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Iridoid Glycosides from the Aerial Parts of *Galium spurium* L.

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Abstract – Nine iridoid glycoside derivatives were elucidated from the methanolic extract of the aerial parts of *Galium spurium* (Rubiaceae) through repeated column chromatography. Their chemical structures were characterized as 10-*O*-*trans*-*p*-coumaroylscandoside (**1a**), 10-*O*-*cis*-*p*-coumaroylscandoside (**1b**), 10-*O*-*trans*-*p*-coumaroyl-10-*O*-deacetyldaphylloside (**2**), 10-*O*-*cis*-*p*-coumaroyl-10-*O*-deacetyldaphylloside (**3**), asperulic acid methylester (**4**), asperuloside (**5**), asperulosidic acid (**6**), scandoside (**7**), and deacetyl asperulosidic acid (**8**) by spectroscopic analysis. This is the first report of the characterization of compounds **1a**, **1b**, **2**, **3** and **7** from this plant.
Keywords – *Galium spurium,* Rubiaceae, Iridoid glycoside

Introduction

Galium spurium L. is a type of annual or biannual plant widely distributed in Asia, Europe, and Africa. Generally, fresh *G. spurium* is consumed as a wild greens, and whole plant has been used as a medicinal plant in Korea (Lee, 2006). In Turkey, *Galium* species are traditionally used to coagulate milk because of an enzyme in their composition, so this plant is known as "Yogurt herb". And also the aerial parts of *G. spurium* have long been used as a folk medicine for the treatments of the bones and sinews pain, hematuria, and cancer (Orhan *et al*., 2012). Alkaloids, anthraquinones, flavonoids, iridoids, naphthalene derivatives, and triterpene saponines were reported from this plant (Koyama *et al*., 1993; Deliorman *et al*., 2001; Cai *et al*., 2009; Orhan *et al*., 2012). In previous study, author *et al*. reported two iridoid derivatives, and seven phenolic compounds as antioxidant constituents from the antioxidative ethyl acetate fraction (Yang *et al*., 2011). As part of an ongoing investigation, phytochemical study was performed and nine iridoid compounds were characterized.

Experimental

General experimental procedures – NMR spectra were determined on a JEOL JMN-EX 400 spectrometer. IR spectra were obtained on a JASCO FT/IR 410 spectrometer and UV spectra were recorded on Shimadzu UV-1601 UV-Visible spectrophotometer. Mass spectra were acquired on a JEOL JMSAX 505-WA. Prep-HPLC was carried out on a Jaigel GS310 column (Tokyo, Japan). Sephadex LH-20 was used for column chromatography (25 - 100 μm; GE Healthcare, Uppsala, Sweden). TLC was carried out on Merck (Darmstadt, Germany) precoated silica gel F_{254} plates, and silica gel for column chromatography was Kiesel gel 60 (230 - 400 mesh, Merck). Spots were detected under UV and by spraying with 10% H_2SO_4 in ethanol followed by heating at 100 - 120 °C for 3 min. Methanol-d_4 (CD_3OD) for NMR experiment was obtained from Merck (Darmstadt, Germany). Solvents used for analyses were of HPLC grade and purchased from Fisher Scientific Korea (Seoul, Korea). Methanol, *n*-hexane, ethyl acetate, methylene chloride and *n*-butanol, which were used for extraction and solvent fractionation, were of extra pure quality and were obtained from Samchun Chemical (Pyeongtack, Korea).

Plant materials – The aerial parts of *G. spurium* were collected and air-dried in August 2010 at Wanju, Jeonbuk, Korea. A voucher specimen was deposited in the herbarium of the laboratory (WSU-10-012).

