Natural Product Research

Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

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To cite this article: Hua-Wei Lv, Yu-Xia Li, Meng Luo, Jia-Meng Qi, Ze-Fei Fu, Hong-Jian Zhang, Yuan-Qiang Guo, Chu Chu, Han-Bing Li & Ji-Zhong Yan (2020): Two new *nor*-lignans from *Selaginella pulvinata* (Hook. & Grev.) Maxim and their antihyperglycemic activities, Natural Product Research, DOI: 10.1080/14786419.2020.1779267

To link to this article: https://doi.org/10.1080/14786419.2020.1779267

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https://doi.org/10.1080/14786419.2020.1779267

Two new *nor*-lignans from *Selaginella pulvinata* (Hook. & Grev.) Maxim and their antihyperglycemic activities

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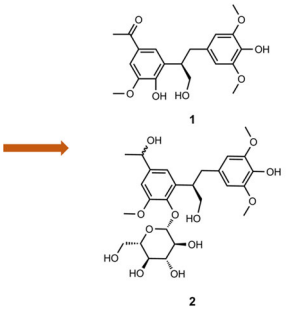
ABSTRACT

Two new *nor*-lignans, pulvin A (**1**) and moellenoside C (**2**), along with two known compounds (**3**–**4**) were isolated from the whole plant of *Selaginella pulvinate* (Hook. & Grev.) Maxim. The structures of the new compounds were established on the basis of spectroscopic data and acid hydrolysis. All the isolates were investigated for their antihyperglycemic activities in 3T3-L1 adipocytes. The results showed that compounds **1** and **2** promoted the glucose consumption prominently in 3T3-L1 adipocytes in a dose-response manner. Compound **1** and **2** induced 1.14–1.73 folds and 1.03–1.55 folds changes relative to the basal level, respectively, in the concentration range of 12.5 μM to 50 μM.

Selaginella pulvinata



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ARTICLE HISTORY
Received 9 March 2020
Accepted 23 May 2020

KEYWORDS
Pulvin A; moellenoside C; *Selaginella* pulvinate (Hook. & Grev.) Maxim; Selaginellaceae; antihyperglycemic activity; 3T3-L1 adipocyte

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Supplemental data for this article can be accessed at https://doi.org/10.1080/14786419.2020.1779267.

1. Introduction

The genus *Selaginella P. Beauv.*, belonging to the Selaginellaceae family, consists of approximately 700 species worldwide and 66 species in China (Little et al. 2007). *Selaginella pulvinata* (Hook. & Grev.) Maxim is a traditional Chinese medicine for promoting blood circulation, and is commonly used to treat amenorrhoea, dysmenorrhoea, traumatic injury (Cao et al. 2010; Liu et al. 2014). The whole plants of *S. pulvinata* and *Selaginella tamariscina* (P. Beauv.) Spring have been recorded officially as the original material of 'juanbai' in the Chinese Pharmacopoeia (National Pharmacopoeia Committee 2015). *S. pulvinata* is lithophytic pteridophyte that can survive severe drought conditions, maintaining the plant's structural stability, and resurrect during rains. Rhizophores of the whole plants are restricted to base of stem and much forked at end, forming thick massive rootstock. Stems present typical rosette and the main stems are pinnately branched near and above base. Primary leafy branches are 4–7 pairs, 2 or 3 times pinnately branched. Axillary leaves on main stems are larger than those on branches, and axillary leaves on branches are symmetrical. Phytochemical studies of *S. pulvinata* have led to discovering the occurrence of several polyphenol (Cao et al. 2010; Liu et al. 2014; Cao et al. 2015; Liu et al. 2018) and flavonoids (Tan et al. 2004). As part of an ongoing search for new antihyperglycemic agents from genus *Selaginella*, the phytochemical investigation was performed. As a result, two new compounds, pulvin A (**1**) and moellenoside C (**2**), along with two known compounds syringaresinol (**3**) and (2*R*,3*S*)-dihydro-2-(3,5-dimethoxy-4-hydroxy-phenyl)-7-methoxy-5-acetylbenzofuran (**4**), were isolated from the whole plants of *S. pulvinata*. Herein, we describe the structural elucidation of the new compounds as well as their *in vitro* antihyperglycemic activities in 3T3-L1 adipocytes.

