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Coumarins and Chromones from *Angelica genuflexa*

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Abstract – Thirteen compounds were isolated from the roots of *Angelica genuflexa* through repeated silica gel column chromatography. Nine coumarins, isoimperatorin (**1**), osthol (**2**), demethylsuberosin (**3**), oxypeucedanin (**4**), heraclenin (**5**), pabulenol (**7**), umbelliferone (**8**), oxypeucedanin hydrate (**9**) and marmesinin (**11**), and four chromones, hamaudol (**6**), cimifugin (**10**), *sec-O*-glucosylhamaudol (**12**) and *prim-O*-glucosylcimifugin (**13**), were identified by physicochemical and spectroscopic analysis. Among these, compounds **3**, **5**, **6**, **8**, **12**, and **13** were isolated for the first time from the roots of *Angelica genuflexa*. These coumarins and chromones were examined for their anticomplement activity. Demethylsuberosin (**3**) showed a weak anticomplement activity with an IC_{50} value of 390 μM.
Keywords – *Angelica genuflexa*, demethylsuberosin, heraclenin, hamaudol, umbelliferone, *sec-O*-glucosylhamaudol, *prim-O*-glucosylcimifugin, anticomplement activity

Introduction

Angelica genuflexa is commonly known as "Gangwhal", in Korea (Sun *et al.*, 2000). The roots of this plant have been used in Korea as a traditional medicine to treatment the common cold, headache, neuralgia, arthralgia *etc.* (Woo *et al.*, 1982). Previous phytochemical studies on *A. genuflexa* have led to the isolation of several coumarin compounds, such as isoimperatorin, imperatorin, oxypeucedanin, byakangelicol, oxypeucedanin hydrate, oxypeucedanin methanolate, bergapten, pabulenol and heraclenin (Ryu *et al.*, 2001; Lee & Woo, 1982; Lee *et al.*, 2003; Ryu, 1968); a sesquiterpene, bisabolangeone (Bae *et al.*, 1994); and a chromones, cimifugin (Kwon *et al.*, 2000). Using chromatographic separation, we isolated nine coumarins; isoimperatorin (**1**), osthol (**2**), demethylsuberosin (**3**), oxypeucedanin (**4**), heraclenin (**5**), pabulenol (**7**), umbelliferone (**8**), oxypeucedanin hydrate (**9**) and marmesinin (**11**), and four chromones; hamaudol (**6**), cimifugin (**10**), *sec-O*-glucosylhamaudol (**12**), and *prim-O*-glucosylcimifugin (**13**). This paper describes the isolation of these compounds, their structural determination using spectroscopic analysis, and their anticomplement activity.

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Experimental

General experimental procedures – Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter in $CHCl_3$. The NMR spectra were recorded on a Bruker AMX 600 spectrometer, with chemical shifts being represented in ppm and tetramethylsilane used as an internal standard. The FAB-MS was measured on a JMS-HX 110/110A mass spectrometer (JEOL). Medium pressure liquid chromatography (MPLC) separations were performed over LiChroprep RP C-18 (Merck, size B). The spots were detected under UV radiation and by spraying with 10% H_2SO_4, followed by heating.

Plant materials – The root of *A. genuflexa* cultivated in Jinbu-Myeon, Gangwon-do, Korea was used in this study. There are two types of roots in the market according to the shape and seedling method. One is "Namgangwhal", which has more secondary root branches at the tap root and multiply by seeds. The other is "Bukgangwhal", which has less secondary root branches and multiply with budding. We used "Namgangwhal" for this study. Although, "Gangwhal" was reported to be a member of *A. geneflexa* by Sun *et al.* (2000), a taxonomic revision of the origin of *A. genuflexa* still needs to be done. Dr. Joongku Lee, Korea Research Institute Bioscience and Biotechnology, Korea verified the identity of this

plant. A voucher specimen (PBC-014) was deposited at the Plant Extract Bank, Korea Research Institute of Bioscience and Biotechnology, Daejeon, Korea.

Extraction and isolation – The dried and powdered roots of *A. genuflexa* (5 kg) were extracted with MeOH (3 ×5L) for 7 days at 25°C. The combined extracts were concentrated under reduced pressure. The residue (1.2 kg) was diluted with water (1L), and then partitioned successively with hexane (3×1L) and EtOAc (3×1L) to afford the hexane- (280 g) and EtOAc-soluble fractions (40 g), respectively.

