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Short communication

Neolignan and monoterpene glycoside from the seeds of *Pharbitis nil*

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ABSTRACT

Phytochemical investigation of an EtOH extract of *Pharbitis nil* seeds (Convolvulaceae) resulted in the isolation and identification of a new neolignan, 7*R*,8S-*threo*-dihydroxydehydrodiconiferyl alcohol (**1**), and a new monoterpene glycoside, (3*Z*,7*S*)-7-hydroxy-3,7-dimethyl-3,8-octadienyl-β-D-glucopyranoside (**2**), together with a known compound, ethyl α-L-arabinofuranoside (**3**). The chemical structures of these compounds were unambiguously determined using physical data, HR-ESI–MS and spectroscopic evidence, including 1D and 2D NMR experiments. The anti-inflammatory activities of the isolates were evaluated by estimating the inhibition of nitric oxide (NO) production. Compounds **1** and **2** reduced NO levels in lipopolysaccharide (LPS)-stimulated murine microglial BV-2 cells. In addition, compound **2** showed weak cytotoxicity against the HCT-15 cell line with an IC_{50} value of 28.6 μM.

1. Introduction

Morning glory (*Pharbitis nil*), an annual climbing plant belonging to the family of Convolvulaceae, is widely distributed throughout Southeast Asia and it is well-known as an ornamental plant. The seeds of *P. nil* (Pharbitis Semen) have traditionally been used as a purgative agent in Korea, China, and Japan. Pharbitis Semen has a variety of medicinal usages in Korean and Chinese traditional medicine for the prevention of liver, renal, and parasitic diseases (Oh and Cha, 2001; Saito et al., 1994). Previous phytochemical investigations of Pharbitis Semen have reported the isolation of bioactive chemical constituents, such as resin glycosides, triterpenoids, diterpenoids, flavonoids and phenolic compounds (Das et al., 1999; Jung et al., 2008; Kim et al., 2008; Ono et al., 1990, 2010). The seeds of *P. nil* exhibited a number of pharmacological effects, including antioxidant, antitumor, and anti-hyperlipidemia effects (Ko et al., 2004; Oh and Cha, 2001; Wang et al., 2014b).

As part of our ongoing endeavor to find new bioactive compounds from Korean medicinal plants (Eom et al., 2016, 2015; Lee et al., 2016, 2015a; Kang et al., 2015, 2016; Park et al., 2016; Yu et al., 2016a,b; Choi et al., 2015; Kim et al., 2015a), our group has investigated the active constituents of the seeds of *P. nil* and reported various new and bioactive compounds with anti-inflammatory and cytotoxic effects (Kim et al., 2008, 2009, 2010, 2011, 2013, 2014; Park et al., 2016). The present study describes the isolation and structural identification of a new neolignan (**1**) and a new monoterpene glycoside (**2**), together with one known compound (**3**) from the EtOAc-soluble fraction of the seeds of *P. nil*. Additionally, an evaluation of their biological activities with respect to cytotoxic and anti-inflammatory activities was performed.

2. Results and discussion

The EtOH extract of the seeds of *P. nil* was successively partitioned with hexane, $CHCl_3$, EtOAc, and *n*-BuOH. The EtOAc-soluble fraction was separated using a combination of separation methods, including silica column chromatography, RP-C18 column chromatography, Sephadex LH-20, and preparative HPLC, resulting in the isolation of a new neolignan (**1**) and a new monoterpene glycoside (**2**) along with one known compound (**3**) (Fig. 1).

Compound **1** was isolated as an optically active colorless gum with a positive optical rotation value ([α] + 18.5, MeOH) and its molecular formula was deduced to be $C_{20}H_{24}O_8$ (unsaturation degree of 9) from the positive mode HR-ESIMS data at *m/z* 415.1361 $[M+Na]^+$ (calcd for $C_{20}H_{24}O_8Na$, 415.1369). The characteristic absorption bands of hydroxy (3357 cm^{-1}) and aromatic ring (2946 and 1451 cm^{-1}) functionalities were observed in the IR spectrum of **1**. The ^1H NMR data (Table 1) of **1** showed the presence of two substituted aromatic rings, including one tetrasubstituted aromatic ring at δ_H 6.95 (1H, br s, H-2′) and 6.93 (1H, br s, H-6′) and one trisubstituted aromatic ring with ABX spin system resonance at δ_H 6.91 (1H, d, J = 2.0 Hz, H-2), 6.82 (1H, dd, J = 8.0, 2.0 Hz, H-6), and 6.76 (1H, d, J = 8.0 Hz, H-5). A distinguished oxygenated methine resonance at δ_H 5.53 (1H, d, J = 6.5 Hz, H-7) and a methine resonance at δ_H 3.49 (1H, ddd, J = 7.0, 6.5, 5.5 Hz, H-8) typical of a dihydrobenzofuran-type lignan

