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Flavonoid Glycosides from the Flowers of *Pulsatilla koreana* Nakai

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Abstract – Extraction and fractionation of *Pulsatilla koreana* flowers followed by, repeated open column chromatography for EtOAc and *n*-BuOH fractions yielded four flavonoid glycosides, namely, astragalin (**1**), tiliroside (**2**), buddlenoide A (**3**), and apigenin-7-*O*-(3"-*E*-*p*-coumaroyl)-glucopyranoside (**4**). The chemical structures of these flavonoid glycosides were elucidated on the basis of various spectroscopic methods including electronic ionization mass spectrometry (EI-MS), 1D NMR (^{1}H, ^{13}C, DEPT), 2D NMR (gCOSY, gHSQC, gHMBC), and infrared (IR) spectrometry. This study represents the first report of the isolation of the flavonoid glycosides from the flowers of *P. koreana*.

Keywords – Buddlenoide A, Flower, *Pulsatilla koreana*, Nuclear magnetic resonance, Tiliroside

Introduction

Pulsatilla koreana (Ranunculaceae) is a perennial herb used in Korean traditional medicine for the treatment of amoebic dysentery and malaria.[1] Additionally, *P. koreana* has been reported to have anti-angiogenic, cytotoxic, anti-inflammatory, and anti-tumor activities.[2-4] Oleanane-type triterpenoid saponins, lupane-type triterpenoid saponins, quinones, phenylpropanoids, and flavonoid glycosides have been isolated from the root and aerial parts of *P. koreana* in previous phytochemical studies.[5-9] However, there have been few studies that have specifically aimed to identify compounds from the flowers of *P. Koreana*. Flowers are a very important aspect of the reproductive system of plants. Together, the stamen, petal, pistil, and sepal comprise the different parts of a flower, serving to protect the plant at the stage of differentiation, as well as to facilitate male and female reproduction, and attract insects. Many flowers have UV-visible patterns that specifically visible to insects, with the UV absorbing pigments concentrated in the center of the flower acting to increase attractiveness of a flower.[10] Thus, another goal of this study was to identify pharmacologically active constituents from the flowers of *P. koreana*. To that end, we describe our isolation procedures including solvent extraction, systematic solvent fractionation, and repeated open column chromatography using silica gel (SiO_2) and octadecyl silica gel (ODS) as resins, as well as structure determination based on spectroscopic analyses such as nuclear magnetic resonance (NMR), EI-MS, polarimetry, and IR.

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Experimental

General experimental procedures – Kiesel gel 60 (63 - 20 μm, Merck) and Lichroprep RP-18 (46 - 60 μm, Merck) were used as resins for column chromatography (c.c.). Thin layer chromatography (TLC) analysis was carried out using Kiesel gel 60 F_{254} and RP-18 F_{254}s plates (Merck), TLC spots were detected using a UV lamp Spectroline Model ENF-240 C/F (Spectronics Corporation) and spraying with 10% H_2SO_4 solution followed by heating. Deuterium solvents for NMR measurements were purchased from Merck Co. Ltd. NMR spectra were recorded on a 400-MHz FT-NMR spectrometer (Varian), and chemical shifts were calibrated for the solvents used for NMR. IR spectra were obtained from a Perkin Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured using a JASCO P-1010 digital polarimeter. EI/MS data were recorded using a JMSAX-700 (JEOL). Uncorrected melting points were determined using a Fisher-John's melting point apparatus (Fisher Scientific).

Plant materials – Flowers of *P. koreana* were collected at Kyung Hee University, Yongin, Korea in April 2014 and identified by Prof. Seung-Woo Lee, Department of Horticultural Biotechnology, Kyung Hee University, Yongin, Korea. A voucher specimen (KHU-NPCL-140410) was

deposited at the Laboratory of Natural Products Chemistry, Kyung Hee University, Yongin, Korea.

