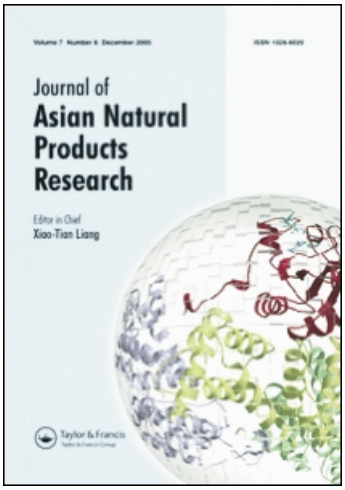

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TWO NEW ELLAGIC ACID GLYCOSIDES FROM LEAVES OF *DIPLOPANAX STACHYANTHUS*

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Two new ellagic acid glycosides, named stachyanthuside A (**1**) and B (**6**), have been isolated along with four known ellagic compounds (**2**–**5**) from the leaves of *Diplopanax stachyanthus*. The structures of the new compounds were established as 3′-*O*-methylellagic acid 4-*O*-β-D-glucopyranoside (**1**) and 3,3′,4′-tri-*O*-methylellagic acid 4-*O*-β-D-(2″-acetyl)-glucopyranoside (**6**) on the basis of detailed spectroscopic analysis and comparison with related model compounds.

Keywords: *Diplopanax stachyanthus*; Ellagic acid glycosides; Stachyanthuside A; Stachyanthuside B

INTRODUCTION

Diplopanax stachyanthus Hand.-Mazz is the only member of the genus *Diplopanax* (Family Araliaceae), which has been used as medicinal plant in the treatment of rheumatism in traditional Vietnamese medicine. A previous phytochemical investigation of the stem bark of *D. stachyanthus* collected in Vietnam resulted in the isolation of several phenolic lactones with an ellagic acid skeleton [1]. However, the Chinese species has not been chemically studied. In searching for new bioactive substances, we have analyzed the title plant collected from Hunan, in the southern part of China. Two new ellagic acid glucosides, stachyanthuside A (**1**), B (**6**), along with four known related compounds, 3′-*O*-methylellagic acid 4-*O*-β-D-xylopyranoside (**2**) [2,3], 3,3′-di-*O*-methylellagic acid 4-*O*-β-D-xylopyranoside (**3**) [1], 3,3′,4′-tri-*O*-methylellagic acid 4-*O*-β-D-glucopyranoside (**4**) [1] and 3,3′,4′-tri-*O*-methylellagic acid (**5**) [1], were isolated from this Chinese species. The new and known compounds were characterized by detailed spectroscopic analysis (NMR, MS, UV and IR) and comparison of their spectral data with the reported values in literatures.

RESULTS AND DISCUSSION

The leaves of *D. stachyanthus* were exhaustively extracted with MeOH, and the methanolic extract was partitioned between various organic solvents and water to afford

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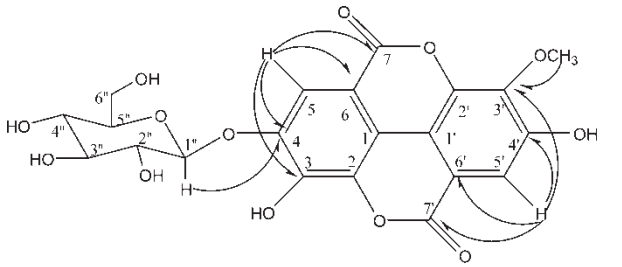
EtOAc-soluble and *n*-BuOH-soluble extracts. The *n*-BuOH-soluble portion was subjected to column chromatography on silica gel eluting with a $CHCl_3$–MeOH gradient system. This procedure led to the isolation of compound **1**, named stachyanthuside A, together with three known compounds **2**–**4**. The EtOAc-soluble portion was also subjected to column chromatography on silica gel, eluting with a petroleum–acetone system. This procedure resulted in the isolation of compound **6**, named stachyanthuside B, and the known compound **5**.