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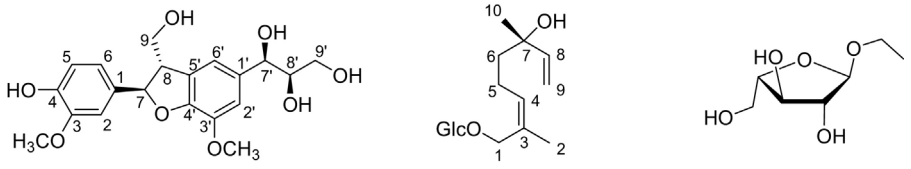

Fig. 1. Chemical structures of the isolated compounds **1–3**.

Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data for **1** and **2** in CD_3OD.[a] (δ in ppm).

Position	1		Position	2	
	δ_C	δ_H		δ_C	δ_H
1	134.8 s		1	67.9 t	4.38 d (11.0) 4.23 d (11.0)
2	110.7 d	6.91 d (2.0)	2	22.0 q	1.80 d (1.0)
3	149.0 s		3	132.7 s	
4	147.7 s		4	131.6 d	5.42 m
5	116.3 d	6.76 d (8.0)	5	23.6 t	2.15 m
6	119.8 d	6.82 dd (8.0, 2.0)	6	43.7 t	1.57 m
7	89.3 d	5.53 d (6.5)	7	73.9 s	
8	55.5 d	3.49 ddd (7.0, 6.5, 5.5)	8	146.3 d	5.96 dd (17.0, 11.0)
9	65.0 t	3.85 dd (11.5, 5.5) 3.76 dd (11.5, 7.0)	9	112.2 t	5.23 dd (17.0, 2.0) 5.05 dd (17.0, 2.0)
1′	137.0 s		10	27.9 q	1.30 s
2′	112.8 d	6.95 br s	Glc		
3′	145.4 s		1′	102.5 d	4.20 d (7.5)
4′	149.0 s		2′	75.1 d	3.23 m
5′	129.9 s		3′	78.3 d	3.38 m
6′	116.7 d	6.93 br s	4′	71.8 d	3.33 m
7′	75.5 d	4.59 d (6.0)	5′	78.0 d	3.26 m
8′	77.6 d	3.70 ddd (6.5, 6.0, 4.0)	6′	62.9 t	3.92 dd (12.0, 2.0) 3.72 dd (12.0, 5.0)
9′	64.4 t	3.54 dd (11.5, 6.5) 3.40 dd (11.5, 4.0)			
OMe-3	56.5 q	3.82 s			
OMe-3′	56.8 q	3.88 s			

[a] Well-resolved couplings are expressed with coupling patterns, and coupling constants (in parentheses) are in Hz.

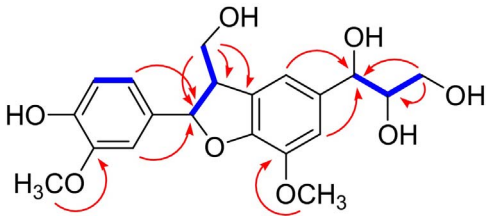

Fig. 2. Key ^{1}H-^{1}H COSY (blue bold) and HMBCs (→) of **1**. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