Extraction and isolation – Dried flowers of *P. koreana* (80 g) were chopped and extracted in 80% MeOH at room temperature for 24 h, filtered and concentrated *in vacuo*. The concentrated MeOH extracts (8 g) were then poured into water and successively extracted with EtOAc and *n*-BuOH. Each solvent layer was concentrated to yield EtOAc (PKE, 560 mg), *n*-BuOH (PKB, 920 mg), and water (PKW, 6.5 g) fractions, respectively. The EtOAc fraction (PKE, 560 mg) was subjected to SiO_2 c.c. and eluted with $CHCl_3$/MeOH (10:1) with monitoring by TLC to provide 10 fractions (PKE1-PKE10). Fraction PKE5 (65 mg) was subjected to ODS c.c. eluted with MeOH/water (3:2) as to give four fractions (PKE5-1-PKE5-4), along with compound **4** (8.2 mg). Fraction PKE7 (39 mg) was subjected to ODS c.c. eluted with MeOH/water (1:1), yielding seven fractions (PKE7-1-PKE7-7) that ultimately afforded compound **2** (14.6 mg). Fraction PKE9 (77 mg) was subjected to ODS c.c. eluted with MeOH/water (1:1), yielding seven fractions (PKE9-1-PKE9-7), and ultimately afforded compound **1** (16.0 mg). The concentrated *n*-BuOH fraction (PKB, 920 mg) was subjected to ODS c.c. eluted with acetone-water (1:2) to yielding 13 fractions (PKB1-

Table 1. ^{1}H- (400 MHz, coupling pattern, *J* in Hz) and ^{13}C-NMR (100 MHz) data of compounds **1** - **4** from the flowers of *Pulsatilla koreana*

	1[a]		**2**[b]		**3**[a]		**4**[a]	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		158.0		157.6		164.5		164.9
3		135.3		134.9		133.7	6.47 (s)	105.0
4		179.2		178.6		177.9		182.6
5		162.7		162.2		156.9		163.3
6	6.19 (d, 2.0)	99.8	6.68 (br.s)	99.9	6.12 (d, 2.0)	98.5	6.62 (br.s)	99.6
7		165.7		166.3		164.9		165.3
8	6.37 (d, 2.0)	94.8	6.68 (br.s)	94.8	6.29 (d, 2.0)	93.3	6.62 (br.s)	94.5
9		158.8		157.7		157.9		157.5
10		105.6		105.8		104.1		105.6
1'		122.5		121.8		121.2		121.4
2'	8.05 (d, 9.2)	132.1	8.41 (d, 8.4)	131.8	7.98 (d, 8.8)	129.7	7.86 (d, 7.6)	128.2
3'	6.89 (d, 9.2)	115.9	7.20 (d, 8.4)	116.0	6.79 (d, 8.8)	115.3	6.92 (d, 7.6)	115.6
4'		161.2		161.7		160.0		161.7
5'	6.89 (d, 9.2)	115.9	7.20 (d, 8.4)	116.0	6.79 (d, 8.8)	115.3	6.92 (d, 7.6)	115.6
6'	8.05 (d, 9.2)	132.1	8.41 (d, 8.4)	131.8	7.98 (d, 8.0)	129.7	7.86 (d, 7.6)	128.2
1"	5.21 (d, 7.6)	104.0	6.19 (d, 6.4)	104.1	5.39 (d, 7.6)	102.5	5.58 (d, 7.6)	102.6
2"	3.43 (dd, 8.4, 7.6)	75.6	4.17 (overlapped)	75.9	3.44 (overlapped)	74.2	3.52 (overlapped)	73.2
3"	3.43 (overlapped)	78.2	4.35 (overlapped)	78.3	3.48 (overlapped)	76.5	3.68 (overlapped)	76.4
4"	3.43 (overlapped)	71.2	4.17 (overlapped)	71.2	3.42 (overlapped)	70.2	3.49 (overlapped)	69.8
5"	3.21 (m)	78.0	4.35 (overlapped)	75.9	3.46 (overlapped)	74.3	3.29 (overlapped)	76.9
6"a	3.69 (dd, 12.0, 2.4)	62.4	4.97 (br.d, 11.6)	64.4	4.31 (dd, 12.0, 2.4)	63.8	3.94 (br.d, 12.0)	62.8
6"b	3.53 (dd, 12.0, 5.6)		4.83 (dd, 11.6, 5.6)		4.20 (dd, 12.0, 5.8)		3.70 (overlapped)	
1"'				126.0		125.6		125.6
2"'			7.48 (d, 8.4)	130.6	7.30 (d, 8.8)	130.7	7.48 (d, 8.4)	129.6
3"'			7.14 (d, 8.4)	116.7	6.81 (d, 8.8)	114.5	6.82 (d, 8.4)	115.3
4"'				161.3		159.7		159.8
5"'			7.14 (d, 8.4)	116.7	6.81 (d, 8.8)	114.5	6.82 (d, 8.4)	115.3
6"'			7.48 (d, 8.4)	130.6	7.30 (d, 8.8)	130.7	7.48 (d, 8.4)	129.6
7"'			7.82 (d, 16.0)	145.1	7.40 (d, 16.0)	145.1	7.61 (d, 16.0)	144.0
8"'			6.48 (d, 16.0)	114.8	6.08 (d, 16.0)	113.2	6.33 (d, 16.0)	113.4
9"'				167.2		167.3		168.3

[a]in CD_3OD; [b]in pyridine-d_5.