2. Results and discussion

Compound **1** was obtained as a white, amorphous powder. The negative HRESIMS data at *m/z* 375.1466 $[M\text{-}H]^-$ (calcd. 375.1499) established its molecular formula as $C_{20}H_{24}O_7$. The UV spectrum of **1** showed absorption peaks at 208 and 278 nm. In The ^1H NMR spectrum, four characteristic aromatic protons signals at δ_H 6.34 (2H, s), δ_H 7.39 (1H, d, $J = 1.8$ Hz) and δ_H 7.41 (1H, d, $J = 1.8$ Hz) indicated the presence of one symmetrical 1,2,3,5-tetrasubstituded benzene ring and one asymmetrical 1,2,3,5-tetrasubstituded benzene ring, respectively. Signals at δ_H 3.70 (6H, s) and δ_H 3.89 (3H, s) were attributed to three methoxy groups. The ^{13}C NMR spectrum revealed the presence of 20 carbon resonances comprising of twelve aromatic carbons, one ketocarbonyl carbons, three methoxyl carbons and four aliphatic carbons. The 1D NMR data of **1** were similar to those of moellenoside B (Feng et al. 2011) which contains an additional C-9 glucosyl unit. Further analysis of the HSQC and HMBC spectra verified the planar structure of **1**. In the HMBC spectrum, correlations of H-2′ (δ_H 7.41)/C-7′ (δ_C 199.9), H-8′ (δ_H 2.49)/C-1′ (δ_C 129.5) indicated the ketocarbonyl was located at C-1′. The HMBC correlations of H-7 to C-3′, C-2 and C-9, H-9 to C-3′, confirmed the linkage between two benzene rings. The absolute configuration of **1** was established as (8*R*) on the basis of the negative *Cotton* effect at 270 nm in its CD spectrum (Zhuo et al.

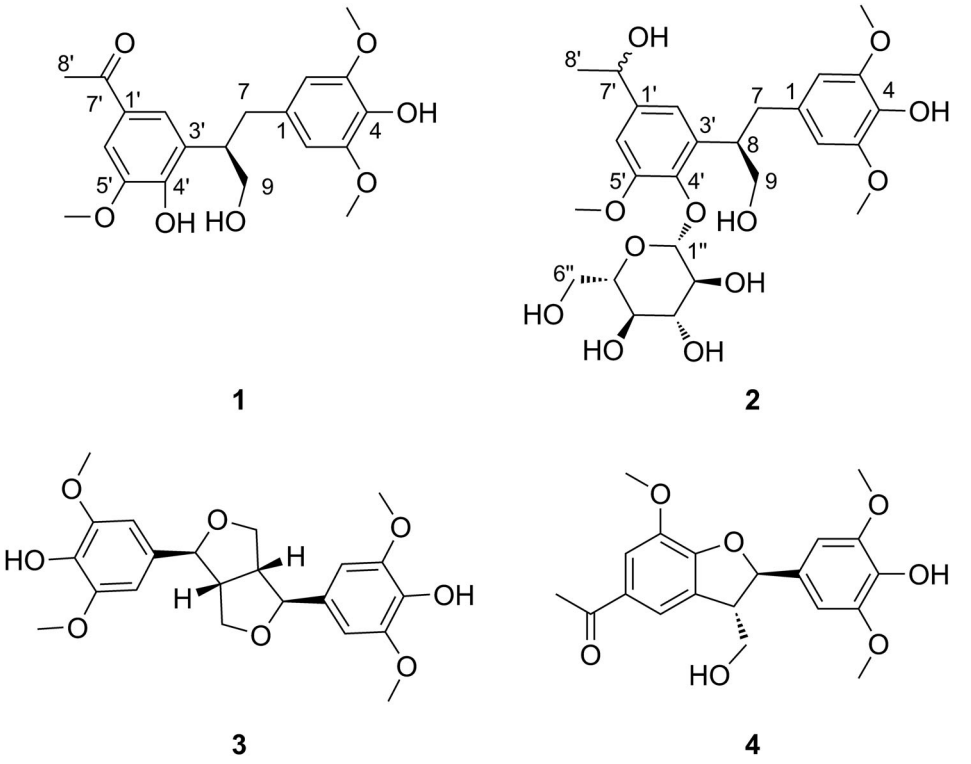

Figure 1. The structures of compounds **1–4**.