Extraction and isolation – The shade dried plant material (1.8 kg) was extracted three times with methanol at 50 °C and filtered. The extracts were combined and evaporated *in vacuo* at 50 °C. The resultant methanolic extract (306 g) was subjected to successive solvent partitioning to give *n*-hexane (50.4 g), methylene chloride (1.9 g), ethyl acetate (3.0 g), *n*-butanol (30.0 g) and H_2O soluble fractions. The ethyl acetate soluble extract was subjected to chromatography on a Sephadex LH-20 column and give eight fractions (E1-E8). Fraction E2 (980 mg)

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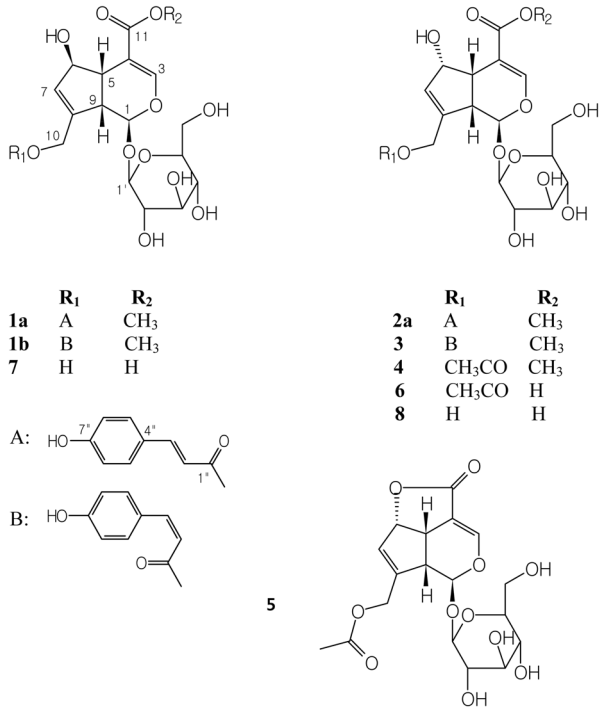

Fig. 1. Structures of isolated compounds.

was chromatographed on silica gel column chromatography ($CHCl_3$-MeOH-H_2O, 60 : 10 : 1) to give eight subfractions (E21-E28). Subfraction E26 (56 mg) was purified by Sephadex LH-20 (MeOH) to give the mixture of compounds **1a** and **1b** (14 mg). Fraction E3 (490 mg) was chromatographed on silica gel column chromatography ($CHCl_3$-MeOH-H_2O, 50 : 10 : 1) to give three subfractions (E31-E33). Subfraction E32 (190 mg) was further chromatographed on silica gel column chromatography ($CHCl_3$-MeOH-H_2O, 50 : 10 : 1) to give five subfractions (E321-E325). Subfraction 325 was purified on Lobar cloumn (EtOAc-MeOH-H_2O, 45 : 5 : 1), and Jai-GS310 column (MeOH) to give compounds 2 (5 mg) and 3 (4 mg), respectively. *n*-Butanol soluble extract was subjected to chromatography on a Sephadex LH-20 column and give four fractions (B1-B4). Fraction B1 (3.0 g) was chromatographed on silica gel column chromatography ($CHCl_3$-MeOH-H_2O, 50 : 10 : 1) to give nine subfractions (B11-B19). Subfractions B12 (80 mg), B13 (53 mg), B18 (48 mg), and B19 (96 mg) were purified by Jai-GS310 column (MeOH) to give compounds **4** (28 mg), **5** (12 mg), **6** (10 mg), **7** (11 mg), and **8** (15 mg), respectively.

10-trans-*p*- and cis-*p*-coumaroylscandoside (1a and 1b) – An amorphous powder; FABMS m/z 573 $[M + Na]^+$ (calc. $C_{26}H_{30}NaO_{13}^+$); UV λ_{max} (MeOH) nm 230, 312, IR (Nujol) cm^{-1} 3422, 2920, 1698, 1630, 1602, 1512; ^{1}H-NMR and ^{13}C-NMR Tables 1 and 3.

10-*O*-*trans*-*p*-coumaroyl-10-*O*-deacetyldaphylloside (2) – An amorphous powder; HR-FABMS 573.1578 $[M + Na]^+$ ($C_{26}H_{30}NaO_{13}^+$, calc. 573.1579); UV λ_{max} (MeOH) nm 228, 314; ^{1}H-NMR and ^{13}C-NMR Tables 1 and 3.

