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Phenolic glycosides from *Sanguisorba officinalis* and their anti-inflammatory effects

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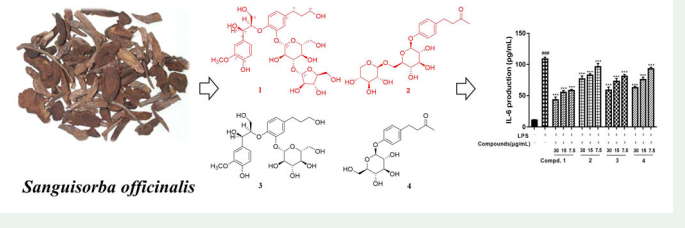
ABSTRACT

Two new phenolic glycosides 7*R*,8*R*-threo-4,7,9,9′-tetrahydroxy-3-methoxy-8-*O*-4′-neolignan-3′-*O*-(3″-α-L-arabinofuranosyl)-*β*-D-glucopyranoside. (**1**), 4-(4′-hydroxyphenyl)-2-butanone-4″-*O*-(6-*β*-D-xylosyl)-β-*D*-glucopyranoside (**2**), along with two known related analogues 7*R*,8*R*-threo-4,7,9,9′-tetrahydroxy-3-methoxy-8-*O*-4′-neolignan-3′-*O*-β-*D*-glucopyranoside (**3**), 4-(4′-hydroxyphenyl)-2-butanone-4′-*O*-β-*D*-glucopyranoside (**4**) were obtained from the roots of *Sanguisorba officinalis*. Combined with acid hydrolysis derivatization, the absolute configurations of these new compounds were elucidated by comprehensive analyses of spectroscopic data including nuclear magnetic resonance (NMR), electrospray ionization high resolution mass (HRESIMS) as well as circular dichroism (CD). Compounds **1**-**4** exhibited anti-inflammatory properties in vitro by attenuating the production of inflammatory mediators, such as nitric oxide (NO) as well as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).



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Sanguisorba officinalis; phenolic glycosides; structural elucidation; anti-inflammatory effects

1. Introduction

Sanguisorba officinalis is a common perennial plant belonging to Rosaceae family (Gawron et al. 2016). Its roots have been used for thousands of years in the Chinese

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This Paper is Dedicated to Professor Youyou Tu, the 2015 Nobel Prize Laureate of Physiology or Medicine on the Occasion of Her 90th Birthday.

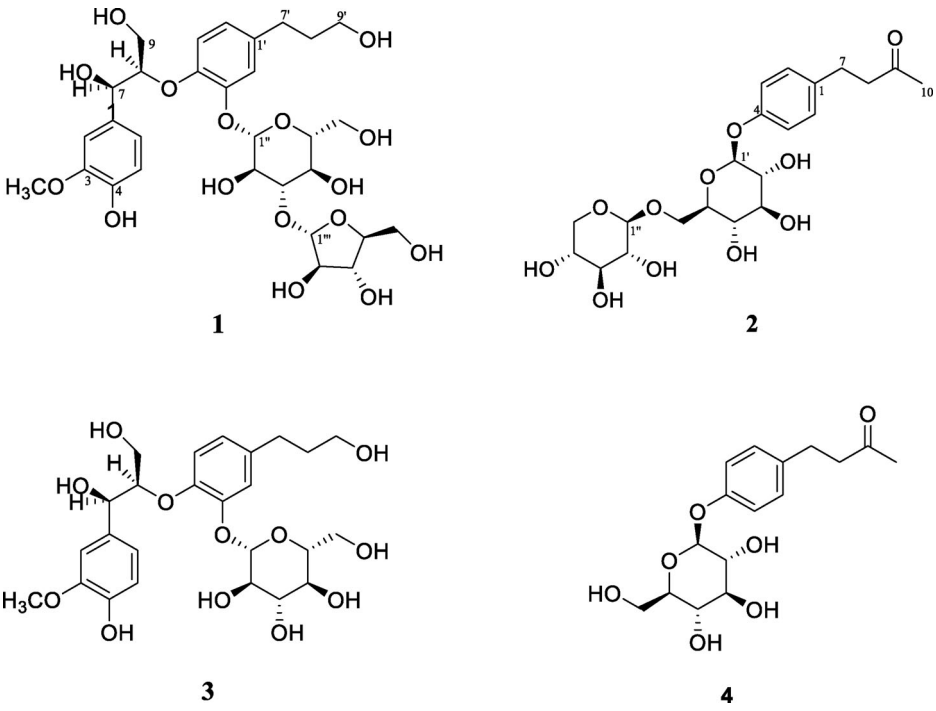

Figure 1. Structures of compounds **1**-**4**.

