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Alpha-pyrone glycosides from *Scutellaria salviifolia* Benth

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Abstract: *Scutellaria salviifolia* Benth. is an endemic species growing in Turkey that belongs to the family Lamiaceae. As a result of a phytochemical study on the aerial parts of *S. salviifolia* Benth., two new and 10 known compounds were isolated from the aqueous fraction of methanolic extract. The new compounds are methyl-α-pyrone glucosides, 3,4-dihydroxy-6-methylpyran-2-one 3-O-β-glucopyranoside (=scusalvioside A, **1**), and 3,4-dihydroxy-6-methylpyran-2-one 3-O-β-(6′-O-E-caffeoyl) glucopyranoside (=scusalvioside B, **2**) with new skeletal structures. Along with them, 3 phloroglucinol glucosides [phlorin (**3**), tadehaginoside (**4**), and 6″-O-Z-p-coumaroyl phloroglucinol-1-O-β-glucopyranoside (**5**)], 6 flavonoids [apigenin (**6**), apigenin 5-O-β-glucopyranoside (**7**), isoschaftoside (**8**), luteolin 7-O-β-glucuronide (**9**), luteolin 4′-O-β-glucopyranoside (**10**), and hispidulin (**11**)], and one phenylethanoid glycoside [martynoside (**12**)] were also isolated as known compounds. Compounds **2** and **8** were isolated as a mixture. Structure elucidations of the isolated compounds were carried out using UV, ^{1}H NMR, ^{13}C NMR, 2D NMR, and HR-ESI-MS analyses. Moreover, the phenylethanoid glycosides acteoside (**13**) and leucosceptoside A (**14**) were also detected in the plant by HPLC-DAD study. Tadehaginoside, 6″-O-Z-p-coumaroyl phloroglucinol-1-O-β-glucopyranoside, and luteolin 4′-O-β-glucopyranoside were reported for the first time from a *Scutellaria* species with this study.

Key words: *Scutellaria* species, methyl-α-pyrone glucosides, scusalviosides A and B, phloroglucinol derivatives, flavonoids

1. Introduction

Scutellaria is a widespread genus throughout the world represented by 350 species. There are 25 *Scutellaria* species with 32 taxa, 14 of which are endemic in Turkey.[1] Some important therapeutic effects of this genus are antitumor, antiangiogenesis, hepatoprotective, antioxidant, anticonvulsant, antibacterial, antiviral, antiinflammatory, and neuroprotective effects and memory improvement.[2–5] The root of *S. baicalensis*, the aerial part of *S. barbata*, and the aerial part of *S. lateriflora* have different therapeutic uses worldwide.[6–10]

The root of *S. baicalensis* is generally used for the treatment of inflammatory diseases such as dermatitis, gingivitis, and gastric ulcer due to its antiinflammatory effects.[3–5] Water extract from the aerial parts of *S. barbata* is used for its antitumor effects.[8,11,12] Water or ethanolic extracts from the aerial parts of *S. lateriflora* have anticonvulsant and anxiolytic effects.[13–16] In Turkey, different subspecies of *S. orientalis* are used as an astringent, carminative, and analgesic; for wound healing; and for therapy of abdominal pain, nephralgia, headache, throat diseases, gastric ulcer, cancer, and hemorrhoids.[17–20] There is only one record of the use of *S. salviifolia* Benth. for gastric ailments in folk medicine.[21]

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There are many studies on the phytochemical ingredients of *Scutellaria* species. The genus contains many phytochemicals from different chemical groups, such as flavonoids, iridoid glycosides, phenylethanoid glycosides, diterpenes, triterpenes, and alkaloids.[2] There have been several phytochemical studies on *S. salviifolia*.[22–24] In our previous study, we isolated phenylethanoid glycosides from the plant.[22] Zengin et al. studied the title plant to screen its bioactive compounds by HPLC-ESI-MS. The results of that study showed that the plant was rich in flavonoids and phenolic acids.[23] Additionally, essential oil from *S. salviifolia* was studied and the main components of the essential oil were determined as germacrene D (40%), bicyclogermacrene (14%), and β-caryophyllene (11%) by GC-MS.[24]