10-*O*-*cis*-*p*-coumaroyl-10-*O*-deacetyldaphylloside (3) – An amorphous powder; HR-FABMS 573.1578 $[M+Na]^+$ ($C_{26}H_{30}NaO_{13}^+$, calc. 573.1579); UV λ_{max} (MeOH) nm 230, 315; ^{1}H-NMR and ^{13}C-NMR Tables 1 and 3.

Asperulosidic acid methyl ester (4) – An amorphous powder; UV λ_{max} (MeOH) nm 235; IR ν_{max} (KBr) cm^{-1} 1745, 1732, 1650; ^{1}H-NMR and ^{13}C-NMR Tables 2 and 3.

Asperuloside (5) – An amorphous powder; UV λ_{max} (MeOH) nm 230; IR ν_{max} (KBr) cm^{-1} 1750, 1735, 1655; ^{1}H-NMR and ^{13}C-NMR Tables 2 and 3.

Table 1. ^{1}H-NMR spectral data of compounds **1a**, **1b**, **2**, and **3**

C	1a	1b	2	3
1	5.223 (d, *J* = 6.8)	5.186 (d, *J* = 6.4)	5.088 (d, *J* = 9.2)	5.066 (d, *J* = 8.8)
3	7.530 (d, *J* = 0.8)	7.519 (d, *J* = 0.8)	7.678 (s)	7.660 (s)
5	3.030 (m)	3.030 (m)	2.678 (t, *J* = 8.0)	2.613 (t, *J* = 8.0)
6	4.579 (m)	4.579 (m)	4.810 (m)	4.788 (m)
7	5.862 (br. s)	5.796 (br. s)	6.051 (d, *J* = 2.0)	5.970 (d, *J* = 2.0)
9	3.093 (t, *J* = 7.2)	3.093 (t, *J* = 7.2)	3.058 (m)	3.018 (m)
10	4.936 (d, *J* = 14.4)	4.936 (d, *J* = 14.4)	5.093 (d, *J* = 16.4)	5.092 (d, *J* = 16.4)
	4.858 (d, *J* = 14.4)	4.858 (d, *J* = 14.4)	5.074 (d, *J* = 16.4)	5.074 (d, *J* = 16.4)
1'	4.686 (d, *J* = 8.0)	4.679 (d, *J* = 8.0)	4.724 (d, *J* = 8.0)	4.721 (d, *J* = 8.0)
2"	6.379 (d, *J* = 16.0)	5.826 (d, *J* = 13.2)	6.381 (d, *J* = 15.6)	5.825 (d, *J* = 12.8)
3"	7.660 (d, *J* = 16.0)	6.901 (d, *J* = 13.2)	7.653 (d, *J* = 15.6)	6.899 (d, *J* = 12.8)
5"	7.477 (d, *J* = 8.8)	7.634 (d, *J* = 8.8)	7.471 (d, *J* = 8.4)	7.626 (d, *J* = 8.4)
6"	6.804 (d, *J* = 8.8)	6.749 (d, *J* = 8.8)	6.800 (d, *J* = 8.4)	6.745 (d, *J* = 8.4)
8"	6.804 (d, *J* = 8.8)	6.749 (d, *J* = 8.8)	6.800 (d, *J* = 8.4)	6.745 (d, *J* = 8.4)
9"	7.477 (d, *J* = 8.8)	7.634 (d, *J* = 8.8)	7.471 (d, *J* = 8.4)	7.626 (d, *J* = 8.4)
OCH_3	3.750 (s)	3.750 (s)	3.735 (s)	3.731 (s)