traditional medicines for the treatment of diseases such as burns, scalds, inflammation and bleeding due to its astringency and analgesic properties (Su et al. 2018). Triterpenoids (Zhang et al. 2005), triterpenoid glycosides (Kim et al. 2008), lignans (Wang et al. 2019), lignosides (Hu et al. 2012), polysaccharides (Cai et al. 2012), hydrolyzable tannins (Li et al. 2019) and monoterpene glycosides (Sun et al. 2012, Guo et al. 2019) have been reported as the constituents which are partially accountable for the therapeutic effects of *S. officinalis*.

In the course of our ongoing search for compounds with anti-inflammatory effects from *S. officinalis*, two new phenolic glycosides along with two known analogues were obtained (Figure 1). Their relative structures were identified by comprehensive analyses of spectroscopic data, and the absolute configuration of C-7 and C-8 of compound **1** was confirmed by a CD comparing study. The nature and absolute configurations of monosaccharides in compounds **1** and **2** were deduced by acid hydrolysis and derivatizations. This paper reports the details of the separation, structure identification and bioactivity assessment of these compounds.

2. Results and discussion

Compound **1** was obtained as a white gum. The molecular formula of compound **1** was determined as $C_{30}H_{42}O_{16}$ by the HRESIMS ion peak at *m/z* 681.2354 $[M+Na]^+$ (calcd 681.2473). The ^{1}H NMR and HSQC spectra (Table S1) of **1** showed the signals of two methines at δ 4.87 (overlapped with solvent signal), 4.34 (1H, td, $J = 5.6$, 3.1 Hz),

four methylenes at δ 3.89 (1H, dd, $J = 12.0$, 5.8 Hz), 3.73 (1H, dd, $J = 12.0$, 3.2 Hz), 2.61 (2H, dd, $J = 8.9$, 6.7 Hz), 1.81 (2H, dddd, $J = 13.9$, 7.9, 6.7, 1.4 Hz) and 3.57 (2H, t, $J = 6.5$ Hz), a methyl at δ 3.81 (3H, s), six aromatic protons at δ 7.05 (1H, d, $J = 2.0$ Hz), 7.01 (1H, d, $J = 1.9$ Hz), 6.86 (1H, dd, $J = 8.2$, 1.9 Hz), 6.82 (1H, d, $J = 8.2$ Hz), 6.79 (1H, dd, $J = 8.2$, 2.0 Hz), 6.76 (1H, d, $J = 8.2$ Hz) as well as seven protons for one glucose at 4.77 (1H, d, $J = 7.7$ Hz), 3.53 (1H, ddd, $J = 9.9$, 6.2, 2.2 Hz, H-2′′), 3.36 (1H, dd, $J = 9.3$, 2.8 Hz, H-3′′) 3.45 (1H, t, $J = 9.0$ Hz, H-4′′), 3.49 (1H, dd, $J = 9.3$, 7.6 Hz, H-5′′), 3.83 (1H, dd, $J = 7.6$, 5.8 Hz, H_a-6′′), 3.73 (1H, dd, $J = 5.6$, 3.2 Hz, H_b-6′′), and six protons for one arabinose at δ 4.93 (1H, d, $J = 1.3$ Hz, H-1′′′), 4.00 (1H, dd, $J = 3.3$, 1.4 Hz, H-2′′′), 3.82 (1H, d, $J = 3.3$ Hz, H-3′′′), 3.95 (1H, td, $J = 5.6$, 3.3 Hz, H-4′′′), 4.06 (1H, dd, $J = 10.9$, 2.2 Hz, H_a-5′′′) and 3.62 (1H, dd, $J = 10.9$, 5.4 Hz, H_b-5′′′). The interpretation of the ^{13}C NMR and HSQC spectra (Table S1) of **1** revealed the presence of thirty carbon signals, including two methine carbons at δ 73.4 (C-7) and 87.1 (C-8), four methylene carbons at δ 61.6 (C-9), 32.6 (C-7′), 35.5 (C-8′) and 62.3 (C-9′), a methyl carbon at δ 56.5 (C-OCH_3), twelve aromatic carbons at δ134.1 (C-1), 111.7 (C-2), 148.8 (C-3), 147.3 (C-4), 115.9 (C-5), 120.9 (C-6), 138.3 (C-1′), 120.4 (C-2′), 149.4 (C-3′), 147.9 (C-4′), 120.2 (C-5′) and 124.5 (C-6′) and six carbons for one glucose at δ 103.7 (C-1′′), 76.9 (C-2′′), 71.9 (C-3′′), 77.7 (C-4′′), 75.3 (C-5′′), 63.1 (C-6′′) and five carbons for one arabinose at 109.7 (C-1′′′), 83.2 (C-2′′′), 79.0 (C-3′′′), 85.9 (C-4′′′) and 68.0 (C-5′′′). The HMBC correlations from H-7 to C-1, C-2, C-6, C-8 and C-9 and from -OCH_3 to C-3 as well as the ^1H-^1H COSY correlations of H-7/H-8, H-8/H-9 and H-5/H-6 can determine the structure of a phenylpropanoid. Further analysis of the HMBC correlations from H-7′ to C-1′, C-2′, C-6′, C-8′ and C-9′ and the ^1H–^1H COSY correlations (Figure S1) from H-7′ to H-8′, from H-8′ to H-9′ and from H-5′ to H-6′ can determine the structure of the second phenylpropanoid unit.