The hexane-soluble fraction (280 g) was subjected to silica gel column chromatography with a hexane–EtOAc mixture (EtOAc 10-100%, step gradient) to give seven fractions (A-F). Fraction B was crystallized in EtOAc to yield compound **1** (800 mg). Fraction C (6.35 g) was chromatographed on a silica gel column using hexane-acetone (5 : 1) to yield compound **2** (1.67 g). Fraction D (3.5 g) was further fractionated by a silica gel column chromatography with hexane–acetone (5 : 1) to afford 3 subfractions (D1-D3). Fraction D2 (1.1 g) was chromatographed twice with $CHCl_3$–acetone (50 : 1) on a silica gel column to give compound **3** (4.9 mg). Compound **4** (2.1 g) was isolated from fraction D3 (3.0 g) by silica gel column chromatography ($CHCl_3$–acetone, 40 : 1). Fraction E (42 g) was subjected to a silica gel column (hexane-acetone, 3 : 1) to obtain two subfractions (E1, E2). From fraction E1 (9.4 g), compound **5** (183.6 mg) was obtained by silica gel column chromatography with $CHCl_3$-EtOAc (30 : 1). Fraction E2 (7.1 g) was chromatographed to on a silica gel column with $CHCl_3$-EtOAc (30 : 1) to give compounds **6** (83 mg) and **7** (55.3 mg). Fraction F (12 g) was subjected to silica gel column (hexane–acetone, 2 : 1) to give compounds **8** (10 mg) and **9** (943.6 mg). The EtOAc-soluble fraction was purified on a silica gel column with $CHCl_3$-MeOH (19:1) to afford compound **10** (184 mg).

The resulting H_2O layer was subjected to Diaion HP-20 column chromatography (eluted with H_2O, 50% MeOH, and MeOH) to give three fractions. The MeOH-soluble fraction (10.2 g) was purified by silica gel chromatography to give compound **11** (111 mg). The 50% MeOH-soluble fraction (14 g) was further purified by silica gel flash column chromatography (MeOH-$CHCl_3$ gradient) and MPLC (ODS, H_2O-MeOH, 1 : 2) to give compounds **12** (48.5 mg) and **13** (1.3 g).

Demethylsuberosin (3): light yellow plates (hexane-EtOAc); mp 130-132°C. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2.

Heraclenin (5): white plates (hexane-EtOAc); mp 111-113°C. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2.

Hamaudol (6): light yellow needles (hexane-EtOAc); mp 201-203°C. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2.

Umbelliferone (8): colorless plates (hexane-EtOAc); mp 224-226°C. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2.

Table 1. ^{1}H-NMR spectroscopic data of compounds **3**, **5**, **6**, **8**, **12**, and **13** (600 MHz in $CDCl_3$ & DMSO-d_6)

	3[a]	**5**[a]	**6**[a]	**8**[a]	**12**[b]	**13**[b]
3	6.25 d (9.6)	6.39 d (9.6)	6.00 s	6.16 d (9.6)	6.17 s	6.30 s
4	7.64 d (9.6)	7.79 d (9.6)		7.72 d (9.6)		
5	7.21 s	7.42 s		7.35 d (8.4)		
6				6.77 dd (8.4, 2.4)		
8	6.93 s		6.33 s	6.73 d (2.4)	6.36 s	
9						4.51 d (15), 4.64 d (15)
1'	3.40 d (7.2)					
2'	5.34 t (7.2)	7.71 d (2.4)	3.89 t (5.4)		3.96 dd (6.6, 5.4)	4.70 t (8.4)
3'		6.84 d (2.4)	2.75 dd (17.2, 5.4)		2.59 dd (17.1, 6.6)	3.23 dd (8.4, 6.0)
4'			2.98 dd (17.2, 5.4)		2.87 dd (17.1, 5.4)	
1"		4.60 dd (5.7,				
2"		3.3)				
CH_3	1.79 (C3")	3.34 t (5.7)	1.37 (C2')		1.27 (C2')	1.14 (C4')
	1.81 (C3")	1.30 (C3")	1.41 (C2')		1.32 (C2')	1.15 (C4')
		1.36 (C3")	2.34 (C2)		2.34 (C2)	
OCH_3						3.82 s
Glc-1					4.32 d (7.5)	4.28 d (7.8)
-2					2.92 ddd (8.3, 7.5, 5.3)	3.0–3.18 m
-3					3.15 dd (8.8, 4.9)	3.0–3.18 m
-4					3.02 dd (9.2, 5.1)	3.0–3.18 m
-5					3.13 ddd (9.3, 6.1, 1.9)	3.0–3.18 m
-6					3.41 ddd (11.7, 5.9, 5.6)	3.44 dd (12.0, 6.0)
					3.67 ddd (11.7, 6.3, 1.9)	3.67 dd (12.0, 2.4)