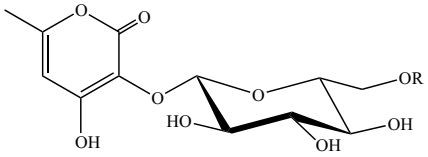
Because of the rich phytochemical content of this species and important uses of the genus, we selected the endemic *Scutellaria salviifolia* to investigate its aerial parts in terms of phytochemical contents.

2. Results and discussion

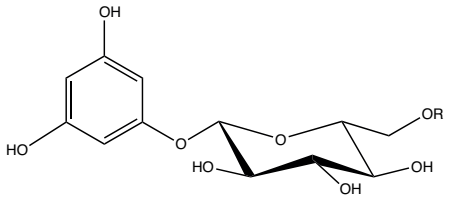
Aerial parts of *S. salviifolia* were extracted with methanol, the dried methanol extract was dissolved in water, and the water-soluble part of the extract was partitioned with chloroform to discard lipophilic constituents. Repeated column chromatography was conducted on the remaining aqueous extract for purification of its chemical contents. As a result of the phytochemical study, two new compounds, scusalvioside A (**1**) and scusalvioside B (**2**), along with ten known compounds were isolated (Figure 1; Table). The known compounds were identified as phlorin (**3**),[25,26] tadehaginoside (**4**),[27] 6″-*O*-*Z*-*p*-coumaroyl phloroglucinol-1-*O*-β-glucopyranoside (**5**),[28] apigenin (**6**),[29] apigenin 5-*O*-β-glucopyranoside (**7**),[30,31] isoschaftoside (**8**),[32] luteolin 7-*O*-β-glucuronide (**9**),[33,34] luteolin 4′-*O*-β-glucopyranoside (**10**),[35,36] hispidulin (**11**),[37,38] and martynoside (**12**)[39] by comparison of their NMR spectral data with those in the literature. In addition to these isolated compounds, two more phenylethanoid glycosides, acteoside (**13**) and leucosceptoside A (**14**), were detected by HPLC-DAD analysis performed on the extract.

Compound **1** had the molecular formula $C_{12}H_{16}O_9$ when it was evaluated together with ^{13}C NMR data (see Table) and the peak observed at 303.07121 $[M–H]^-$ in the negative ion mode of the HR-ESI mass spectrum.

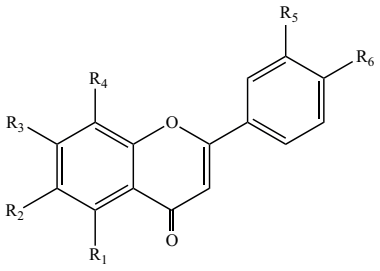
When the anomeric proton and carbon signals at δ_H 4.49 (d, $J = 7.5$ Hz, H-1′) and δ_C 108.7 (CH, C-1′) in the ^1H and ^{13}C NMR spectra of the compound were evaluated together with other sugar signals, it was understood that the compound had a monoglycosidic structure and the bond configuration was β due to the coupling constant of the anomeric proton ($J = 7.5$ Hz). The 5 carbon resonances observed between 62.6 and 78.5 ppm and proton signals observed between 3.27 and 3.91 ppm confirmed the presence of a hexose unit in the molecule (Table). After joint evaluation of the COSY and HSQC spectra, it was also precisely determined that the sugar was β-glucose. When the carbon atoms belonging to the sugar unit were omitted, it was found that the remaining aglycone structure consisted of a ring system with 5 carbon atoms (one methine and four quaternary carbons) and a methyl group. The carbon signals were observed at δ_C 167.2 (C, C-2), 124.8 (C, C-3), 173.9 (C, C-4), 108.7 (CH, C-5), 159.4 (C, C-6), and 19.3 (CH_3) in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum indicated that three of the quaternary carbons were bearing oxygen atoms. On the other hand, there were only two proton signals observed in the ^1H NMR spectrum corresponding to these carbons. δ_H 5.80 (1H, s, H-5) and 2.12 (3H, s, CH_3) signals indicated the presence of a methyl-α-pyrone skeleton in the structure. The resonances corresponding to these protons in the ^{13}C NMR spectrum were found to be δ_C 108.7 and 19.3, respectively, by means of the HSQC spectrum. Long distance correlations between H-5/C-3,