The absolute configurations at C-7 and C-8 of the 1-phenyl-2-aryloxypropane-1,3-diol moiety in **1** were confirmed by the analyses of its nuclear Overhauser effect (NOE) spectrum and CD spectroscopic evidence (Figure S2). The cross peaks between H-8 and H-2/H-6, and H-8 and H-7 in NOESY spectrum (Matsuda and Kikuchi 1996) as well as the coupling constant constant ($J = 5.6$ Hz) between H-7 and H-8 (Greca et al. 1994) indicated **1** has a relative *threo*-configuration. The absolute configuration at C-7 and C-8 was determined to be 7*R* and 8*R* from the CD spectrum of **1** showing a negative Cotton effect in the region 220-250 nm (Lee et al. 2015). The sugar component was identified as a D-glucose and an L-arabinose by HPLC analysis after acid hydrolysis and derivatization of **1** combined with optical rotation comparison. Finally, the structure of compound **1** was confirmed to be 7*R*,8*R*-threo-4,7,9,9′-tetrahydroxy-3-methoxy-8-*O*-4′-neolignan-3′-*O*-(3′′-α-L-arabinofuranosyl)-β-D-glucopyranoside.

Compound **2** was obtained as a colorless gum. Its molecular formula was defined as $C_{21}H_{30}O_{11}$ by HRESIMS ion peak at *m/z* 481.16779 $[M + Na]^+$ (calcd 481.17881). The ^1H NMR and HSQC spectrum (Table S2) of **2** showed signals of a two methylenes at δ 2.76-2.79 (2H, m, H-7) and 2.79-2.82 (2H, m, H-8), one methyl at δ2.12 (3H, s), four aromatic protons at δ 7.12-7.16 (2H, m, H-2, 6) and 7.01-7.04 (2H, m, H-3, 5) and seven protons for one glucose at δ 4.85 (overlapped with solvent signal, H-1′), 3.43-3.44 (1H, m, H-2′), 3.42-3.43 (1H, m, H-3′), 3.35-3.39 (1H, m, H-4′), 3.63 (1H, ddd, $J = 9.9$, 6.2, 2.1 Hz, H-5′), 4.10 (1H, dd, $J = 11.5$, 2.1 Hz, H-6′), 3.75 (1H, dd, $J = 11.6$, 6.2 Hz, H-6′), and