[a]$CDCl_3$ [b]DMSO-d_6. δ values in ppm and coupling constants (in parentheses) in Hz

Table 2. ^{13}C-NMR spectroscopic data of compounds 3, 5, 6, 8, 12, and 13 (150 MHz in $CDCl_3$ & DMSO-d_6)

carbon	3[a]	5[a]	6[a]	8[a]	12[b]	13[b]
2	162.2	160.7	167.1	162.2	167.8	162.3
3	112.8	115.2	108.7	112.0	107.7	110.0
4	144.2	144.6	182.9	145.5	181.9	175.3
4a	113.1	116.9	104.8	112.5	103.5	111.4
5	128.7	114.2	160.1	129.9	158.7	164.5
6	125.6	126.4	103.3	114.2	103.4	117.4
7	158.6	148.7	159.4	163.4	158.7	158.8
8	103.8	131.9	95.2	103.3	94.3	93.2
8a	154.6	144.1	156.6	156.5	155.4	155.1
9						65.1
1'	29.1					
2'	121.3	147.2	78.8		77.9	91.0
3'	135.8	107.2	69.2		72.7	26.9
4'			25.8		21.5	69.9
1"		72.9				
2"		61.7				
3"		58.5				
CH_3	18.3 (C3')	19.2 (C3")	20.9 (C2)		20.0 (C2)	24.7 (C4')
	26.2 (C3')	24.9 (C3")	22.4 (C2')		21.7 (C2')	25.7 (C4')
			25.2 (C2')		25.3 (C2')	
OCH_3						60.2
Glc-1					100.5	102.3
-2					73.3	73.3
-3					76.8	77.0
-4					70.3	70.0
-5					76.9	76.5
-6					61.4	61.1

[a]$CDCl_3$
[b]DMSO-d_6

***sec-O*-glucosylhamaudol (12):** yellow needles (MeOH); mp 230-232°C. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2.

***prim-O*-glucosylcimifugin (13)** yellow needles (MeOH), mp 120-122°C. ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2.

Anti-complement assay – Measurement of anti-comple ment activity was carried out according to the published by Min *et al.* (2003). Tiliroside and rosmarinic acid were used as positive controls (Jung *et al.*, 1998). Anti-complement activity was determined as a mean of triplicate measurements and expressed as the 50% inhibitory concentrations (IC_{50}) values from complement-dependent hemolysis of the control.

Results and Discussion

Repeated column chromatography of the MeOH extraction from the roots of *A. genuflexa* led to the isolation of thirteen compounds (**1-13**). Among these, isoimperatorin (**1**) (Baek *et al.*, 2000), osthol (**2**) (Lee & Woo, 1982; Zhou *et al.*, 2000), oxypeucedanin (**4**) (Lee & Woo, 1982), pabulenol (**7**) (Lee *et al.*, 2003), oxypeucedanin hydrate (**9**) (Baek *et al.*, 2000), cimifugin (**10**) (Sasaki *et al.*, 1982), and marmesinin (**11**) (Kwon *et al.*, 1991) were identified by comparison of physical and spectroscopic data (mp, optical rotation, ^{1}H- and ^{13}C-NMR) with literature values.

Table 3. Inhibitory effects of the compounds **1-13** on complement system of classical pathway

Compound	IC_{50} values (mM)[a]
Isoimperatoin (**1**)	> 500
Osthol (**2**)	> 500
Demethylsuberosin (**3**)	390
Oxypeucedanin (**4**)	> 500
Heraclenin (**5**)	> 500
Hamaudol (**6**)	> 500
Pabulenol (**7**)	> 500
Umbelliferone (**8**)	> 500
Oxypeucedanin hydrate (**9**)	> 500
Cimifugin (**10**)	> 500
Marmesinin (**11**)	> 500
sec-O-glucosylhamaudol (**12**)	> 500
prim-O-glucosylcimifugin (**13**)	> 500
Tiliroside[b]	102
Rosmarinic acid[b]	180

[a]The values represent the mean±S.D. of three experiments.
[b]Used as positive controls.