Recorded at 400 MHz in CD_3OD

Table 2. ^{1}H-NMR spectral data of compounds **4 - 8**

C	4	5	6	7	8
1	5.02 (d, J = 9.6)	5.96 (br. s)	5.04 (d, J = 8.8)	4.86 (d, J = 7.2)	5.02 (d, J = 9.2)
3	7.61 (s)	7.29 (d, J = 2.0)	7.59 (s)	7.33 (s)	7.57 (s)
5	2.60 (t, J = 8.4)	3.65 (m)	3.02 (dd, J = 8.0, 6.4)	3.65 (m)	3.01 (m)
6	4.75 (m)	5.56 (br. d, J = 6.8)	4.82 (br. s)	4.53 (m)	4.84 (d, J = 6.4)
7	5.98 (s)	5.72 (s)	6.01 (s)	5.82 (s)	6.00 (s)
9	2.99 (m)	3.30 (m)	2.61 (dd, J = 8.8, 8.0)	2.89 (m)	2.55 (m)
10	4.89 (d, J = 15.2)	4.77 (d, J = 14.4)	4.93 (d, J = 15.6)	4.36 (d, J = 15.6)	4.45 (d, J = 15.6)
	4.75 (d, J = 15.2)	4.66 (d, J = 14.4)	4.80 (d, J = 15.6)	4.17 (d, J = 15.6)	4.20 (d, J = 15.6)
1'	4.68 (d, J = 8.4)	4.67 (d, J = 8.0)	4.72 (d, J = 8.0)	4.71 (d, J = 8.4)	4.71 (d, J = 8.0)
2"	2.05 (s)	2.07 (s)	2.08 (s)		
OCH_3	3.75 (s)				

Recorded at 400 MHz in CD_3OD

Table 3. ^{13}C-NMR spectral data of compounds **1 - 8**

C	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	98.43	98.50	101.40	101.38	100.6	100.0	101.1	99.4	101.3
3	153.95	153.95	155.37	155.35	155.4	150.3	154.4	150.3	154.2
4	110.64	110.64	108.11	108.11	108.1	106.2	109.8	116.0	110.3
5	45.58	45.58	42.43	42.44	42.4	37.4	42.8	47.3	43.2
6	82.31	82.31	75.36	75.38	75.3	86.3	75.5	83.1	75.6
7	132.58	132.77	131.73	132.05	131.8	128.9	131.9	129.9	129.8
8	142.29	142.07	146.20	146.00	145.9	144.3	146.0	147.4	151.5
9	47.61	47.55	46.34	46.28	46.2	45.3	46.4	48.3	46.1
10	62.97	62.97	63.63	63.59	63.7	62.8	63.8	61.6	61.8
11	170.25	170.25	169.35	169.35	169.3	172.2	172.5	173.1	172.5
1'	100.51	100.51	100.73	100.64	101.3	93.4	100.5	100.3	100.4
2'	74.78	74.78	74.90	74.91	74.9	74.6	75.0	75.0	75.0
3'	78.45	78.45	78.53	78.59	78.5	78.4	78.6	78.4	78.5
4'	71.46	71.45	71.54	71.62	71.5	71.6	71.6	71.5	71.7
5'	77.92	77.92	77.92	77.93	77.8	77.9	77.9	77.8	77.8
6'	62.80	62.80	62.98	63.04	62.9	61.9	63.0	62.6	62.9
1"	168.83	168.84	168.92	168.93	172.5	172.6	172.5		
2"	115.91	114.78	115.88	115.62	20.8	20.6	20.7		
3"	147.08	145.68	147.02	145.60					
4"	127.11	127.59	127.15	127.63					
5"	131.29	133.72	131.28	133.68					
6"	116.85	115.91	116.79	116.33					
7"	161.42	160.92	161.39	160.10					
8"	116.85	115.91	116.79	116.33					
9"	131.29	133.72	131.28	133.68					
OCH_3	52.10	52.10	51.85	51.85	51.9				

Recorded at 100 MHz in CD_3OD

Asperulosidic acid (6) – An amorphous powder; UV λ_{max} (MeOH) nm 230; IR ν_{max} (KBr) cm^{-1} 1730, 1640; ^{1}H-NMR and ^{13}C-NMR Tables 2 and 3.

Scandoside (7) – An amorphous powder; UV λ_{max} (MeOH) nm 235; IR ν_{max} (KBr) cm^{-1} 3350, 1685, 1634; ^{1}H-NMR and ^{13}C-NMR Tables 2 and 3.