2016). Thus, the structure of **1** was determined as shown (Figure 1) and named pulvin A.

Compound **2** was obtained as a white, amorphous powder. The molecular formula of **2** was determined to be $C_{26}H_{36}O_{12}$ based on the HRESIMS signal at *m/z* 539.2152 $[M\text{-}H]^-$ (calcd. for $C_{26}H_{35}O_{12}$, 539.2134). The UV spectrum of **2** showed absorption peaks at 254 and 282 nm. The ^{1}H NMR data of **2** suggested characteristic signals of four aromatic protons at δ_H 6.30 (2H, s), δ_H 6.89 (1H, d, $J = 1.8$ Hz) and δ_H 6.88 (1H, d, $J = 1.8$ Hz), three methoxy groups at δ_H 3.70 (6H, s) and δ_H 3.82 (3H, s), one terminal hydrogen at δ_H 4.62 (1H, d, $J = 7.8$ Hz) and one methyl signal at δ_H 1.41 (3H, d, $J = 6.6$ Hz). The ^{13}C NMR spectrum revealed the presence of 26 carbon signals consisting of twelve aromatic carbons, six glycosyl carbons, three methoxyl carbons and five aliphatic carbons. The ^{1}H and ^{13}C NMR data of **2** were similar to those of **1**, with the main differences being the presence of one glucosyl group in **2**. Acid hydrolysis of **2** affords D-glucose based on HPLC analysis of their chiral derivatives. The D-glucose units were determined to have β-configurations from the $^3J_{H1,H2}$ coupling constants (7.8 Hz). In the HMBC spectrum, correlations from H-1″ (δ_H 4.62) to C-4′ (δ_C 144.6) suggested that the glucosyl unit is linked at C-4′. Correlations of H-8′ (δ_H 1.41)/C-1′ (δ_C 144.5) and H-2′ (δ_H 6.88)/C-7′ (δ_C 70.9) revealed one 1-hydroxyethyl linked to C-1′. Complete assignment of ^{1}H and ^{13}C NMR data was achieved by further analysis of the HSQC and HMBC spectra. The absolute configuration of C-8 in **2** was established as *R* by comparison of its CD spectrum (negative *Cotton* effect at 270 ~ 295 nm) with that

of selaginellol 4′-*O*-*β*-D-glucopyranoside (Zhuo et al. 2016). Therefore, the structure of **2** was identified as shown and named moellenoside C.

The known compounds were identified as syringaresinol (**3**) (Ouyang et al. 2007) and (2*R*,3*S*)-dihydro-2-(3,5-dimethoxy-4-hydroxy-phenyl)-7-methoxy-5-acetylbenzofuran (**4**) (Bi et al. 2004), by comparison of their spectroscopic data with previously reported values.

The *Selaginella* species, belonging vascular plants, have the potential to synthesise a repertoire of novel secondary metabolites for the existing of many independent diversification of gene families (Banks et al. 2011). The *nor*-lignans mentioned above contain the units of syringyl, indicating that the *nor*-lignans in the *Selaginella* species may be synthesised via the shikimic acid pathway which is the biosynthetic pathway of angiospermous lignans. Previous studies indicate the genus *Selaginella* is rich in benzofuran lignans. However, *nor*-lignans without furan-rings, such as analogues of compounds **1** and **2**, are only found in *Selaginella moellendorffii* Hieron (Feng et al. 2011; Zhuo et al. 2016) and *S. tamariscina* (Dat et al. 2017). To our knowledge, compound **3** is discovered in several *Selaginella* species, such as *S. tamariscina* (Bi et al. 2004), *S. moellendorffii* (Zhu et al. 2018). *S. sinensis* (Feng et al. 2008) and *S. picta* (Cheng et al. 2018), while compound **4** is only isolated from *S. tamariscina* (Bi et al. 2004). Therefore, it was the first isolation of compounds **3** and **4** from *S. pulvinata*. As a result, The isolation of compounds **1–4** provides a certain relationship between *S. pulvinata* and *S. tamariscina* in terms of chemotaxonomy.

