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A New Phenylbutanone Glucoside from *Salvia plebeia*

Qianghao Jin[1], Xiang Hua Han[1], Ji Hye Hwang[1], Seong Su Hong[1,2], Mieon Park[1], Chul Lee[1], Chang Hee Lee[1], Dongho Lee[2], Mi Kyeong Lee[1], and Bang Yeon Hwang[1,*]

[1]*College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea*
[2]*School of Life Science and Biotechnology, Korea University, Seoul 136-713, Korea*

Abstract – Phytochemical investigations of the EtOAc-soluble fraction of the whole plants of *Salvia plebeia* using repeated column chromatography with preparative HPLC led to the isolation of a new phenylbutanone glucoside, 4-{4-*O*-[6-(4-hydroxybenzoyl)-*O*-β-D-glucopyranosyl]-3-hydroxyphenyl}-butan-2-one (salviaplebeiaside, **1**) along with two known phenolic compounds, rosmarinic acid methyl ester (**2**) and luteolin-7-*O*-β-D-glucoside (**3**). The structures of these compounds were determined on the basis of spectroscopic methods including 1D-, 2D-NMR and MS spectrometry and comparison of spectroscopic data with those of values reported in the literatures.
Keywords – *Salvia plebeia*, Lamiaceae, Phenylbutanone glucoside

Introduction

The *Salvia* is an important genus consisting of ca 900 species in the family Lamiaceae. *Salvia plebeia* R. Br. is an annual or biennial plant and distributed widely in Korea, China, and Japan. This plant has been used in traditional medicines for the treatment of hepatitis, inflammation, and haemorrhoids (Lu and Foo, 2002). Previous phytochemical studies on *S. plebeia* reported that it contained flavones (Gupta *et al.*, 1975; Weng and Wang, 2000), lignans (Powell and Plattner, 1976; Plattner and Powell, 1978), diterpenoids (Garcia-Alvarez *et al.*, 1986), and caffeic acid derivatives (Lu and Foo, 2002). Pharmacological studies have shown that *S. plebeia* exhibits various biological activities such as antihepatotoxic (Oshima *et al.*, 1984), antioxidant (Gu and Weng, 2001; Weng and Wang, 2000), and cytotoxic and antimicrobial activities (Shin *et al.*, 2001). This study was undertaken to further investigate the phytochemical constituents of this plant.

In our ongoing study to find bioactive compounds from medicinal plants, a new phenylbutanone glucoside, 4-{4-*O*-[6-(4-hydroxybenzoyl)-*O*-β-D-glucopyranosyl]-3-hydroxyphenyl}-butan-2-one (salviaplebeiaside, **1**) along with two known phenolic compounds were isolated from the EtOAc-soluble fraction of the whole plant of *S. plebeia* by repeated column chromatographic separation. The structures of these compounds were determined on the basis of spectroscopic methods including 1D-, 2D-NMR and MS spectrometry and comparison of spectroscopic data with those of values reported in the literatures.

*Author for correspondence
Tel: +82-43-261-2814; E-mail: byhwang@chungbuk.ac.kr

Experimental

Plant Material – The dried whole plants of *S. plebeia* were collected on the herb garden at Chungbuk National University, in May 2007 and identified by emeritus professor Kyong Soon Lee, a plant taxonomist at Chungbuk National University. The voucher specimens (CBNU 07009) were deposited at the Herbarium of College of Pharmacy, Chungbuk National University.

General Experimental Procedures – Melting points were measured using a Büchi B-540 melting point apparatus without correction. Optical rotations were determined on JASCO DIP-370 polarimeter at 25 °C. UV and IR spectra were obtained using a JASCO UV-550 and Perkin-Elmer model LE599 spectrometer, respectively. NMR spectra were obtained using a Bruker AMX-500 MHz NMR spectrometer. ESI-MS was recorded on Waters Q-TOF micro mass spectrometer. Open column chromatography was performed using a silica gel 60 (Kieselgel 60, 700 - 230 and 230 - 400 mesh, Merck), a Sephadex LH-20 (25 - 100 μM, Pharmacia), and LiChroprep RP-18 (particle size 40 - 63 μM, Merck). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} (0.25 mm, Merck). All other chemicals and reagents were analytical grade.