Deacetyl asperulosidic acid (8) – An amorphous powder; UV λ_{max} (MeOH) nm 235; IR ν_{max} (KBr) cm^{-1} 3450, 1685, 1645; ^{1}H-NMR and ^{13}C-NMR Tables 2 and 3.

Results and Discussion

The methanolic extract was successively fractionated into *n*-hexane, methylene chloride, ethyl acetate, *n*-butanol and H_2O soluble fractions through solvent fractionation. Repeated column chromatographies of the ethyl acetate and *n*-butanol soluble fractions identified nine iridoid glycoside derivatives. Structure characterization of compounds **4 - 6** and **8** was carried out by interpretation of their spectral data and comparison with the data previously reported in the literature from this plant.

Compounds **4** - **6** and **8** were identified as asperulic acid methylester (**4**), asperuloside (**5**), asperulosidic acid (**6**), and deacetyl asperulosidic acid (**8**), respectively (Bailleul *et al*., 1977; Chaudhuri, 1980; El-Naggar and Beal, 1980).

Compounds **1a**, **1b** and **7** have similar patterns in their NMR spectra except for the the acyl signals in the aromatic region and methoxyl group. Compound **7** was obtained as an amorphous powder. Its IR spectrum showed absorbance bands due to the hydroxyl (3350 cm^{-1}), carbonyl (1685 cm^{-1}), and olefin (1634 cm^{-1}) groups. In the ^{1}H-NMR spectrum of compound **7** showed a doublet at δ 7.33 (1H, s) which was assigned to the enol ether proton at C-3, and two signals at δ 3.65 (1H, m) and 2.89 (1H, m) were assigned to the protons at C-5 and C-9. In the ^{13}C-NMR spectrum, 16 carbon signals were observed, which included a carbonyl group at δ 173.1, four olefinic carbons at δ 150.3, 147.4, 129.9 and 116.0, and sugar carbons at δ 100.3, 78.4, 77.8, 75.0, 71.5 and 62.6. The characteristic peak of β-configuration of hydroxyl group at C-6 of the iridoid compounds was observed at δ 83.1 in the ^{13}C-NMR spectrum. From these results, compound **7** was indicated to be an iridoid glycoside. The structure of compound **7** was determined to be scandoside on the basis of the above evidences, together with a comparison of the above data with those published in the literature (El-Naggar and Beal, 1980; Kim *et al*., 2005).

Compound **1** was obtained as an amorphous mixture (**1a** and **1b**), and it showed a single spot on thin layer chromatogram (EtOAc : EtOH : H_2O = 35 : 5 : 1). Its molecular composition was determined to be $C_{26}H_{30}O_{13}$ by FABMS. Its UV spectrum showed maximum absorption at 230 nm from an aromatic ring, conjugated with a ketone function, and its IR spectrum revealed the presence of a conjugated ester at 1698 and 1630 cm^{-1}. In the ^{13}C-NMR spectrum of **1**, acyl moiety composed of six aromatic signals and a carbonyl carbon signal was observed, which is accordance with those of coumaric acid. Except for the acyl portion and methoxyl group, NMR chemical shifts of compound **1** showed very similar patterns that of compound **7**. NMR spectra indicated that compound **1** was an acylated derivative of scandoside methyl ester. However, those NMR spectra showed some complexity. A large number of ^{13}C-NMR peaks of compound **1** for aglycone and glucose moieties appeared with smaller satellite peaks. In the ^{1}H-NMR spectrum, two sets of doublets at δ 7.660 (1H, d, J = 16.0 Hz) and 6.379 (1H, d, J = 16.0 Hz), and δ 6.901 (1H, d, J = 13.2 Hz) and 5.826 (1H, d, J = 13.2 Hz) indicated the existence of *trans* and *cis* double bonds, respectively. Aromatic proton signals were observed as doublets at δ 7.477 (1H, d, J = 8.8 Hz) and 6.804 (1H, d, J = 8.8 Hz), together with smaller signals at δ 7.634 (1H, d, J = 8.8 Hz) and 6.749 (1H, d, J = 8.8 Hz), which are assumed to be due to a *cis* isomer. These data implied the acyl portions are *trans* and *cis*-*p*-coumaric acids. The *trans* and *cis* ratio was calculated to be approximately 75:25 from the proton signal integrals. Therefore, the compound **1** was deduced to be the mixture of *trans* and *cis*-*p*-coumaroylscandosides. Finally, the structure of **1** was determined to be 10-*O*-*trans*-*p*-coumaroylscandoside (**1a**) and 10-*O*-*cis*-*p*-coumaroylscandoside (**1b**) on the basis of the above evidences, together with a comparison of the above data with those published in the literature (Otsuka *et al*., 1991).