Antihyperglycemic activities of the isolates were evaluated *in vitro* in 3T3L-1 adipocytes. Compounds **1** and **2** show activities on promoting glucose consumption in 3T3L-1 adipocytes in preliminary screening experiments (Data not shown). Then, different concentration levels of compounds **1** and **2** were set to evaluate their activities. As a result, compounds **1** and **2** induced the glucose consumption with 1.14–1.73 folds and 1.03–l.55 folds changes relative to the basal level (normalized to 1.0), respectively, by a dose-response manner in the concentration range of 12.5 μM to 50 μM. Insulin (0.1 μM) was used as positive control and caused 1.47 folds to change relative to the basal level (Figure 2).

3. Experimental

3.1. General

Optical rotations were measured using a JASCO P-1020 polarimeter (Jasco Tokyo Japan); UV spectra were recorded in MeOH using a Shimadzu UV spectrometer-1800 (Shimadzu Corp., Kyoto, Japan); IR spectra (KBr) were recorded on a Nicolet 6700 FT-IR spectrometer (Thermoelectric nicoli, United States); A JASCO J-810 spectrometer was used to detect CD spectra; 1D and 2D NMR spectra were recorded on a Bruker AVANCE III 600 MHZ spectrometer (600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR) equipped with a 5 mm TCI cryoprobe (Bruker company, Switzerland) at 298 K, and TMS was used as internal standard; HRESIMS were measured with an Agilent 6210 TOF LC/MS (Agilent Technologies, Santa Clara, CA); ESIMS were measured with a Thermo LCQ Deca XP plus (Thermo Finnigan, San Jose, CA). The compounds were purified by LUMTECH prepared HPLC (Lumiere Tech Ltd, China) equipped with a LUMTECH dual-

wavelength UV-detector and a Shim-pack GIST C18 column (20 × 250 mm, 5 μm, Shimadzu Corp., Kyoto, Japan); HPLC was carried out using Agilent-1260 (Agilent, USA) equipped with an Agilent single wavelength UV-detector and an Inertsustain C_{18} column (4.6 × 250 mm, 5 μm particle size, Shimadzu Corp., Kyoto, Japan); TLC was conducted on silica gel G (Qingdao Haiyang Chemical Co., Ltd., China); HPLC solvents was used from TEDIA in American (TEDIA company, American); All others reagents were of the analytical grade.

3.2. Plant material

Whole *Selaginella pulvinata* plants were purchased from Guangzhou Qingping market, Guangdong Province, China, in June 2017. The seller collected the plants from Meizhou City at 116°*07*′ E and 24°*19*′ N, Guangdong Province. This sample was identified by Professor Chu Chu, College of Pharmaceutical Science, Zhejiang University of Technology. A voucher specimen (201706ST) was deposited at the Herbarium of Chinese medicine, Zhejiang University of Technology, China.