were also seen. In addition, two methoxy group resonances at δ_H 3.88 (3H, s, OMe-3′) and 3.82 (3H, s, OMe-3); two oxygenated methylene resonances at δ_H 3.85 (1H, dd, J = 11.5, 5.5 Hz, H-9a), 3.76 (1H, dd, J = 11.5, 7.0 Hz, H-9b) and δ_H 3.54 (1H, dd, J = 11.5, 6.5 Hz, H-9′a), 3.40 (1H, dd, J = 11.5, 4.0 Hz, H-9′b) and two oxygenated methine resonances at δ_H 4.59 (1H, d, J = 6.0 Hz, H-7′) and 3.70 (1H, ddd, J = 6.5, 6.0, 4.0 Hz, H-8′) were revealed. The ^{13}C NMR combined with HSQC data indicated the presence of 20 carbon resonances, including seven aromatic quaternary carbons, nine methines, two methylenes, and two methoxy signals. Analysis of the 2D NMR (^{1}H-^{1}H COSY, HSQC, and HMBC) data for **1** revealed that the planar structure of **1** was identical to that of meliasendanin D isolated from the fruits of *Melia toosendan* (Wang et al., 2014a) (Fig. 2). However, a detailed inspection of the NMR data suggested that compound **1** had a different stereochemistry compared with that of meliasendanin D. The relative configurations of C-7′ and C-8′ of **1** were determined to be *threo* by the difference in chemical shifts between C-7′ and C-8′ in ^{13}C NMR data ($\Delta\delta_{C8'\text{-}C7'} > 2.0$ ppm is *threo*; $\Delta\delta_{C8'\text{-}C7'} < 1.0$ ppm is *erythro*) because the chemical shift value of $\Delta\delta_{C8'\text{-}C7'}$ was calculated to be 2.1 ppm [δ_C 77.6 (C-8′); δ_C 75.5 (C-7′)] (Gan et al., 2008; Ishikawa et al., 2002; Lin et al., 2007). In addition, the vicinal coupling constant between C-7 and C-8 (J = 6.5 Hz) of **1** indicated a *trans*-configuration based on values reported in the literature (Seidel et al., 2000; Wang et al., 2014a). The absolute configurations of C-7 and C-8 for **1** were unambiguously established to be 7*R* and 8*S*, respectively, from the positive CD cotton effects in the 200–220 nm range and the negative CD cotton effects at 260 and 226 nm (Jiang et al., 2005; Machida et al., 2009; Wang et al., 2014a). Accordingly, the structure of compound **1** was determined to be 7*R*,8*S*-*threo*-dihydroxydehydrodiconiferyl alcohol. Diastereoisomers of compound **1** with 7*S*,8*R* were reported from the fruits of *Melia toosendan* (Wang et al., 2014a), however, to the best of our knowledge, compound **1** is the first natural product with the 7*R*,8*S* and *threo*-configuration of C-7′/C-8′.

Compound **2** was obtained as a colorless oil with a positive optical rotation value ([α] + 23.2, MeOH) and its molecular formula was established as $C_{16}H_{28}O_7$ (unsaturation degree of 3) from the positive mode HR-ESIMS data at m/z 355.1734 $[M+Na]^+$ (calcd for $C_{16}H_{28}O_7Na$, 355.1733) combined with an analysis of the NMR data. In fact, a comparison of the NMR data of **2** with those of betulalbuside A isolated from *Breynia officinalis* suggested that their structures were almost identical, although there were distinctive differences in the proton and carbon chemical shifts of C-1 [δ_C 67.9; δ_H 4.38 (d, J = 11.0 Hz, H-1a), 4.23 (d, J = 11.0 Hz, H-1b)] instead of an oxygenated methylene (δ_C 76.0; δ_H 4.19 and 4.03) attached to C-3 of betulalbuside A (Morikawa et al., 2004). These differences in chemical shift were caused by the conformation of the glycosylated primary alcohol linked to C-3 (Çaliş et al., 1993). Based on these results, the geometric conformation of **2** was established to be *Z*-form, indicating that compound **2** was a geometric isomer compared with betulalbuside A, which has *E*-form (Çaliş et al., 1993; Morikawa et al., 2004). To determine the absolute configuration of C-7, an optical rotation value of **2** was measured ([α] + 23.2), which suggested that the absolute configuration of C-7 was to be *S* (Matsubara et al., 1990). Thus, the structure of **2** was established to be (3*Z*,7*S*)-7-hydroxy-3,7-dimethyl-3,8-octadienyl-β-D-glucopyranoside, and to the best of our knowledge, compound **2** is the first compound isolated as the 3*Z*,7*S*-form in nature.

Compound **3** was structurally determined to be ethyl α-L-arabinofuranoside by comparing its spectroscopic values with previously reported values (Belkacem et al., 2014). To the best of our knowledge, this was the first identification of compound **3** from the seeds of *P. nil*.

In our previous studies, we reported that various compounds isolated from *P. nil* seeds exerted anti-inflammatory activities in over-activated microglia (Kim et al., 2010, 2011, 2013, 2014). Thus, we also investigated the effects of the isolated compounds **1–3** on the produc-

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