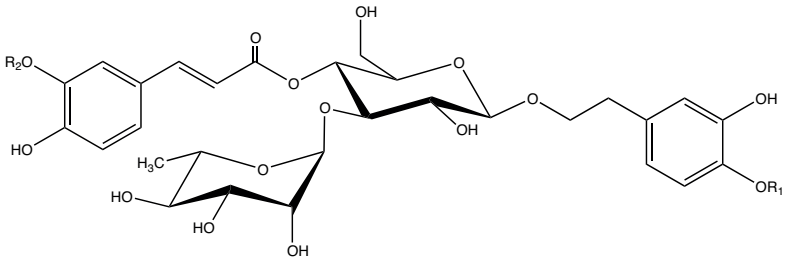
	R
1	H
2	*E*-caffeoyl



	R
3	H
4	*E*-*p*-coumaroyl
5	*Z*-*p*-coumaroyl



	R_1	R_2	R_3	R_4	R_5	R_6
6	OH	H	OH	H	H	OH
7	O-β-Glu	H	OH	H	H	OH
8	OH	C-α-Ara	OH	C-β-Glu	H	OH
9	OH	H	O-β-GlcA	H	OH	OH
10	OH	H	OH	H	OH	O-β-Glu
11	OH	OCH_3	OH	H	H	OH



	R_1	R2
12	CH_3	CH_3
13	H	H
14	H	CH_3

Figure 1. Identified secondary metabolites (compounds **1**–**14**) from *S. salviifolia*.

H-5/C-6, CH_3/C-5, and H-1′/C-3 in the HMBC spectrum (Figure 2) confirmed the binding sites and the structure of compound **1** was determined as 3,4-dihydroxy-6-methylpyran-2-one 3-*O*-β-glucopyranoside; it was named scusalvioside A. The spectral data for the α-pyrone ring that was obtained synthetically or present in styrylpyrone were similar to those in the literature.[40–42]

The ^{1}H NMR spectrum of **2** was similar to that of **1**, with the aglycone consisting of a methyl-α-pyrone

Table. ^{13}C and ^{1}H NMR data of compounds **1** (^{13}C: 125 MHz, ^{1}H: 500 MHz) and **2** (^{13}C: 150 MHz, ^{1}H: 600 MHz).

C/H atom	**1**		**2**	
	δ_C ppm	δ_H ppm J (Hz)	δ_C ppm	δ_H ppm J (Hz)
Aglycone				
2	167.2		166.7	
3	124.8		124.9	
4	173.9		173.9	
5	108.7	5.80 s	108.7	5.73 s
6	159.4		159.0	
CH_3	19.3	2.12 s	19.3	2.05 s
Glucose				
1′	108.7	4.49 d (7.5)	108.6	4.48 d (7.2)
2′	74.7	3.38-3.41†	75.2	3.42 dd (t) (7.2)
3′	77.6	3.39 t (9.0)	77.9	3.55 t (9.0)
4′	71.3	3.27 dd (t) (9.0)	71.2	3.39-3.41†
5′	78.5	3.38-3.41†	76.4	3.50 m
6′	62.6	3.60 dd (11.5/7.0)	64.6	4.38 dd (12/5.4)
		3.91 bd (11.5)		4.53 dd (12/2.0)
Acyl moiety				
1″			127.8	
2″			115.1	7.06 d (1.8)
3″			146.8	
4″			149.6	
5″			116.5	6.79 d (7.8)
6″			123.1	6.97†
α			115.0	6.30 d (15.6)
β			147.2	7.59 d (16.2)
C=O			169.5	
† Signal pattern unclear due to overlapping.				