3.3. Extraction and isolation

Dry plants of *S. pulvinata* (15 kg) were ground into a coarse powder, and extracted with 25 L of 95% ethanol at room temperature for 3 times (48 h for each time). The extracted solvent was combined and concentrated under reduced pressure by a rotary evaporator to yield 1.7 kg of crude extract. The crude extract was suspended with water and extracted with CH_2Cl_2, EtOAc and *n*-BuOH to obtain three fractions, a CH_2Cl_2 fraction (540 g), an EtOAc fraction (122 g), and an *n*-BuOH fraction (212 g). The CH_2Cl_2 fraction was subjected to an MCI column, eluting with MeOH-H_2O (30:70–100:0, *v/v*), to obtain four subfractions A–F. Subfraction B (12.6 g) was separated by a silica gel column with CH_2Cl_2:MeOH (20:1 to 10:1, *v/v*, total volume: 2100 mL) to obtain eighteen subfractions B1–B18. Subfraction B3 (180 mg) was separated by medium pressure preparative liquid chromatography, eluting with MeOH:H_2O (20:80 to 100:0, *v/v*), to obtain five fractions B3a to B3e. B3a (34 mg) was separated by a silica gel column to give two fractions B3a-1 and B3a-2. B3a-2 (13.2 mg) was subsequently purified by *prep*-HPLC to obtain compound **2** (10.0 mg). Fractions B3b (16.4 mg) was separated by *prep*-HPLC (MeCN:H_2O, 25:75, *v/v*) to yield compound **3** (8.9 mg). B3c (41 mg) was subjected to a silica gel column to obtain two fractions B3c-1 and B3c-2. Fraction B3c-2 (26.6 mg) was performed on *prep*-HPLC to afford compound **1** (4.0 mg) and **4** (18.6 mg).

Compound **1**: white, amorphous powder; [α]25 D -23.6 (c 0.11, MeOH); CD (MeOH): 211 (neg), 270 (neg); UV (MeOH) λ_{max} (log ε) 278 (3.03), 258 (4.87) nm; IR ν_{max} (KBr) 3393, 2934, 1612, 1518, 1459, 1428, 1326, 1218, 1154, 1114, 1073 cm^{-1}; ^1H NMR (600 MHz, MeOH-d_4): δ 7.41 (1H, d, J = 1.8 Hz, H-2′), 7.39 (1H, d, J = 1.8 Hz, H-6′), 6.34 (each 1H, s, H-2 and H-6), 3.89 (3H, s, 5′-OCH_3), 3.81 (2H, m, H-9), 3.70 (each 3H, s, 3,5-OCH_3), 3.55 (1H, m, H-8), 3.03, (1H, dd, J = 13.8, 6.0 Hz, H-7a), 2.91 (1H, dd, J = 13.8, 9.0 Hz, H-7b), 2.49 (3H, s, H-8′); ^{13}C NMR (150 MHz, MeOH-d_4): δ 199.9 (C-7′), 151.6 (C-4′), 148.9 (C-3, C-5), 148.8 (C-5′), 134.6 (C-4), 132.4 (C-1), 129.5 (C-1′), 129.4 (C-3′), 125.0

(C-2′), 109.6 (C-6′), 107.5 (C-2, C-6), 65.4 (C-9), 56.7 (3,5-OCH_3), 56.6 (5′-OCH_3), 45.0 (C-8), 37.9 (C-7), 26.3 (C-8′); HRESIMS *m/z* 375.1466 $[M\text{-}H]^-$ (calcd. for $C_{20}H_{23}O_7$, 375.1449).