1-PKB1-13), which ultimately afforded compound **3** (14.5 mg).

Astragalin (1) – Yellow powder. $[\alpha]_D$: +16.1 (*c* 1.1, MeOH); IR (KBr) ν_{max} cm^{-1}: 3340, 2925, 2358, 1660, 1608, 1512; ^1H, ^{13}C NMR : see Table 1.; EIMS *m/z* 448 $[M]^+$.

Tiliroside (2) – Yellow powder. $[\alpha]_D$: −62.5 (*c* 0.22, MeOH); IR (KBr) ν_{max} cm^{-1}: 3230, 1684, 1610, 1559, 1508; ^1H, ^{13}C NMR : see Table 1.; EIMS *m/z* 594 $[M]^+$.

Buddlenoide A (3) – Yellow powder. IR (CaF_2) ν_{max} cm^{-1}: 3306, 1684, 1662, 1512; ^1H, ^{13}C NMR : see Table 1.; EIMS *m/z* 594 $[M]^+$.

Apigenin-7-*O*-(3''-*E*-*p*-coumaroyl)-glucopyranoside (4) – Amorphous yellow powder. $[\alpha]_D$: –43.5 (*c* 0.5, MeOH); IR (KBr) ν_{max} cm^{-1}: 3330, 1658, 1520; ^1H, ^{13}C NMR : see Table 1.; EIMS *m/z* 578 $[M]^+$.

Result and Discussion

Four flavonoid glycosides were isolated from the EtOAc and *n*-BuOH fractions of *P. koreana* flowers through repeated SiO_2 and ODS open column chromatography. The chemical structures of the isolated flavonoid glycosides were determined based on interpretation of spectroscopic data including NMR, IR, and MS.

Compound **1** was isolated as a yellow powder and exhibited UV absorption characteristics as well a yellow color on TLC plates by spraying with 10% H_2SO_4 followed by heating. The molecular formula was determined as $C_{21}H_{20}O_{11}$ from a molecular ion peak $[M]^+$ *m/z* 448 in the EIMS. The optical rotation showed dextrorotatory characteristics of $[\alpha]_D$+16.1 (*c* 1.1 MeOH). The IR spectrum (KBr, ν) showed absorption bands for the hydroxyl (3340 cm^{-1}), C=O (1660 cm^{-1}), and olefin (1512 cm^{-1}) groups. The ^1H-NMR spectrum (Table 1) of compound **1** indicated the presence of four olefin methine proton signals at δ_H 8.05 (2H, d, J = 9.2 Hz, H-2', 6') and 6.89 (2H, d, J = 9.2 Hz, H-3', 5') due to a parasubstituted benzene ring and two additional olefin methine proton signals at δ_H 6.37 (1H, d, J = 2.0 Hz, H-8) and 6.19 (1H, d, J = 2.0 Hz, H-6) due to a 1,2,3,5-tetrasubstituted benzene ring and a flavonol moiety. In addition, a hemiacetal proton signal at δ_H 5.21 (1H, d, J = 7.6 Hz, H-1"), four oxygenated methine proton signals at δ_H 3.43 (1H, dd, J = 8.4, 7.6 Hz, H-2"), 3.43 (2H, overlapped, H-3", 4"), and 3.21 (1H, m, H-5"), and one oxygenated methylene proton signal at δ_H 3.69 (1H, dd, J = 12.0, 2.4 Hz, H-6"a) and 3.53 (1H, dd, J = 12.0, 5.6 Hz, H-6"b) indicated the presence of an aldohexose moiety. Collectively, the ^1H-NMR data suggested that compound **1** was a flavonol monoglycoside. Consistently, the ^{13}C-NMR spectrum revealed 21 carbon signals associated with a flavonoid and hexose moieties. In the downfield region, a conjugated ketone carbon signal at δ_C 179.2 (C-4), six oxygenated olefin quaternary carbon signals at δ_C 165.7 (C-7), 162.7 (C-5), 161.2 (C-4'), 158.8 (C-9), 158.0 (C-2), and 135.3 (C-3), two olefin quaternary carbon signals at δ_C 122.5 (C-1') and 105.6 (C-10), and six olefin methine carbon signals at δ_C 132.1 (C-2', 6'), 115.9 (C-3', 5'), 99.8 (C-6), and 94.8 (C-8) were observed, which indicated the presence of kaempferol as an aglycone moiety. The hemiacetal carbon signal at δ_C 104.0 (C-1"), four oxygenated methine carbon signals at δ_C 78.2 (C-3"), 78.0 (C-5"), 75.6 (C-2"), and 71.2 (C-4"), and one oxygenated methylene carbon signal at δ_C 62.4 (C-6") indicated that the sugar was a *β*-glucopyranose. The location of the glucose in compound **1** was determined using a gradient heteronuclear multiple bonding connectivity (gHMBC) experiment. In the gHMBC spectrum, the cross peak between the anomer proton signal of the glucopyranosyl moiety (δ_H 5.21, H-1") and the oxygenated olefin quaternary carbon signal (δ_C 135.3, C-3) of the kaempferol indicated that the glucopyranose was linked to the hydroxyl of C-3 in ring C. Finally, compound **1** was identified as astragalin, a kaempferol-3-*O*-glucopyranoside.