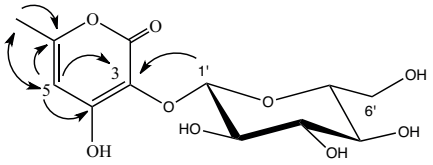


Figure 2. Important heteronuclear multiple bond correlations (HMBCs) for compound **1**.

ring and a sugar unit (Table). It was understood that the differences came from the 3 aromatic and 2 olefinic signals of a total of 5 protons in the range of 7.59–6.30 ppm, which suggests that compound **2** may be an acyl derivative of compound **1**. The difference in the HR-ESI-MS spectra (m/z465.10367 [M–H]$^-$) of these two compounds indicates that there was a caffeoyl moiety in compound **2**. Resonances belonging to an ABX system in total of 3H at 7.06 (d, J = 1.8 Hz, H-2″), 6.97 (H-6″), and 6.79 (d, J = 7.8 Hz, H-5″) ppm with 2 *trans* olefinic proton signals observed as an AB system at 7.59 (d, J = 16.2 Hz, H-β) and 6.30 (d, J = 15.6 Hz, H-α) ppm in the ^{1}H NMR spectrum confirmed that the acyl moiety was caffeic acid. The coupling constant value of olefinic signals was characteristic for the *trans* isomer. In the ^{1}H NMR spectrum, the CH_2O signals of the glucopyranose unit were shifted downfield around 0.7 ppm, indicating the location of the E-caffeoyl unit in

compound **2**. In the ^{13}C NMR spectrum, observation of the glucose-6 carbon (C-6′) signal at 2 ppm downfield and the glucose-5 carbon (C-5′) signal at 1.8 ppm upfield (acylation effect) confirmed that the esterification was via C-6′ (OH). According to these findings, the structure of compound **2** was 3,4-dihydroxy-6-methylpyran-2-one 3-*O*-β-(6′-*O*-*E*-caffeoyl)-glucopyranoside and it was named scusalvioside B.

In our previous study on this plant, four phenylethanoid glycosides, acteoside, leucosceptoside A, teucrioside, and martynoside, were isolated.[22] In the present study, an HPLC method was developed to identify phenylethanoid glycosides using previously isolated compounds from the plant as a standard. Three phenylethanoid glycosides, acteoside, leucosceptoside A, and martynoside, were identified in the phenylethanoid-rich fraction (Fr. C) of the polyamide column (Figure 3).