Compound **2**: white, amorphous powder; [α]25 D -30.3 (c 0.12, MeOH); CD (MeOH): 217 (neg), 289 (neg); UV (c 0.02, MeOH) λ_{max} (log ε) 254 (3.74), 282 (4.05) nm; IR ν_{max} (KBr) 3405, 2939, 1662, 1591, 1518, 1427, 1305, 1359, 1215, 1116 cm^{-1}; ^1H NMR (600 MHz, MeOH-d_4): δ 6.89 (1H, d, $J = 1.8$ Hz, H-6′), 6.88 (1H, d, $J = 1.8$ Hz, H-2′), 6.30 (each 1H, s, H-2 and H-6), 4.78 (1H, m, H-7′), 4.62 (1H, d, $J = 7.8$ Hz, H-1″), 4.00 (1H, m, H-8), 3.82 (3H, s, 5′-OCH_3), 3.80 (1H, m, H-6″a), 3.77 (2H, m, H-9), 3.70 (each 3H, s, 3,5-OCH_3), 3.68 (1H, m, H-6″b), 3.45 (1H, m, H-2″), 3.39 (1H, m, H-4″), 3.37 (1H, m, H-3″), 3.11 (1H, m, H-5″), 3.01 (1H, dd, $J = 13.8$, 5.4 Hz, H-7a), 2.72 (1H, dd, $J = 13.8$, 9.6 Hz, H-7b), 1.41 (3H, d, $J = 6.6$ Hz, H-8′); ^{13}C NMR (150 MHz, MeOH-d_4): δ 153.3 (C-5′), 148.7 (C-3, C-5), 144.6 (C-4′), 144.5 (C-1′), 134.3 (C-4), 138.7 (C-3′), 132.5 (C-1), 117.2 (C-2′), 108.8 (C-6′), 107.2 (C-2, C-6), 105.6 (C-1″), 78.1 (C-5″), 77.9 (C-3″), 76.0 (C-2″), 71.3 (C-4″), 70.9 (C-7′), 67.1 (C-9), 62.5 (C-6″), 56.7 (3,5-OCH_3), 56.4 (5′-OCH_3), 42.8 (C-8), 39.6 (C-7), 25.9 (C-8′); HRESIMS *m/z* 539.2152 $[M\text{-}H]^-$ (calcd. for $C_{26}H_{35}O_{12}$, 539.2134).

3.4. Acid hydrolysis of 2

Compound **2** (1.0 mg) was dissolved in 2 M HCl (aq) (5.0 mL) at 100 °C refluxed for 4 h. After removal of the solvent, the compound was dissolved in water and filtered to obtain a monosaccharide sample, the solvent was removed, and dried under vacuum overnight. The sample was then dissolved in pyridine (1.0 mL) containing 1 mg/mL L-cysteine methyl ester. The mixture was heated at 60 °C for 1 h. *o*-Tolylisothiocyanate (2.0 μL) was added, and heating was continued for an additional hour. The mixture was concentrated under vacuum to afford a residue that was dissolved in MeOH and analyzed by RP-HPLC at 30 °C, with isocratic elution of CH_3CN-H_2O-HCOOH (25:75:0.1, *v/v*) for 40 min and subsequent washing of the column with 90% CH_3CN at a flow rate of 0.8 mL/min. D-glucose derivative was detected in the acid hydrolysate of **2** by comparing the retention time of its derivatives (t_R 21.51 min) with those of the authentic D-glucose and L-Glucose derivatives (t_R 21.38 min and t_R 19.38 min) prepared in the same manner (Lv et al. 2014)[12].

3.5. Glucose consumption in 3T3-L1 adipocytes

The differentiation of 3T3-L1 preadipocytes was performed as previously reported (Lv et al. 2014). The adipocytes were incubated with or without the test compounds, as well as with insulin (0.1 μM), for an additional 24 h. Their glucose concentrations were determined using the glucose oxidase method with commercially available kits. Insulin, 0.1 μM (Sigma-Aldrich, St. Louis, MO, USA), served as the positive control. The amount of glucose consumption was calculated by subtracting the glucose concentrations of the treated wells from those of the blank wells. Glucose consumption due to cell proliferation could be determined by calculating the ratio of glucose consumption to MTT (GC/MTT). The final results were expressed as the GC/MTT value in each treated group compared with that of the vehicle control group.

All results are presented as the mean ± standard deviation (S.D.) of three replicate determinations. Significant differences were determined by one-way analysis of variance (ANOVA), followed by Dunnett's post hoc test using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA). Statistical significance was set at $^{*}p < 0.05$ and $^{**}p < 0.01$.

4. Conclusions

Two new *nor*-lignans, pulvin A **(1)** and moellenoside C (**2**), along with two known compounds, syringaresinol (**3**) and (2 *R*,3*S*)-dihydro-2-(3,5-dimethoxy-4-hydroxy-phenyl)--7-methoxy-5-acetylbenzofuran (**4**), were isolated from the whole plants of *S. pulvinata*. Compounds **1** and **2** show potential antihyperglycemic activities in 3T3-L1 adipocytes.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by National Natural Science Foundation of China under Grant NO.81603255.

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