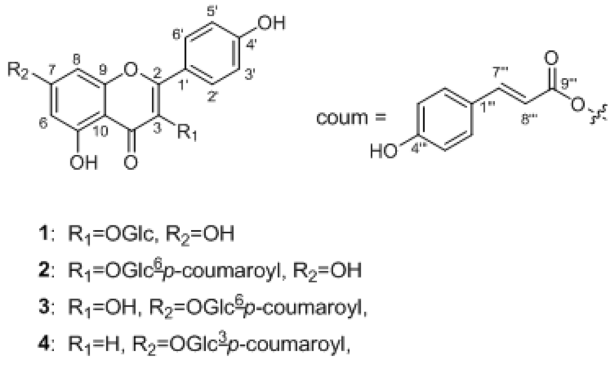

Fig. 1. Chemical structures of compounds **1** – **4** from the flowers of *Pulsatilla koreana*. OGlc: *O*-*β*-D-glucopyranosyl; Glc: *β*-D-glucopyranosyl; coum: *p*-coumaroyl.

Compound **2** was isolated as an amorphous yellow powder and exhibited UV absorption characteristics as well a yellow color on TLC plates after spraying with 10% H_2SO_4 followed by heating. The molecular formula of compound **2** was determined as $C_{30}H_{26}O_{13}$ based on the molecular ion peak $[M]^+$ *m/z* 594 in the EIMS. The optical rotation showed levorotatory characteristics of $[\alpha]_D$ −62.5 (*c* 0.22, MeOH). The IR spectrum (KBr, ν) showed absorption bands for the hydroxyl (3230 cm^{-1}), C=O (1684 cm^{-1}), and olefin (1559, 1508 cm^{-1}) groups. Compound **2** exhibited similar ^1H- and ^{13}C-NMR spectra as

those of astragalin (**1**) with the exception of the additional signals indicative of a phenylpropanoid moiety. The ^{1}H-NMR spectrum revealed four olefin methine proton signals at δ_H 7.48 (2H, d, J = 8.4 Hz, H-2‴, 6‴) and 7.14 (2H, d, J = 8.4 Hz, H-3‴, 5‴) due to a parasubstituted benzene ring and two additional olefin methine proton signals at δ_H 7.82 (1H, d, J = 16.0 Hz, H-7‴) and 6.48 (1H, d, J = 16.0 Hz, H-8‴) due to a double bond in the *trans* configuration. The ^{13}C-NMR data confirmed the presence of one carboxyl carbon signal at δ_C 167.2 (C-9‴), one oxygenated olefin quaternary carbon signal at δ_C 161.3 (C-4‴), one olefin quaternary carbon signal at δ_C 126.0 (C-1‴), and six olefin methine carbon signals at δ_C 145.1 (C-7‴), 130.6 (C-2‴, 6‴), 116.7 (C-3‴, 5‴), and 114.8 (C-8‴), which together indicated that the phenylpropanoid was a *p*-coumaroyl group. The esterification shift of the oxygenated methylene proton signals (δ_H 4.97, H-6"a; δ_H 4.83, H-6"b) indicated that the *p*-coumaroyl group was linked to the OH-6" of the glucopyranose moiety, which was confirmed by the gHMBC spectrum, in which the oxygenated methylene proton signal (δ_H 4.97, H-6"a; δ_H 4.83, H-6"b) appeared to be correlated with the carboxyl carbon signal (δ_C 167.2, C-9‴). Compound **2** was finally identified as tiliroside, a kaempferol-3-*O*-β-D-(6"-*O*-coumaroyl)-glucopyranoside.