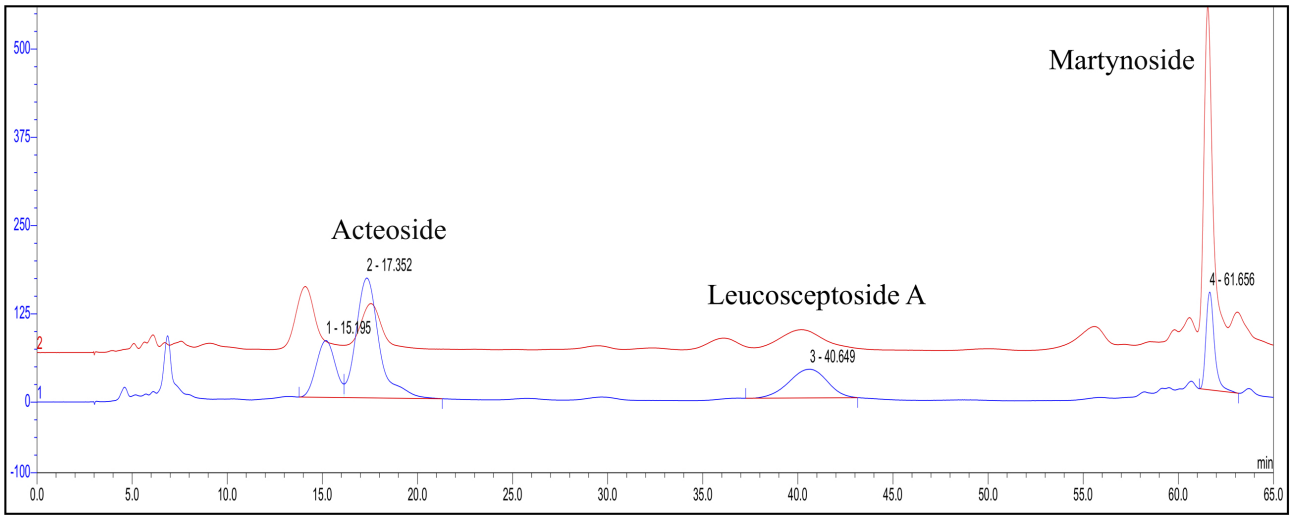


Figure 3. HPLC-DAD chromatograms of the phenylethanoid fraction (red line) and standards (blue line) at 330 nm.

Detailed phytochemical analysis of the title plant was conducted for isolation of different types of secondary metabolites in the present study. Two new compounds with a new skeletal structure, scusalvioside A (**1**) and scusalvioside B (**2**), and 10 known phenolic compounds (**3**–**10**) were isolated. The α-pyrone skeleton of 4-hydroxy-6-methylpyran-2-one was obtained by bacterial biosynthesis from glucose in a previous study.[43] This compound appears to be the starting compound in the synthesis of phloroglucinol, which plays an important role in obtaining many bioactive compounds.[43] It is also known that flavonoids are formed from α-pyrone.[44] Isolation of compounds **1** and **2** with phenolic compounds like phloroglucinol derivatives (**3**–**5**) and flavonoids (**6**–**11**) was also supported biosynthetically with this study.

Scutellaria salviifolia is a member of subgen. *Scutellaria* sect. *Salviifoliae*, one of the sections of the genus *Scutellaria*. The section *Salviifoliae* includes 4 species: *S. salviifolia*, *S. pontica*, *S. diffusa*, and *S. heterophylla*.[45] Although there are few phytochemical studies on this section, phenolic compounds such as flavonoids and phenylethanoid glycosides were isolated from the aerial parts of *S. salviifolia* and *S. pontica*.[22,26] In our study, we also isolated phenolic compounds and phenolic precursors such as phlorin derivatives and α-pyrone glucosides. Phlorin (**3**) was isolated from only two *Scutellaria* species, *S. baicalensis* and *S. pontica*. Other phlorin derivatives, tadehaginoside (**4**) and 6″-*O*-*Z*-*p*-coumaroyl phloroglucinol-1-*O*-β-glucopyranoside (**5**), were reported for the first time from a *Scutellaria* species with our study. The flavonoid aglycones apigenin (**6**)

and hispidulin (**11**) with the phenylethanoid glycosides martynoside (**12**), acteoside (**13**), and leucosceptoside A (**14**) were isolated from various *Scutellaria* species.[22,26,46–63] The apigenin glycosides apigenin 5-*O*-β-glucopyranoside (**7**) and isoschaftoside (**8**) were isolated from *S. barbata* and detected in *S. baicalensis* by LC-MS/MS, respectively.[64,65] Although luteolin 7-*O*-β-glucuronide (**9**) was isolated from some *Scutellaria* species,[49,63,66,67] luteolin 4′-*O*-β-glucopyranoside (**10**) was not isolated before from the genus. When we discuss all the phenolic compounds isolated in the previous study, we see that all the compounds were isolated from three different sections: sect. *Scutellaria* and sect. *Salviifoliae* from subgen. *Scutellaria* together with subgen. *Apeltanthus* sect. *Lupulinaria* subsect. *Lupulinaria*. This information supports the conclusion that sect. *Salviifoliae* is intermediate between the two subgenera and directly related to sect. *Scutellaria* and subsect. *Lupulinaria*.[45] When evaluating all of these points, our study can be considered the first detailed phytochemical study and the first chemotaxonomic report on *S. salviifolia*.

