3.6)	133.9 d	6.08 dt (9.6, 3.6)	131.9 d
4⁗a	2.40 m	27.7 t	2.39 m	26.2 t
4⁗b	2.63 m		2.46 m	
5⁗a	2.45 m	37.4 t	2.45 m	36.0 t
5⁗b	2.85 m		2.68 m	
6⁗		207.9 s		206.3 s
7⁗		171.7 s		170.2 s

* Measured in CD_3OD at 75 MHz for ^{13}C, 300 MHz for ^1H.
† Measured in DMSO-d_6 at 75 MHz for ^{13}C, 300 MHz for ^1H.. δ in ppm, J (in parentheses) in Hz.

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proton signals for the sugar moiety were in good agreement with those found in strictinin [15], indicating that there is a β-D-glucopyranose unit in **1**. In the aromatic region of the ^{1}H NMR spectrum, four signals at δ 7.25 (br d, 1H, $J = 7.5$, H-3′), 6.97 (br dd, 1H, $J = 7.5$, and 7.5 Hz, H-4′), 7.28 (br dd, 1H, $J = 8.1$, and 7.5 Hz, H-5′), and 7.10 (br d, 1H, $J = 8.1$ Hz, H-6′) revealed the presence of an ortho-disubstituted phenyl unit in the molecule of **1**. The protonated carbon signals were assigned by HMQC experiment. The HMBC spectrum (Fig. 1) showed two- and three-bond correlations from two geminal protons with an AB coupling pattern at δ 5.12 (d, 1H, $J = 12.3$ Hz, H-7′a) and 5.39 (d, 1H, $J = 12.3$ Hz, H-7′b) to C-1′, C-2′ and C-3′, respectively. These data proved that the ortho-disubstituted phenyl unit is a 2-oxymethylphenoxy group. Furthermore, in the HMBC spectrum, a three-bond correlation from the anomeric proton to C-1′ established the linkage of 2-oxymethylphenoxy group and the β-D-glucopyranose moiety.

In addition, the ^{1}H NMR spectrum showed two aromatic signals at δ 6.49 (s, 1H, H-3″), and 6.65 (s, 1H, H-3‴), the ^{13}C NMR spectrum showed seven pairs of sp^2 carbon signals including a pair of methine, and six pairs of quaternary carbons among which there was a pair of carbonyl carbons (Table I). These data suggested that there is a hexahydroxydiphenoyl (HHDP) group in the molecule of **1**. A negative cotton effect at 261 nm and a positive effect at 234 nm in the CD spectrum of **1** showed that the HHDP group possesses an *S* configuration [11]. In the HMBC spectrum, the correlations from H_2-6 to C-7″, and from H-4 to C-7‴ clearly demonstrated that the hydroxyl groups at C-6 and C-4 of the β-D-glucopyranose moiety were esterified by HHDP group. Moreover, the ^{1}H, ^{13}C NMR and DEPT spectral data of **1** (Table I) showed the presence of signals for an additional unit composed of two methylenes, two methines, one carboxyl group, as well as a ketone group and an oxygenated quaternary carbon in the molecule of **1**. The coupling pattern of proton signals of this unit in the ^{1}H NMR spectrum revealed the presence of a partial structure $-CH{=}CH-CH_2-CH_2-$, which was confirmed by ^{1}H–^{1}H COSY and HMQC experiments. The HMBC experiment (Fig. 1) unambiguously established this unit as a 1-hydroxy-6-oxocyclohex-2-ene-1-carboxyl moiety. The correlation from H_2-7′ to the carboxyl carbon in the HMBC spectrum unequivocally indicated that this unit was esterified at the oxymethylene group of the 2-oxymethylenephenoxy moiety.

Treatment of **1** with sodium methoxide in methanol yielded a complex mixture and two main products salicin and ellagic acid (**4**) identified by their spectral data [16]. The mixture was not separated for the limited amount, and proposed to arise from decomposition of 1-hydroxy-6-oxocyclohex-2-ene-1-carboxyl unit. Accordingly, the structure of **1** was elucidated as 1-*O*-[2-(1-hydroxy-6-oxocyclohex-2-ene-1-carboxymethyl)-phenyl]-4,6-*O*-[(*S*)-4,4′, 5,5′, 6,6′-hexahydroxydiphenoyl]-β-D-glucopyranose (**1**).

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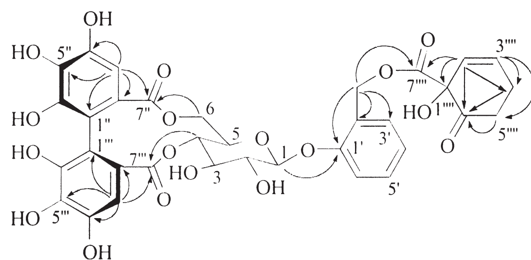

FIGURE 1 HMBC correlations of **1**.

EXPERIMENTAL SECTION

General Experimental Procedures

Mps were determined on an XT-4 micro melting point apparatus and are uncorrected. Optical rotations were measured with Rudolph Research Autopol III automatic polarimeter. UV spectra were acquired on Perkin–Elmer Lambda 4B UV/Vis spectrometer and CD spectra on a JASCO J-500C spectropolarimeter. IR spectra were recorded as KBr disks on a Nicolet 170 SX FT–IR instrument. NMR spectra were recorded on a Varian VXR-300 spectrometer in CD_3OD or DMSO-d_6 with TMS as internal standard, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. The positive-ion FABMS and HRFABMS were obtained using a glycerol matrix on a Micromass Autospec-Ultima ETOF spectrometer. Adsorption column chromatography was performed with silica gel (200–300 mesh). TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV and by spraying with 10% H_2SO_4 in 95% EtOH followed by heating. All solvents used were either spectral grade or were distilled prior to use.