Compound **3** was isolated as an amorphous yellow powder and exhibited UV absorption characteristics as well a yellow color on TLC plates after spraying with 10% H_2SO_4 followed by heating. The molecular formula of compound **3** was determined to be $C_{30}H_{26}O_{13}$ based on the molecular ion peak $[M]^+$ *m*/*z* 594 in the EIMS. The IR spectrum (CaF_2, ν) indicated the presence of absorption bands for the hydroxyl (3306 cm^{-1}), C=O (1684 cm^{-1}), and olefin (1512 cm^{-1}) groups. The NMR signals of compound **3** were very similar to those of compound **2** with the exception of the position for the *O*-glc-*p*-coumaroyl moiety, whose specific linkage was determined on the basis of the glycosidation effect in the ^{13}C-NMR spectrum as well in the gHMBC experiment. Specifically, *O*-glc-*p*-coumaroyl moiety of compound **3** was determined to be attached to the OH-7 position of the kaempferol aglycone. The oxygenated olefin quaternary carbon signal of C-7 (δ_C 164.9) shifted by 3.0 ppm upfield compared to those of kaempferol derivatives,[11] which was verified from the cross peak between the olefin methine proton signals at δ_H 6.29 (1H, d, J = 2.0 Hz, H-8), 6.12 (1H, d, J = 2.0 Hz, H-6) and the anomer carbon signal at δ_C 102.5 (C-1") in the gHMBC experiment. Finally, compound **3** was identified as buddlenoide A, a kaempferol-7-*O*-β-D-(6"-*O*-coumaroyl)-glucopyranoside.

Compound **4** was isolated as an amorphous yellow powder and exhibited UV absorption characteristics as well as a yellow color on TLC plates after spraying with 10% H_2SO_4 followed by heating. The IR spectrum (KBr, ν) showed absorption bands for the hydroxyl (3330 cm^{-1}), C=O (1658 cm^{-1}), and olefin (1520 cm^{-1}) groups. The molecular formula was determined as $C_{30}H_{26}O_{12}$ based on the molecular ion peak $[M]^+$ *m*/*z* 578 in the EIMS, which was 16 amu lower than those of **2** and **3**, suggesting that **4** had one less hydroxyl group than each of compounds **2** and **3**. The ^{1}H- and ^{13}C-NMR spectra of **4** were very similar to those of **3** with the exception of the structure of the aglycone and the linkage of the *p*-coumaroyl moiety. The NMR spectrum showed an additional olefin methine signal (δ_H 6.47, 1H, H-3; δ_C 105.0, C-3) instead of an oxygenated olefin quaternary signal in compounds **2** and **3**, indicating that the aglycone of compound **4** was apigenin. In addition, the esterification shift of the oxygenated methine proton signal (δ_H 3.68, H-3") indicated that the *p*-coumaroyl was linked at the C-3" of glucopyranose. This was confirmed by the gHMBC spectrum, in which the oxygenated methine proton signal (δ_H 3.68, H-3") appeared to be correlated with the carboxyl carbon signal at δ_C 168.3 (C-9‴). Compound **4** was finally identified as apigenin-7-*O*-(3"-*E*-*p*-coumaroyl)-glucopyranoside.

This study is the first report of the isolation of compounds **1** – **4** from the flowers of *P. koreana*. However, compounds **1** – **4** were previously isolated from tea leaves, the leaves of *Tilia argentea*, the aerial parts of *Buddleia coriacea*, and the aerial parts of *Chrozophora Rottleri*, respectively.[12-15]

Compound **1** has been reported to have anti-inflammatory, anti-influenza virus, and anti-diabetic activities.[16-18] Likewise, compound **2** has been reported to inhibit CYP enzymes, has anti-allergy effects, and can be used to treat type II diabetes.[19-21] Lastly, compound **3** inhibits tyrosinase activity,[22] while compound **4** exhibits cytotoxic/cytostatic effects against human cancer cell.[23]

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