3. Experimental

3.1. Materials

Chromatography was performed on polyamide (50–160 μm, Sigma-Aldrich, St. Louis, MO, USA), silica gel (Kieselgel 60, 230–400 mesh, Merck, Darmstadt, Germany), Sephadex LH-20 (GE Healthcare, Chicago, IL, USA), and a thin-layer chromatography plate (Kieselgel 60 F_{254}, 0.20 mm, Merck, Darmstadt, Germany). The medium pressure liquid chromatography (MPLC) system was equipped with a Buchi Pump Module C-605, Buchi Fraction Collector C-660, and Buchi column (3.5 × 45 cm, Flawil, Switzerland) filled with LiChroprep C18 (40–63 μm, Merck). UV spectra were recorded using a Shimadzu 20A HPLC-photodiode array detector (DAD) (Kyoto, Japan). Mass spectra were measured by a JEOL JMS-T100LP AccuTOF LC-plus 4G spectrometer (Tokyo, Japan) and Applied Biosystems 3200 Q-Trap LC-MS/MS (Foster City, CA, USA). NMR spectra were recorded for ^{13}C NMR and ^{1}H NMR by an Agilent Varian VNS500 spectrometer (Santa Clara, CA, USA) at 125 MHz and 500 MHz, and a Bruker AVANCE600 spectrometer (Billerica, MA, USA) at 150 MHz and 600 MHz, respectively. Chemical shifts (ppm) were referenced to the residual solvent peaks (δ_H 3.31 and δ_H 49.0 for CD_3OD). Samples were dissolved in CD_3OD. HPLC studies were performed on a Dionex HPLC instrument (Thermo Fisher Scientific, Waltham, MA, USA) consisting of a P680 HPLC pump, Dionex ASI-100 autosampler, and Dionex DAD, using a Hichrom-Nucleosil 100-5 C18 column (5 μm, 250 mm × 4.6 mm, Sigma). The solvents used were analytical grade.

3.2. Plant material

Scutellaria salviifolia Benth. was collected from the Kıbrıs neighborhood of Mamak, Ankara, in June 2012. A voucher specimen was deposited in the herbarium of the Faculty of Pharmacy, Hacettepe University, Ankara, Turkey [HUEF 12003]. The plant material was identified by Prof Dr Zeki Aytaç (Faculty of Science, Gazi University, Ankara, Turkey).

3.3. Extraction and fractionation

Air-dried aerial parts of the plant (682 g) were extracted with methanol (7 × 2 L) at 40 °C, the extracts were combined, and methanol was evaporated by means of a rotary evaporator under vacuum at 40 °C. Dried methanol extract (143 g) was dissolved in water. An equal volume of petroleum ether was used for partitioning with the water-soluble fraction (92.4 g) to remove lipophilic compounds. Aqueous fractions were combined and

dried under vacuum. The aqueous fraction was lyophilized and an aliquot of the fraction (40.0 g) was applied to the polyamide column for the main fractionation. Elution was started with 100% water (0% methanol) and continued at 25%, 50%, 75%, and 100% methanol, respectively, to get fractions A–E.

3.4. HPLC-DAD analysis of the phenylethanoid fraction

The mobile phase consisted of water containing 0.1% ortho-phosphoric acid (A) and methanol (B). A gradient program was used as follows: 35% B in the first 4 min, 30% B during 4–50 min, 45% B at 55 min, and then B held at 45% for 10 min. The flow rate was set at 1 mL/min and the injection volume of the phenylethanoid fraction (Fr. C, eluted with 50% methanol) was 20 μL. The column was at room temperature. The UV chromatogram was screened at 330 nm.