Compound **3** was obtained as light yellow plates. The presence of 7-hydroxy-6-substituted coumarin was indicated from the typical signals at δ 6.25 and 7.64 (each 1H, d, J = 9.6 Hz) for H-3 and H-4, and two singlet aromatic protons at δ 6.93 (H-8) and 7.21 (H-5) in the ^{1}H-NMR

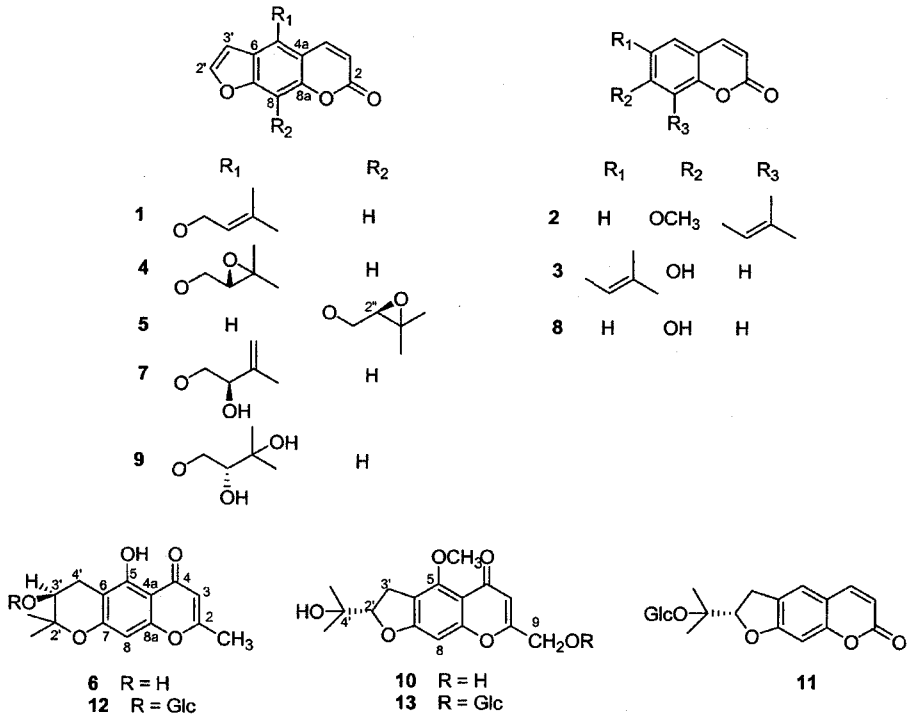

Fig. 1. Structures of Compounds 1-13 from *Angelica genuflexa*.

spectrum. The ^{1}H-NMR spectrum also exhibited the presence of a 3-methylbut-2-enyl moiety at δ 5.34 (1H, t, J = 7.2 Hz), 3.40 (2H, d, J = 7.2 Hz), 1.81 (3H, s), and 1.79 (3H, s). This moiety was further supported by the ^{13}C-NMR spectrum signals for a methylene carbon (δ 29.1), two olefinic carbons (δ 121.3, 135.8), and two methyl carbons (δ 18.3, 26.2). Based on these results and on values previously reported in the literature (Masuda *et al.*, 1998), compound **3** was identified as demethylsuberosin.

Compound **5** was obtained as white plates. In the ^{1}H-NMR spectrum, doublet signals at δ 7.79 (1H, J = 9.6 Hz) and 6.39 (1H, J = 9.6 Hz), and two doublet signals at δ 7.71 (1H, J = 2.4 Hz) and 6.84 (1H, J = 2.4 Hz) were assigned a furanocoumarin skeleton (Baek *et al.*, 2000). The ^{1}H-NMR spectrum also showed the presence of a 3-methyl-2,3-epoxybutyloxy moiety at δ 4.60 (2H, dd, J = 5.7, 3.3 Hz), 3.34 (1H, t, J = 5.7 Hz), 1.36 (3H, s), 1.30 (3H, s). In addition, the configuration at C-2" was *S*, as determined by its negative optical rotation value $[\alpha]_D$ −20° (*c* 0.1, $CHCl_3$); lit. $[\alpha]_D$ −22° (*c* 3.19, pyridine). Based on these results and on values previously reported in the literature (Razdan *et al.*, 1987), compound **5** was identified as heraclenin.

