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New anti-glycative flavonoids from Cirsium setidens with potent radical scavenging activities

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ABSTRACT

Two new methoxylated flavonoids, setidenosides A (**1**) and B (**2**), together with three known constituents, linarin (**3**), 5-O-E-p-coumarolyquinic acid methyl ester (**4**), and syringin (**5**), were isolated from a methanol extract of the aerial parts of Cirsium setidens Nakai (Asteraceae) through bioassay-guided fractionation using advanced glycation end products (AGEs) formation assay. The structures of the new compounds were elucidated by spectroscopic and chemical methods Among these isolated compounds, new compounds **1** and **2** showed significant inhibitory effects on AGEs formation with IC_{50} values of 6.5 ± 0.2 and 9.7 ± 0.3 μM, respectively. In addition, these two new compounds showed significant radical scavenging capacities in an $ONOO^-$ scavenging assay.

1. Introduction

Diabetes mellitus is a polygenic metabolic disease characterized by elevated blood sugar levels. This syndrome is prevalent worldwide and is accompanied by vascular complications, including coronary heart disease, nephropathy and neurodegeneration (Fava, 2008; Anselmino, 2009), resulting in increased rates of mortality. Diabetes-associated metabolic syndrome manifests itself as hyperglycemia, high levels of triacylglycerol (TG), and low levels of high-density lipoprotein (HDL) dyslipidemia. In particular, hyperglycemia arising from diabetes may play a crucial role in the pathogenesis of diabetic complications via several mechanisms such as increased of advanced glycation end products (AGEs) formation, overexpression of AGE receptor, activation of protein kinase C isoform, excessive oxidative stress, and increased aldose reductase (AR)-related polyol pathway flux (Peyrou and Sternberg, 2006). Several recent reports have shown that synthetic and natural antioxidants may be implicated in diabetic complications in humans (Jung et al., 2005; Jung et al., 2008). Therefore, prevention of the AGE formation and oxidative stress is considered as a promising therapeutic approach for diabetic complications.

Perennial and biennial flowering plants belonging to the genus Cirsium (Asteraceae) are mostly native to Eurasia and northern Africa and comprise about 60 species, mainly grown in Asia, Europe, and North Africa. One of these, Cirsium setidens Nakai is found only in Korea, and its young leaves are used as a mountainous vegetable (Nugroho et al., 2011). Aerial parts of this wild plant are edible and rich in vitamins, protein, and phenolic constituents, making them useful as ingredients in folk remedies for the treatment of hemostasis, hematuria, and hypertension (Lee, 1996). Previous phytochemical investigations on C. setidens have described the occurrence of terpenoids, steroids, and fatty acids from its aerial parts, as well as quinic acids, phenylpropanoids, and flavonoids from its leaves (Lee et al., 2002; Nugroho et al., 2011). Especially, the major flavonoid glycosides pectolinarin and linarin isolated from C. setidens leaves displayed potent biological properties such as sedative and hepatoprotective effects (Nugroho et al., 2011; Yoo et al., 2008).

In an effort to discover of naturally occurring anti-diabetic complications agents from medicinal plants, the n-BuOH-soluble portion from aerial parts of C. setidens extract exhibited significant activity toward AGEs formation inhibition with an IC_{50} value of 38.04 ± 2.3 μg/mL. Herein, we present the isolation and structural elucidation of new compounds **1** and **2**, along with three known constituents, linarin (**3**), 5-O-E-p-coumarolyquinic acid methyl ester (**4**), and syringin (**5**) (Fig. 1), as well as their inhibitory effects against oxidative stress-related diabetic complications using in vitro AGEs formation and $ONOO^-$ scavenging assays.

2. Results and discussion

Compound **1** was isolated as an amorphous yellow optically active

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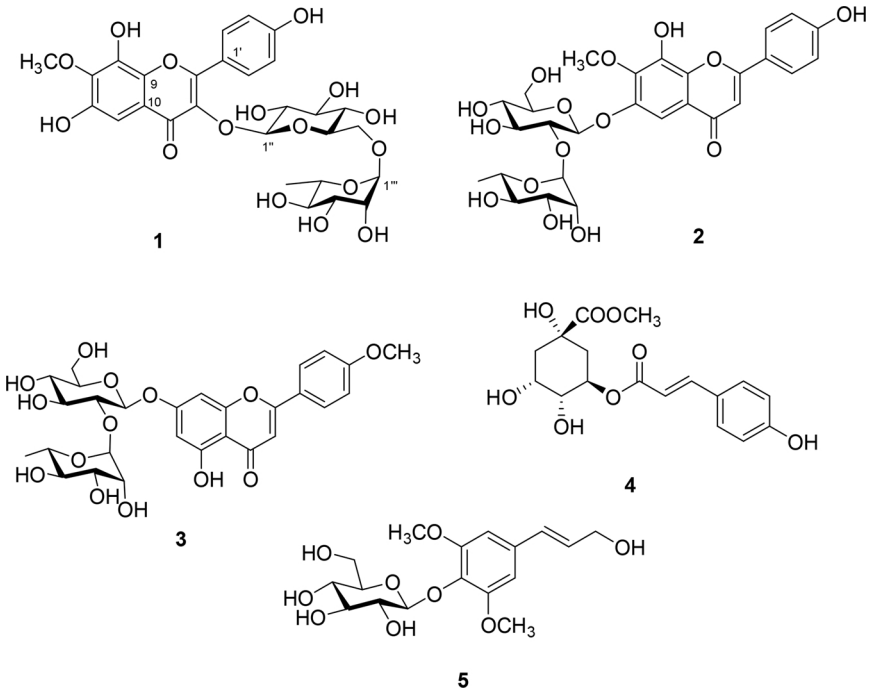

Fig. 1. Structures of compounds **1** – **5** isolated from Cirsium setidens.