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Plant Material

Stem barks of *Alangium plantanifolium* were collected in Jiangxi Province, China in August 1998. The plant identification was verified by Professor Wanzhi Song (Department of Medicinal Plants, Institute of Materia Medica, Beijing 100050, China). Voucher specimens (No. 98097) were deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica.

Extraction and Isolation

Air-dried and ground whole plants (2 kg) were extracted with EtOH at room temperature for 4×24 h, and the solvent was removed under reduced pressure at $< 40°C$ to give a residue (75 g). The residue was chromatographed on a silica gel (500 g) column, eluting with $CHCl_3$–MeOH (50:1–0:1) gradient (1000 ml each step). The fraction (1.7 g) eluted with $CHCl_3$–MeOH (5:1) was repeatedly chromatographed on silica gel using $CHCl_3$–MeOH (7:1) as eluent to yield pure alangitanifoliside A (**1**) (64 mg) and 4′,6′-*O*-(*S*)-hexahydroxydiphenylsalicin (**2**) (72 mg), and a mixture (1.1 g). The mixture was further purified by silica gel column chromatography eluting with $CHCl_3$–MeOH (12:1) to give salicin (**3**) (22 mg) and gallic acid (18 mg).

Alangitanifoliside A (1)

A white, amorphous powder from $CHCl_3$–MeOH (3:1), $[\alpha]_D^{18} + 6.0$ (c 0.30, MeOH); UV (MeOH) λ_{max} (log ε) 215 (4.61), 235 sh (3.96), 260 sh (2.42) nm; CD (MeOH) λ_{max} ($\Delta\varepsilon$) 234 (+29.1), 261 ($-$ 11.9), 285 ($-$ 3.2); IR (KBr) ν_{max} 3413, 2980, 1736, 1618, 1602, 1503, 1494, 1450, 1312, 1228, 1190, 1141, 1052, 1016, 877, 831, 795, 759 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) and ^{13}C NMR (CD_3OD, 75 MHz) see Table I; FABMS *m/z* 749 $[M+Na]^+$ (26), 727 $[M+H]^+$ (4), 571 (35), 465 (15), 447 (7), 409 (12), 365 (5), 302 (89), 277 (100), 175 (13), 107 (87); HRFABMS *m/z* 749.1329 (calcd for $C_{34}H_{30}O_{18}Na$ 749.1330), 727.1546 (calcd for $C_{34}H_{31}O_{18}$ 727.1510).

Methanolysis of Alangitanifoliside A (1)

A mixture of compound **1** (12 mg) and 2% sodium methoxide (0.2 ml) in methanol (2 ml) was stirred at room temperature for 40 min. The reaction mixture was filtered to obtain a brown

precipitate and a filtrate. The precipitate was dissolved in water (5 ml) and acidified with diluted HCl (1 N) to pH 5, then extracted with EtOAc. The EtOAc phase was evaporated, the resulting residue was recrystallized in acetone to give ellagic acid (3 mg) (**4**) as colorless needles: mp > 360°C, UV (MeOH) λ_{max} (log ε) 254 (4.31), 364 (2.06), nm; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.46 (2H, s, H-3, H-3′); ^{13}C NMR (CD_3OD, 75 MHz) δ 109.5 (C-1, 1′), 111.7 (C-5, 5′), 112.9 (C-6, 6′), 137.8 (C-,3 3′), 142.6 (C-4, 4′), 145.8 (C-2, 2′), 161.7 (C-7, 7′); positive ion FABMS *m/z* 303 $[M+H]^+$. The filtrate was neutralized with acetic acid and the solvent was evaporated in a stream of nitrogen at room temperature. The residue was partitioned between EtOAc and water. The EtOAc phase was evaporated, and the resulting residue was chromatographed over Sephadex LH-20 eluting with CHCl–MeOH (1:1) to yield salicin (4 mg) and a complex mixture (2 mg, not separated for the limited amount). Salicin was obtained as colorless needles in acetone; mp. 192–194°C, UV (MeOH) λ_{max} (log ε) 215 (4.00), 266 (3.41) nm; ^{1}H NMR (CD_3OD, 300 MHz) δ 3.28–3.50 (4H, m, H-2′, H-3′, H-4′, H5′), 3.64 (1H, dd, $J = 12.0$, 6.0 Hz, H-6′), 3.83 (1H, dd, $J = 12.0$, 1.5 Hz, H-6′), 4.51 (1H, d, $J = 12.6$ Hz, H-7), 4.72 (1H, d, $J = 12.6$ Hz, H-7), 4.81 (1H, d, $J = 7.5$ Hz, H-1′), 6.97 (1H, dt, $J = 7.2$, 1.5 Hz, H-4), 7.14 (1H, dd, $J = 8.1$, 1.2 Hz, H-6), 7.19 (1H, dt, $J = 1.5$, 8.1 Hz, H-5), 7.27 (1H, dd, $J = 7.2$, 1.2, H-3); ^{13}C NMR (CD_3OD, 75 MHz) δ 61.3 (C-7), 62.8 (C-6′), 71.6 (C-4′), 75.4 (C-2′), 78.3 (C-5′), 78.5 (C-3′), 103.7 (C-1′), 117.3 (C-6), 124.0 (C-4), 130.2 (C-3), 130.3 (C-5), 132.4 (C-2), 157.4 (C-1); positive-ion FABMS *m/z* 271 $[M+H]^+$.

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