Compound **6** was isolated as light yellow needles, mp 201-203°C. The ^{1}H-NMR spectrum of compound **6** exhibited signals due to a gem-dimethyl group at δ 1.37, 1.41 (each 3H, C2'-CH_3), one allylic methyl group at δ 2.34 (3H, s, C2'-CH_3), ABX type signals assignable to adjacent methylene and methine protons at δ 3.89 (1H, t, J = 5.4 Hz, H-3'), 2.75 (1H, dd, J = 17.2, 5.4 Hz, H-4'), and 2.98 (1H, dd, J = 17.2, 5.4 Hz, H-4'), as well as a signal arising from an olefinic proton at δ 6.00 (1H, br s, H-3) and an aromatic proton at δ 6.33 (1H, s, H-8). These data indicate that compound **6** is a 2-substituted chromone containing a dimethyldihydropyran ring. ^{13}C-NMR spectrum with DEPT showed the presence of eight non-protonated carbons at δ 78.8 (C-2'), 103.3 (C-6), 104.8 (C-4a), 156.6 (C-8a), 159.4 (C-7), 160.1 (C-5), 167.1 (C-2), and 182.9 (C-4) and seven protonated carbons at δ 20.9 (C2-CH_3), 22.4 (C2'-CH_3), 25.2 (C-2', CH_3), 25.8 (C-4'), 69.2 (C-3'), 95.2 (C-8), and 108.7 (C-3). These spectroscopic data suggest that **6** be a pyranocoumarin-type compound. Thus, compound **6** was elucidated as hamaudol by comparison of literature (Fujioka *et al.*, 1999).

Compound **8** was also obtained as colorless plates from hexane-EtOAc. The ^{1}H-NMR spectrum revealed four aromatic protons at δ 6.16 (1H, d, J = 9.6 Hz, H-3) and 7.72 (1H, d, J = 9.6, H-4), ascribable to the *α*-pyrone moiety and another two doublets at δ 6.77 (1H, dd, J = 8.4, 2.4 Hz, H-6) and 7.35 (1H, d, J = 8.4 Hz, H-5). Comparison of spectral data with those of **3**, demonstrated that **8** differed from **3**, for which bearing 3-methylbut-2-enyl moiety at C-7. Based on the spectroscopic data discussed above the structure of **8** was assigned to be

umbelliferone (Razdan *et al.*, 1987).

Compound **12** was isolated as yellow needles (MeOH). The ^{1}H-NMR spectrum of **12** was very similar to that of **6**, except for the signals of a sugar moiety observed at δ 2.05−4.46 (δ 4.32, d, J = 7.5 Hz, anomeric proton). The ^{13}C-NMR spectrum exhibited six signals due to β-D-glucopyranoside moiety, and fifteen signals attributable to an aglycone moiety, which was a close resemblance to these of **6**. The signal of C-3' (δ 72.7) was shifted to lower field by 3.5 ppm, while that of C-4' (*d* 21.5) to higher field by 4.3 ppm, compared to the corresponding carbon signals of compound **6**. This indicated that a sugar moiety was bonded at the C-3' position. On the basis of these findings, **12** was identified as *sec-O*-glucosylhamaudol (Okuyama *et al.*, 2001)

Compound **13** was obtained as yellow needles (MeOH). The ^{1}H-NMR spectrum of **13** was similar to that of **10**, except for the signals assignable to a sugar moiety observed at δ 3.0-4.28 (δ 4.28, d, J = 7.8 Hz, anomeric proton). The ^{13}C-NMR analysis of **13** suggested that **13** might be a glucoside of cimifugin (**10**). On the other hand, the ^{13}C-NMR spectrum of **13** showed downfield shifts of the C-2 hydroxymethyl carbon signal (Δδ + 4.6 ppm) and the C-3 signal (Δδ + 1.1 ppm), and an upfield shift of the C-2 signal (Δδ −5.0 ppm), compared with those of **10**, indicating that the glucosyl moiety is linked to the 2-hydroxymethyl group of **10**, and was identified as *prim-O*-glucosylcimifugin. (Sasaki *et al.*, 1982). Among the isolated compounds **3**, **5**, **6**, **8**, **12**, and **13** were isolated from this plant for the first time.

Compounds **1-13** were tested for their anticomplement activity. Demethylsuberosin (**3**) inhibited the hemolytic activity of the complement system with an IC_{50} value of 390 μM. On the other hand, the other compounds were incapable of inhibiting complement activity. On the survey of literatures, the anticomplement activity of demethylsuberosin is the first report.

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