Extraction and Isolation – The dried whole plants of *S. plebeia* (2 kg) were extracted with MeOH (3 × 4 L) at room temperature. The extract was concentrated in vacuo at 40 °C to afford a MeOH extract (210 g), which was suspended in water and separated with *n*-hexane (3 × 3 L), EtOAc (3 × 3 L), and *n*-BuOH (3 × 3 L), sequentially. The EtOAc-soluble fraction (30 g) was subjected to column chromatography on silica gel (7.0 × 20 cm) eluted with CH_2Cl_2-MeOH gradient system to obtain five fractions (SPE1 - SPE6). SPE2 (9.5 g) was purified on Sephadex LH-20, eluting with 70% MeOH, to give eleven fractions (SPE2-1 - SPE2-11). SPE2-4 (100 mg) was further separated directly by semi-preparative RP-HPLC eluting with acetonitrile-water (35 : 65) to yield compound **1** (4 mg). SPE1-9 (1.0 g) was further purified with flash column chromatography on RP-18 and eluted with acetonitrile-water (50 : 50) to give compound **2** (150 mg). SPE5 (1.8 g) was further chromatographed over Sephadex LH-20 eluted with 80% MeOH to afford five fractions (SPE5-1 - SPE5-5). Compound **3** (25 mg) was obtained by recrystallization in a CH_2Cl_2-MeOH mixture from the fraction SPE5-5.

4-{4-*O*-[6-(4-Hydroxybenzoyl)-*O*-β-D-glucopyranosyl]-3-hydroxyphenyl}-butan-2-one (salviaplebeiaside, 1) – white amorphous powder; UV (MeOH) λmax nm: 220, 280; HRESIMS *m/z*: 461.1448 $[M-H]^-$; ^{1}H-NMR (500 MHz, DMSO-d_6) and ^{13}C-NMR (125 Hz, DMSO-d_6); see Table 1.

Rosmarinic acid methyl ester (2) – white amorphous powder; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 6.30 (1H, d, *J* = 16.4 Hz, H-2), 7.57 (1H, d, *J* = 16.4 Hz, H-3); 7.17 (1H, br d, *J* = 1.8 Hz, H-5), 7.05 (1H, dd, *J* = 8.1, 1.6 Hz, H-8), 6.87 (1H, d, *J* = 8.1 Hz, H-9), 3.67 (3H, s, -OCH_3), 4.51 (1H, m, H-2'), 3.03 (2H, m, H-3'), 6.81 (1H, br d, *J* = 1.8 Hz, H-5'), 6.63 (1H, dd, *J* = 8.0, 1.6 Hz, H-8'), 6.75 (1H, d, *J* = 8.0 Hz); ^{13}C-NMR (125 Hz, DMSO-d_6): δ 166.7 (C-1), 117.2 (C-2), 148.8 (C-3), 128.7 (C-4), 114.6 (C-5), 144.8 (C-6), 146.7 (C-7), 122.7 (C-8), 115.9 (C-9), 170.8 (C-1'), 73.8 (C-2'), 37.4 (C-3'), 127.8 (C-4'), 115.2 (C-5'), 145.7 (C-6'), 146.3 (C-7'), 121.6 (C-8'), 116.3 (C-9').