3.5. Isolation of compounds

Fraction A was eluted with 100% water, dissolved in water, and fractionated with n-butanol to discard sugars. The n-butanol fraction was subjected to silica gel column chromatography (SCC) (eluted with $CHCl_3$:CH_3OH, from 95:5 to 50:50) to get 11 subfractions. Fr. A_8 was subjected to SCC (eluted with $CHCl_3$:CH_3OH, from 100:0 to 70:30) and preparative thin-layer chromatography (PTLC) ($CHCl_3$:CH_3OH:H_2O, 61:32:7) to get phlorin (**3**, 7.2 mg). Fraction A_{11} was subjected to MPLC (eluted with CH_3OH, 5% and 10% at 5 mL/min flow rate, each 10 mL). The first fraction of the MPLC column (Fr. A_{11-1}) was subjected to Sephadex LH-20 CC (CH_3OH) for purification of scusalvioside A (**1**, 24.8 mg). Fraction C eluted with 50% methanol from the polyamide column was subjected to MPLC (CH_3OH, 15%–40% at 5 mL/min flow rate, each 10 mL) to obtain 8 subfractions (Frs. C_{1-8}). Fr. C_5 was subjected to SCC (eluted with $CHCl_3$:CH_3OH, from 100:0 to 90:10) to obtain scusalvioside B (**2**) and isoschaftoside (**8**) (14.7 mg) as a mixture. For the isolation of martynoside (**12**, 42.7 mg), Fr. C_8 was chromatographed using SCC (eluted with $CHCl_3$:CH_3OH:H_2O, from 85:15:1 to 70:30:3). Fraction D eluted with 75% methanol from the polyamide column was subjected to SCC ($CHCl_3$:CH_3OH, from 100:0 to 85:15) to obtain 5 subfractions (Frs. D_{1-5}). Frs. D_2 and D_5 were subjected to Sephadex LH-20 CC and eluted with CH_3OH to yield apigenin (**6**, 6 mg) and apigenin 5-O-β-glucopyranoside (**7**, 4.2 mg), respectively. After repeated Sephadex LH-20 CC with CH_3OH of D_4, tadehaginoside (**4**, 4.5 mg) and a mixture of 6″-O-Z-p-coumaroyl phloroglucinol-1-O-β-glucopyranoside with tadehaginoside (**5**, 7.3 mg, ratio 1:2.5) were isolated. Fraction E eluted with 100% methanol from the polyamide column was applied to MPLC (CH_3OH:H_2O, from 5:95 to 70:30) to obtain luteolin 7-O-β-glucuronide (**9**, 5.2 mg) with 8 different subfractions (Frs. E_{1-8}). Fr. E_4 was chromatographed on a PTLC plate using $CHCl_3$:CH_3OH:H_2O, 61:32:7 as the solvent system to yield luteolin 4′-O-β-glucopyranoside (**10**, 3.8 mg). Purification of Fr. E_8 with SCC ($CHCl_3$:CH_3OH, from 100:0 to 96:4) gave hispidulin (**11**, 3.5 mg).

3,4-Dihydroxy-6-methylpyran-2-one 3-O-β-glucopyranoside (scusalvioside A, **1**): White amorphous powder. $[\alpha]_D^{22}$+8.4 (c 1.0, MeOH). UV λ_{max} (MeOH, nm): 237 and 291. HR-ESI-MS: m/z303.0712 $[M–H]^-$ (calculated for $C_{12}H_{15}O_9$, 303.0716).

3,4-Dihydroxy-6-methylpyran-2-one 3-O-β-(6′-O-E-caffeoyl) glucopyranoside (scusalvioside B, **2**): Light yellow amorphous powder. HR-ESI-MS: m/z465.1037 $[M–H]^-$ (calculated for $C_{21}H_{21}O_{12}$, 465.1033). ^{13}C NMR and ^1H NMR results of the two new compounds are given in the Table.

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