six protons for one arabinose at 4.31 (1H, d, $J = 6.8$ Hz, H-1′′), 3.58 (1H, dd, $J = 8.8$, 6.9 Hz, H-2′′), 3.49 (1H, dd, $J = 8.8$, 3.5 Hz, H-3′′), 3.77 (1H, dd, $J = 3.4$, 1.8 Hz, H-4′′), 3.83 (1H, dd, $J = 12.5$, 3.3 Hz, H-5′′), 3.45 (1H, dd, $J = 12.5$, 4.4 Hz, H-5′′). The interpretation of the ^{13}C NMR and HSQC spectra (Table S2) of **2** revealed the presence of twenty-one carbons signals, including two methylenes carbons at δ 46.0 (C-7) and 30.1 (C-8), a methyl carbon at δ 30.0 (C-10), six aromatic carbons at δ136.3 (C-1), 130.3 (C-2), 117.8 (C-3), 157.3 (C-4), 117.8 (C-5), 130.3 (C-6) and six carbons for one glucose and five carbons for one arabinose at δ 102.2 (C-1′), 74.9 (C-2′), 74.1 (C-3′), 71.5(C-4′), 77.3 (C-5′), 69.3 (C-6′), 104.9 (C-1′′), 72.5 (C-2′′), 74.1 (C-3′′), 69.5 (C-4′′) and 66.7 (C-5′′). The analysis of the HMBC correlations (Figure 2) from H-7 to C-1, C-5 and C-6 and from H-8 to C-2 and the ^{1}H-^{1}H COSY correlations (Figure S1) from H-2 to H-3, from H-5 to H-6 indicated compound **2** to be a di-glycoside of propiophenone. The location of sugar moiety and side chain was confirmed based on HMBC correlations (Figure S1) from H-1′ to C-4 and H-1′′ to C-6′. The sugar component was identified as a D-glucose and a D-xylose by HPLC analysis after acid hydrolysis and derivatization of **2** combined with optical rotation comparison. Finally, the structure of compound **2** was confirmed to be 4-(4′-hydroxyphenyl)-2-butanone-4′′-*O*-(6-β-D-xylosyl)-β-*D*-glucopyranoside.

Compound **3** and compound **4** were identified as 7*R*,8*R*-threo-4,7,9,9′-tetrahydroxy-3-methoxy-8-*O*-4′-neolignan-3′-*O*-β-*D*-glucopyranoside (Yang et al. 2012) and 4-(4′-hydroxyphenyl)-2-butanone-4′-*O*-β-*D*-glucopyranoside (Hu et al. 2014) by spectroscopic analyses and comparing the spectral data with those reported.

To investigate the anti-inflammatory effect of compounds **1**-**4**, the levels of NO, IL-6, and TNF-α in LPS- stimulated RAW264.7 cells were first determined. As shown in Figure S18-S19, LPS significantly upregulated the secretion of the pro-inflammatory cytokines in RAW264.7 cells. However, compounds **1**-**4** diminished the levels of NO, IL-6, and TNF-α significantly in a dose-dependent manner and the best effect on inhibitory is the concentration of 30 μg/mL. These results indicate that compounds **1**-**4** exert the anti-inflammatory activity via suppressing the production of pro-inflammatory cytokines and mediator in LPS-stimulated RAW264.7 cells. Compared with compound **3**, compound **1** give a better anti-inflammatory activity which indicated that a 3′′-α-L-arabinofuranosyl moiety might be beneficial for these compounds to attenuate the production of inflammatory mediators.

3. Experimental

3.1. General experimental procedures

The optical rotations were recorded on a perkin-Elmer-241 polarimeter (PerkinElmer, Inc., Waltham, MA, USA). The CD spectra were measured on a Chirascan circular dichroism spectrometer (Applied Photophysics Ltd., Leatherhead, UK). The IR spectra were recorded on a Cary 600 Series FT-IR (KBr) spectrometer (Agilent Technologies Inc., California, USA). The HRESIMS data were obtained using a Q Exactive UHMR Hybrid Quadrupole-Orbitrap mass spectrometer (Thermo Fisher Scientifc, MA, USA). The 1D (^{1}H and ^{13}C) and 2D (^{1}H-^{1}H COSY, HSQC, HMBC and NOESY) NMR data were obtained using a Bruker Bruker-Ascend-700-MHz spectrometer (Bruker Corporation, Billerica, MA, USA). The semi-preparative HPLC was conducted by a NP7000 serials