Luteolin-7-*O*-β-D-glucoside (3) – Yellow amorphous powder; m.p. 187 - 189 °C; UV λmax (MeOH): 340, 269, 239; ESI-MS m/z: 461 [MH]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 6.75 (1H, s, H-3), 6.78 (1H, br d, *J* = 2.0 Hz, H-6), 6.42 (1H, br d, *J* = 2.0 Hz, H-8), 7.42 (1H, br d, *J* = 2.0 Hz, H-2'), 6.90 (1H, d, *J* = 8.2 Hz, H-5'), 7.45 (1H, dd, *J* = 8.2, 2.0 Hz, H-6'), 5.08 (1H, br d, *J* = 7.5 Hz, H-1"), 12.96 (1H, s, 5-OH); ^{13}C-NMR (125 Hz, DMSO-d_6): δ 164.4 (C-2), 163.2 (C-3), 181.8 (C-4), 161.1 (C-5), 99.9 (C-6), 162.9 (C-7), 94.7 (C-8), 156.9 (C-9), 105.3 (C-10), 121.4 (C-1'), 113.6 (C-2'), 145.8 (C-3'), 149.9 (C-4'), 115.9 (C-5'), 119.2 (C-6'), 99.5 (C-1"), 73.1 (C-2"), 76.4 (C-3"), 69.5 (C-4"), 77.2 (C-5"), 60.6 (C-6").

Table 1. ^{1}H- and ^{13}C-NMR data of salviaplebeiaside (**1**) (DMSO-d_6)[a]

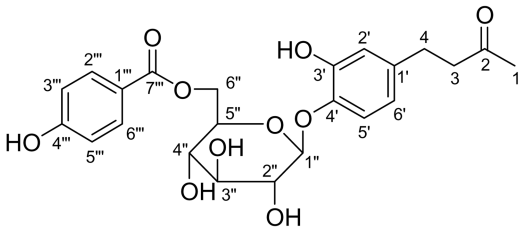
position	^{1}H-NMR	^{13}C-NMR
1	2.00 (3H, s, CH_3)	29.9
2	–	211.0
3	2.58 (2H, d, *J* = 7.0 Hz)	46.0
4	2.53 (2H, d, *J* = 7.0 Hz)	29.7
1'	–	134.4
2'	6.84 (1H, br d, *J* = 2.0 Hz)	118.8
3'	–	146.6
4'	–	146.5
5'	6.68 (1H, dd, *J* = 8.0 Hz)	117.0
6'	6.64 (1H, dd, *J* = 8.0, 2.0 Hz)	124.5
1"	4.75 (1H, br d, *J* = 7.5 Hz)	104.2
2"	3.52 (1H, m)	74.8
3"	3.51 (1H, m)	77.4
4"	3.44 (1H, m)	71.9
5"	3.78 (1H, m)	75.8
6"	4.55 (1H, dd, *J* = 12, 2 Hz) 4.23 (1H, dd, *J* = 12, 7.5 Hz)	65.0
1"'	–	122.1
2"',6"'	7.82 (2H, d, *J* = 9.0 Hz)	132.9
3"', 5"'	6.83 (2H, d, *J* = 9.0 Hz)	116.3
4"'	–	163.7
7"'	–	167.9

[a]) Assignments were confirmed by DEPT, HMQC and HMBC spectra.

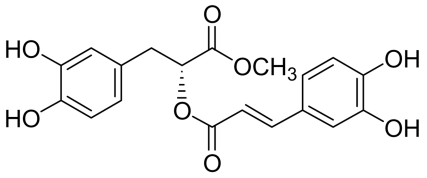
Results and Discussion

The EtOAc-soluble fraction of the whole plants of *S. plebeia* yielded a new phenylbutanone glucoside, 4-{4-*O*-[6-(4-hydroxybenzoyl)-*O*-β-D-glucopyranosyl]-3-hydroxyphenyl}-butan-2-one (salviaplebeiaside, **1**), together with two known phenolic compounds, rosmarinic acid methyl ester (**2**) (Kang *et al.*, 2004) and luteolin-7-*O*-β-D-glucoside (**3**) (Lee *et al.*, 2008).