Compound **1** was obtained as white needle crystals. Its negative ion HR-ESIMS suggested a molecular formula of $C_{21}H_{18}O_{13}$. Its ultraviolet (UV) spectrum (λ_{max} 253.5, 353.5 nm) was similar to that of ellagic acid [1], suggesting that **1** has an ellagic acid skeleton. Its infrared (IR) spectrum showed a hydroxy band at 3423 cm^{-1}, carbonyl band at 1718 cm^{-1} and absorptions for aromatic ring at 1608 and 1500 cm^{-1}. The ^1H NMR spectrum of **1** revealed two protons as singlets at δ 7.78 and 7.51, assignable to H-5 and H-5′, respectively, by comparing with the ^1H NMR data of ellagic acid [2]. The ^1H NMR spectrum of **1** also showed an aromatic methoxy at δ 4.02 (3H, s). The sugar was identified as β-D-glucose from the coupling constant of the anomeric proton (δ 4.99, $J = 7.1$ Hz, H-1″) and by Dinex chromatography of the acid hydrolyzed product of **1**. The position of the glycosidic linkage to the aglycone was confirmed on the basis of HMBC (Fig. 1) and NOESY experiments. The HMBC spectrum of **1** showed that the anomeric proton of glucose (δ 4.99, H-1″) correlated with C-4 (δ 147.1) of ellagic acid, which, in turn, correlated with H-5 (δ 7.78). Furthermore, NOESY experiment revealed clearly that the anomeric proton of glucose (δ 4.99) correlated with H-5 (δ 7.78) of ellagic acid. This interaction is only possible when the sugar residue is glycosidically linked at C-4. The position of the methoxyl linkage to ellagic acid was deduced from the HMBC experiment and comparison with model compound **2** [2,3]. The chemical shift of the methyl carbon (δ 60.9) of **1** was similar to that of the 3-*O*-methyl derivative (δ 60.8, *e.g.* **2**), but different from that of the 4-*O*-methyl derivative (δ 56–57), suggesting that the methoxyl group is located at C-3 or C-3′ [3,4]. The presence of methoxyl group at C-3′ was confirmed by HMBC experiment, in which



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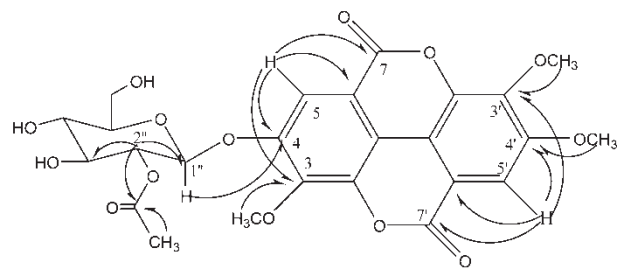


6

FIGURE 1 Selected key HMBC correlations (H → C) of **1** and **6**.

the H-5′ signal (δ 7.51) showed a cross peak with C-3′ (δ 140.5), and the C-3′ signal, in turn, showed a cross peak with the 3′-methoxyl signal (δ 4.02). These observations indicated unequivocally that **1** is 3′-*O*-methylellagic acid 4-*O*-β-D-glucopyranoside.

It is noteworthy that compounds **1** and **2** possess the same aglycone and both compounds showed also almost identical ^{13}C NMR data except for the sugar part. However, careful comparison of ^{13}C NMR assignments of the aglycone moieties of **1** and **2** revealed apparent differences. Since the ^{13}C NMR data assigned for **1** here were based on 2D NMR experiments, while that of **2** were not mentioned in literature [3], it appears that the ^{13}C NMR assignments of **2** probably should be corrected.

Compound **6**, isolated as a white amorphous powder, showed UV, IR and NMR data very similar to those of co-occurring compound **4** [1]. Careful comparison of their ^{1}H and ^{13}C NMR data revealed that the difference between **6** and **4** was only in the sugar part of the molecules. The ^{1}H and ^{13}C NMR spectra of **6** (Table I) clearly indicate the presence of an acetyl group (δc 170.2; δ_H 2.14). The HMBC experiment allowed us to locate the acetyl group at C-2″ of glucose as there are significant ^{1}H–^{13}C long-range correlations from the carbonyl carbon to H-2″ (δ 5.94) and from C-2″ (δ 74.7) to H-1″ (δ 5.87) (Fig. 1). As indicated, compound **6** is a 2″-acetyl derivative of **4**.

Compounds **2**, **4** and **5** have been isolated previously from the Vietnamese species, but compound **3** is reported here for the first time from *D. stachyanthus*. In addition, as compound **4** was, for the first time, isolated in a pure state, its full ^{1}H and ^{13}C NMR assignments are reported (see Experimental section).