Table 1
^{1}H and ^{13}C NMR data of compounds **1** and **2**.[a]

Position	1		2	
	δ_H (J in Hz)[b]	δ_C, mult.	δ_H (J in Hz)[b]	δ_C, mult.
2	–	159.5	–	166.9
3	–	135.2	6.65 (s)	103.7
4	–	179.7	–	184.4
5	6.50 (s)	95.2	6.91 (s)	95.8
6	–	153.7	–	157.5
7	–	132.7	–	134.5
8	–	153.9	–	154.2
9	–	158.9	–	154.1
10	–	106.1	–	107.5
1′	–	122.8	–	123.1
2′	8.06 (d, 8.4)	132.4	7.88 (d, 8.4)	129.7
3′	6.87 (d, 8.4)	116.1	6.93 (d, 8.4)	117.0
4′		161.5	–	162.9
5′	6.87 (d, 8.4)	116.1	6.93 (d, 8.4)	117.0
6′	8.06 (d, 8.4)	132.4	7.88 (d, 8.4)	129.7
1”	5.14 (d, 7.2)	104.5	5.32 (d, 7.2)	100.1
2”	3.42 (m)	75.8	3.43 (m)	79.2
3”	3.41 (m)	78.2	3.40 (dd, 8.4, 2.4)	78.4
4”	3.25 (m)	71.5	3.29 (m)	78.5
5”	3.34 (m)	77.2	3.35 (m)	74.1
6”a	3.79 (m)	68.6	3.80 (dd, 12.0, 2.4)	62.5
6”b	3.50 (m)		3.58 (m)	
1”’	4.51 (d, 1.8)	102.4	5.40 (d, 1.8)	103.7
2”’	3.61 (m)	72.1	3.89 (m)	70.3
3”’	3.53 (m)	72.3	3.56 (m)	71.4
4”’	3.27 (m)	73.9	3.39 (t, 9.6)	72.2
5”’	3.44 (m)	69.7	3.92 (dd, 9.6, 6.0)	72.3
6”’	1.12 (d, 6.0)	17.9	1.24 (d, 5.4)	18.3
OCH_3-7	3.89 (s)	61.0	3.88 (s)	61.4

[a] ^{1}H NMR spectra were measured at 600 MHz, ^{13}C NMR spectra were measured at 150 MHz. Data obtained in CD_3OD. Assignments based on HMQC and HMBC NMR spectra.

[b] J values (Hz) are given in parentheses.

powder, $[\alpha]_D^{20}$ −10.0° (c 0.1, MeOH), with the molecular formula of $C_{28}H_{32}O_{16}$ established by negative-ion mode. HRFABMS showed a pseudomolecular ion peak at *m/z* 623.1606 $[M-H]^-$. The UV spectrum at λ_{max} 270 and 330 nm showed the absorption characteristics of a flavonol nucleus (Mabry et al., 1970). The ^{1}H NMR spectrum of **1** in CD_3OD (Table 1) showed signals of 1,4-disubstituted aromatic protons in the C ring at δ_H 8.06 (2H, d, J = 8.4 Hz, H-2′, 6′) and 6.87 (2H, d, J = 8.4 Hz, H-3′, 5′), an isolated aromatic proton in the A ring at δ_H 6.50 (1H, s, H-5), and a methoxy singlet at δ_H 3.89 (3H, s, OCH_3-7). Besides the diagnostic aglycone protons, the ^{1}H NMR spectrum also displayed signals for two characteristic anomeric protons at δ_H 5.14 (1H, d, J = 7.2 Hz, H− H-1”) and 4.51 (1H, d, *J* = 1.8 Hz, H-1”’), correlating with carbon signals at δ_C 104.5 and 102.4, respectively, confirmed by the HSQC spectrum. The presence of glucose and rhamnose residues further indicated the presence of characteristic signals in the aliphatic region of 10 oxygen-bearing signals at δ_H 3.79–3.25 and secondary methyl signal at δ_H 1.12 (3H, d, J = 6.0 Hz, H-6”’). These NMR data were assigned from a combination of the observed ^{1}H–^{1}H COSY correlations (Fig. 2). The relative stereochemistries of the monosaccharides moieties were established as β-glucopyranoside and α-rhamnopyranoside based on the magnitudes of the coupling constants (Markham and Geiger, 1994) of the above mentioned observed protons. Comparison of the ^{1}H and ^{13}C NMR spectral data of **1** with analogous data for the known flavonol glycoside, 5,6,7,4′-tetrahydroxyflavonol 3-O-rutinoside (Gamez et al., 1998), indicated that **1** has the only unique substituent pattern in the A ring. Connections among sugar moieties at C-3 and a methoxyl group at C-7 were confirmed by key HMBC correlations of H-1” with C-3, H-1”’ with C-6”, and OCH_3 with C-7, as shown in Fig. 2. The absolute configurations of the sugar composition were unambiguously determined as D-glucose and L-rhamnose by HPLC analysis of their arylthiocyanate derivatives using a UV detector based on a previously described convenient process (Tanaka et al., 2007). Thus, the structure of compound **1** was assigned the trivial name setidenoside A.

Compound **2** was purified as a yellow amorphous powder with the molecular formula $C_{28}H_{32}O_{15}$, as shown by a pseudomolecular ion peak at *m/z* 607.1660 $[M-H]^-$ (cald 607.1663) observed in negative-ion mode HRFABMS. The ^{1}H, ^{13}C NMR and UV spectra of compound **2** were quite similar to those of **1**, except for the extra signal that appeared for an aromatic singlet at δ_H 6.65 (1H, s, H-3). These spectral data indicate that compound **2** is a dehydroxylated derivative of **1**. The locations of a