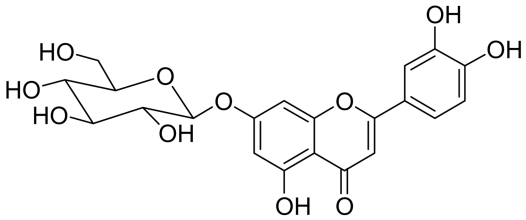
Compound **1** was obtained as an amorphous powder. The molecular formula was established as $C_{23}H_{26}O_{10}$ from the HRESIMS data at *m/z* 461.1448 $[M-H]^-$ ($C_{23}H_{25}O_{10}$, calc. for 461.1448). The ^{1}H- and ^{13}C-NMR spectra were similar to those of phenylbutanone glucosides, and indicated the presence of a 4-(3,4-dihydroxyphenyl)-butan-2-one, a glucose, and a 4-hydroxybenzoyl moiety (Chevalley *et al.*, 2000). The ^{1}H-NMR spectrum showed



Salviaplebeiaside (1)



Rosmarinci acid methyl ester (2)



Luteolin-7-*O*-β-D-glucoside (3)

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

characteristic signals for 1,2,4-trisubstituted benzene protons at δ_H 6.84 (1H, d, J = 2.0 Hz), 6.68 (1H, d, J = 8.0 Hz), and 6.64 (1H, dd, J = 8.0, 2.0 Hz) and a 1,4-disubstituted benzene protons were assigned at δ_H 6.80 (2H, d, J = 9.0 Hz) and 7.91 (2H, d, J = 9.0 Hz). A butanone moiety in the molecule was derived from the protons at δ_H 2.00 (3H, s, CH_3-1), 2.53 (2H, m, CH_2-4), and 2.58 (2H, m, CH_2-3) and the carbons at δ_C 29.9 (C-1), 211.0 (C-2), 46.0 (C-3), and 29.7 (C-4) (Okuyama *et al.*, 1998). The *β*-glucose moiety was observed from the ^{1}H-NMR spectrum by the signals of an anomeric proton at δ_H 4.78, four oxymethine protons at δ_H 3.52, 3.51, 3.44, and 3.78, together with one pair of methylene protons at δ_H 4.70 and 4.17. The configuration of the glucose was assigned to be *β* based on the coupling constant of the anomeric proton δ_H 4.78 (1H, d, J = 7.5 Hz).

The location of 4-hydroxybenzoyl group through an ester linkage to the C-6" of the glucose was determined by the HMBC correlations between CH_2-6" (δ_H 4.55 and 4.23) and the ester carbonyl carbon (δ_C 167.9). In addition, the HMBC correlations between H-1" (δ_H 4.75) of glucose and C-4" (δ_C 146.5) indicated that the 4-(3,4-dihydroxyphenyl)-butan-2-one should be attached to C-1" of the glucose. Thus, the structure of compound **1** was identified as 4-{4-*O*-[6-(4-hydroxybenzoyl)-*O*-β-D-glucopyranosyl]-3-hydroxyphenyl}-butan-2-one, and it was named salviaplebeiaside.

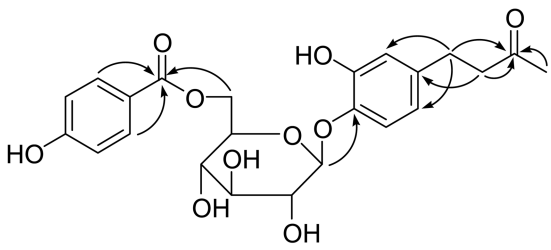


Fig. 2. Selected HMBC correlations for compound **1**.

Phenylbutanones are a group of natural products distributed in the relatively limited species of higher plants belonging to the genus *Vitex* (Okuyama *et al.*, 1998), *Rheum* (Kashiwada *et al.*, 1986; Shikishima *et al.*, 2001), and *Saxifraga* (Chevalley *et al.*, 2000). This is the first report on the identification of a phenylbutanone glucoside from *S. plebeia*.

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