TABLE I ^{1}H and ^{13}C NMR data[a] of compounds **1** and **6** and ^{13}C NMR data of **2**

	1[b]		***2***[b] *[3]*	***6***[c]	
Position	δ *^{1}H (ppm) mult., J in Hz*	δ *^{13}C (ppm) mult.*	δ *^{13}C (ppm) mult.*	δ *^{1}H (ppm) mult., J in Hz*	δ *^{13}C (ppm) mult.*
1		107.3 (s)	114.7 (s)		113.4[d] (s)
2		135.7 (s)	140.8 (s)		142.0[d] (s)
3		140.7 (s)	135.7 (s)		142.9 (s)
4		147.1 (s)	146.9 (s)		152.4 (s)
5	7.78 (s)	111.5 (d)	107.5 (d)	8.39 (s)	113.3[d] (d)
6		114.5 (s)	111.5 (s)		114.7 (s)
7		158.6 (s)	158.6 (s)		158.9 (s)
1′		113.0[d] (s)	113.1 (s)		113.4[d] (s)
2′		141.8 (s)	141.8 (s)		142.0[d] (s)
3′		140.5 (s)	140.7 (s)		141.9 (s)
4′		152.6 (s)	152.6 (s)		155.1 (s)
5′	7.51 (s)	113.3 (d)	111.3 (d)	7.81 (s)	108.2 (d)
6′		113.0[d] (s)	111.5 (s)		113.3[g] (s)
7′		158.5 (s)	158.6 (s)		158.7 (s)
1″	4.99 (d, 7.1)	102.1 (d)	102.8 (d)	5.87 (d, 7.8)	100.5 (d)
2″	3.40 (m)	73.1 (d)	72.9 (d)	5.94 (m)	74.7 (d)
3″	3.35 (m)	75.4 (d)	75.3 (d)	4.44 (m)	75.8 (d)
4″	3.25 (m)	69.5 (d)	69.2 (d)	4.40 (m)	71.1(d)
5″	3.45 (m)	77.2 (d)	65.8 (t)	4.20 (m)	79.4 (d)
6″	3.51, 3.75 (m)	60.4 (t)		4.60, 4.40 (m)	61.9 (t)
3-OMe				4.23 (s)	62.0 (q)
3′-OMe	4.02 (s)	60.9 (q)	61.0 (q)	4.37 (s)	61.5 (q)
4′-OMe				3.80 (s)	56.6 (q)
COCH_3					170.2 (s)
CO**CH_3**				2.14 (s)	21.0 (q)

[a]Bruker AMX 400 MHz; chemical shifts (δ) are expressed relative to TMS; assignments were deduced by analysis of 1D and 2D NMR spectra. [b]Measured in DMSO-d_6. [c]Measured in d_5-pyridine. [d]Overlapping.

It is of interest that ellagic acid and its derivatives have been reported to show potent aldose reductase (AR) inhibitory activity [5]. It thus seems desirable to assay compounds **1**–**6** for possible biological properties.

EXPERIMENTAL

General Experimental Procedures

UV spectra were recorded on a Varian Cary 300 Bio spectrophotometer; λ_{max} (nm). IR spectra were recorded on a Nicolet Magna FT-IR 750 spectrometer; ν_{max} (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. Chemical shifts (δ ppm) are relative to internal TMS, coupling constants (J) are in Hz. ^1H and ^{13}C NMR assignments were supported by ^1H–^1H COSY, HMQC, HMBC and NOESY experiments. The HR-ESIMS spectrum was recorded on a MAT-711 mass spectrometer. Commercial silica gel plates (Qing Dao Hai Yang Chemical Group Co.) were used for TLC. The chromatograms were detected with a UV lamp at 254 nm, and successively sprayed with 0.1% $Ce(SO_4)_2$ in 2N H_2SO_4 and heated at 80°C for 5 min.

Plant Material

The examined sample was collected from Mang mountain, Hunan Province, China in July 2001 and identified by Associate Professor Deng Y.-F. of SCIB, CAS. A voucher specimen is available for inspection at the Herbarium of Institute of Materia Medica, SIBS-CAS.

Extraction and Isolation

Powered leaves of *D. stachyanthus* (4.2 kg) were exhaustively extracted with MeOH at room temperature. The extract was then concentrated under reduced pressure to give a green syrup, which was partitioned between various organic solvents and water to afford EtOAc-soluble (86.5 g) and *n*-BuOH-soluble (225 g) fractions. The EtOAc-soluble fraction was chromatographed on a silica gel column using eluents of increasing polarity, from light petroleum (60–90°C) to acetone to MeOH. The fractions eluted with light petroleum–acetone (3:7) afforded compound **5**. The fractions eluted with acetone were further purified by a Sephadex LH-20 column chromatography using MeOH as eluent to afford compound **6** (2.7 mg).