Compounds **2** and **3** were obtained as an amorphous powder, and molecular compositions of compounds **2** and **3** were determined to be $C_{26}H_{30}O_{13}$ by FABMS. Their UV spectra showed maximum absorption at 228 and 230 nm from an aromatic ring respectively, conjugated with a ketone function. In the ^{13}C-NMR spectra of compounds **2** and **3**, acyl moieties composed of six aromatic signals and a carbonyl carbon signal were observed respectively, which are accordance with those of coumaric acids. Except for the acyl portion and methoxyl group, NMR chemical shifts of compounds **2** and **3** showed very similar patterns that of compound **8**. The characteristic peaks of α-configuration of hydroxyl group at C-6 of the iridoid compounds were observed at δ 75.36 and 75.38 in the ^{13}C-NMR spectrum of compound **2** and **3**. NMR spectra indicated that compound **2** and **3** were acylated derivatives of deacetylasperulosidic acid methyl ester (deacetyldaphylloside). In the ^{1}H-NMR spectra, each a set of doublets at δ 7.653 (1H, d, J = 15.6 Hz) and 6.381 (1H, d, J = 15.6 Hz) of compound **2**, and δ 6.899 (1H, d, J = 12.8 Hz) and 5.825 (1H, d, J = 12.8 Hz) of compound **3** indicated the existence of *trans* and *cis* double bonds, respectively. Aromatic proton signals were observed as doublets at δ 7.471 (1H, d, J = 8.4 Hz) and 6.800 (1H, d, J = 8.4 Hz) of compound **2**, and δ 7.626 (1H, d, J = 8.4 Hz) and 6.745 (1H, d, J = 8.4 Hz) of compound **3**, which are assumed to be due to orth coupling configuration. These data implied the acyl portions are *trans* and *cis*-*p*-coumaric acids, respectively. On the basis of the above evidences, together with a comparison of the above data with those published in the literature, the structure of *trans*-*p*-coumaroyl derivative was determined to be 10-*O*-*trans*-*p*-coumaroyl-10-*O*-deacetyldaphylloside (**2**), which was isolated from *Daphniphyllum angustifolium* (Bai and Ju, 2006). The ^{13}C-NMR data of the acyl moiety of *cis*-*p*-coumaroyl derivative (**3**) showed good agreement with

the acyl moiety of compound **1b**, which has the same *cis-p*-coumaric acid partial moiety. The position of esterification was determined to be the 10-hydroxyl group of aglycone, since when the ^{13}C-NMR spectra of compounds **3** and **8** were compared, the C-10 signal of compound **3** was found to be significantly shifted downfield, by +1.8 ppm on acylation, the β-position (C-8) shifted upfield by -5.5 ppm, and the γ-position (C-7) shifted downfield by +2.3 ppm (Table 3) (Otsuka *et al*., 1991). This was also supported by the results of ^{1}H-NMR spectrum. The two protons on C-10 of compound **3** were shifted downfield by about 0.77 ppm on acylation than that of compound **8** (Table 1, 2). Consequently, the structure of compound **3** was concluded to be 10-*O*-*cis*-*p*-coumaroyl-10-*O*-deacetyldaphylloside (**3**).

To our best knowledge, this is the first report on the elucidation of compound **3** in the nature, but that could be an artifact of its acid form created during the extraction with methanol. And compounds **1a**, **1b**, **2**, and **7** were characterized for the first time from this plant.

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