The *n*-BuOH-soluble fraction was chromatographed on a silica gel column using eluents of increasing polarity, from $CHCl_3$ to MeOH. The fractions eluted with MeOH–$CHCl_3$ (1:9) were further purified by ODS-18 column chromatography using MeOH–H_2O (8:2) as eluent to afford compounds **3** and **4**. The fractions eluted with MeOH–$CHCl_3$ (2:8) were further purified by Sephadex LH-20 column chromatography using MeOH as eluent to afford compound **5**. The fractions eluted with MeOH–$CHCl_3$ (3:7) were further purified by ODS-18 column chromatography with MeOH–H_2O (6:4) as eluent to furnish compound **1** (7.1 mg).

3′-O-Methyellagic Acid 4-O-β-D-glucopyranoside (1)

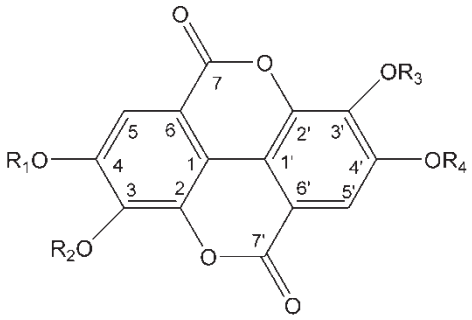
Colorless needles; mp 289–291°C; IR (KBr) ν_{max} (cm^{-1}): 3423.1, 2921.7, 1718.3, 1608.4, 1577.5, 1488.8, 1446.4, 1363.4, 1209.2, 1076.1, 1029.8, 919.9, 756.0; UV λ_{max} (nm) (log ε): 253.5 (4.64), 353.5 (4.17); ESIMS *m/z*: 477 $[M - 1]^-$; HR-ESIMS *m/z*: 477.0669 $[M - H]^-$ (calcd for $C_{21}H_{18}O_3$, 477.0669); ^1H and ^{13}C NMR: see Table I.

3,3′,4′-Tri-O-methylellagic Acid 4-O-β-D-glucopyranoside (4)

A white amorphous powder; ^{1}H NMR (400 MHz, in C_5D_5N) δ (ppm): 8.46 (1H, s, H-5), 7.81 (1H, s, H-5′), 5.93 (1H, d, H-1″, $J = 7.3$ Hz), 4.27 (3H, s, 3-OMe), 4.14 (3H, s, 3′-OMe), 3.85 (3H, s, 4′-OMe), 4.20–4.70 (H-2″-H-6″). ^{13}C NMR (100 MHz, C_5D_5N) δ (ppm): 159.0 (C-7), 158.8 (C-7′), 155.0 (C-4′), 153.0 (C-4), 142.7 (C-3), 142.0 (C-3′), 141.9 (C-2), 141.9 (C-2′), 114.1 (C-6), 113.5 (C-6′), 113.3 (C-1), 113.3 (C-1′), 113.3 (C-5), 108.1 (C-5′), 102.9 (C-1″), 79.1 (C-5″), 78.5 (C-3″), 74.8 (C-2″), 71.0 (C-4″), 62.2 (C-6″), 61.9 (3-OMe), 61.5 (3′-OMe), 56.6 (4′-OMe).

3,3′,4′-Tri-O-methylellagic Acid 4-O-β-D-(2″-acetyl)-glucopyranoside (6)

A white amorphous powder; IR (KBr) ν_{max} (cm^{-1}): 3430.8, 2927.5, 1743.4, 1608.4, 1488.8, 1407.8, 1353.8, 1253.5, 1093.5, 1093.5, 1037.5, 997.0, 757.9; UV λ_{max} (nm) (log ε) 246.5 (4.28), 364.0 (3.68); ESIMS *m/z*: 571 $[M + Na]^+$; HR-ESIMS *m/z*: 571.1047 $[M + Na]^+$ (calcd for $C_{25}H_{24}O_{14}$, 571.1064); ^{1}H and ^{13}C NMR: see Table I



	R_1	R_2	R_3	R_4
1	Glc	H	Me	H
2	Xyl	H	Me	H
3	Xyl	Me	Me	H
4	Glc	Me	Me	Me
5	H	Me	Me	Me
6	(2"-acetyl)-glc	Me	Me	Me
7	Glc	Me	Me	H

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