instrument with a U3000 serial UV detector (Hanbon Sci. & Tech, Jiangsu, China) using a Kromasil 100-5-C18 column (10 × 250 mm, 5 μm) (Akzo Nobel Pulp and Performance Chemicals AB, Bohus, Sweden). Analytic HPLC was performed on an Utimated 3000 series pump (Thermo Scientific, Waltham, MA USA) equipped with a Kromasil Eternity XT-5-C18 column (4.6 × 250 nm, 5 μm) (Akzo Nobel Pulp and Performance Chemicals AB, Bohus, Sweden) using a Utimated 3000 DAD detector (Thermo Scientific, Waltham, MA USA). Column chromatography was performed using D101 CC (Changfeng Chemical Co., Ltd, Shifang, China), HPD400 CC (Shanghai Lanji Technology Development Co., Ltd, Shanghai, China), HP-20 CC (Mitsubishi Chemical Corporation, Tokyo, Japan),and MCI gel (75-150 μm, Mitsubishi Chemical Corporation, Tokyo, Japan). The NO assay kit was purchased from Beyotime Biotechnology Co, Ltd. (Shanghai, China, Batch No: 032519190612). Mouse enzyme-linked immunosorbent assay (ELISA) kits were purchased from NeoBioscience Technology Co, Ltd. (Shenzhen, China, Batch No: M190726-004a, M190726-102a). Lipopolysaccharide was purchased from Beijing Solarbio Science & Technology Co., Ltd. (Beijing, China). Thiazolyl blue was purchased from Sigma-Aldrich (USA). The *L*-arabinose, *D*-xylose and *D*-glucose were purchased from Energy Chemical (Chengdu, China). The *L*-cysteine methyl ester hydrochloride was purchased from Chroma-Biotechnology Co. Ltd (Chengdu, China). The phenylisothiocyanate was purchased from Aladdin (Chengdu, China). All solvents used were of analytical grade.

3.2. Plant material

The roots of *S. officinalis* were purchased from Tianfu Pharmaceutical Co., Ltd. of Chengdu Di'ao group and identified by Longfei (associate professor of school of pharmacy, Chengdu university of TCM). The specimen (20150920) was deposited in the laboratory of traditional Chinese medicine chemistry, school of pharmacy, Chengdu university of TCM.

3.3. Extraction and isolation

The air-dried and powdered of *S. officinalis* (10.00 kg) were extracted with 70% EtOH (100 L, 3 times) under reflux. The extract (1.37 kg) was subjected to D101 macroporous resin CC (8 × 80 cm), using a stepwise elution with ethanol/water (0%, 30%, 50%, 70%, 95%; v/v; 4 L for each steps) to give five fractions. The fraction of 30% ethanol (0.74 Kg) was subjected to a column of HP-20 CC (6 × 50 cm) eluted with ethanol/water (0%, 10%, 20%, 30%, 40%, 50%, 100%, v/v; 900 mL each gradient) to yield seven fractions, F1-F7. Fraction F3 (120 g) was subsequently subjected to HPD-400 CC (6 × 80 cm) eluted with ethanol/water (10%, 30%, 95%, v/v) to afford three fractions, F3a–F3c. F3b (2.4 g) was subjected to a MCI reverse chromatography (5 cm L × 60 cm) eluted with ethanol/water (20%, 25%, 30%, 35%, 100%, v/v) to afford four subfractions, F3b1–F3b3. F3b3 (1.87 g) was purified by a preparative HPLC equipped with a Kromasil RP-C18 column (10 × 250 mm; 210 nm) to afford **1** (2.2 mg; MeOH/H_2O: 20:80, v/v; 3 mL/min; t_R: 19 min), **2** (6.9 mg; MeOH/H_2O: 30:70, v/v; 3 mL/min, t_R: 20 min), **3**

(5.8 mg; MeOH/H_2O: 28:72, v/v; 3 mL/min, t_R: 19 min), **4** (3.2 mg; MeOH/H_2O: 25:75, v/v; 3 mL/min, t_R: 21 min).

3.4. Acid hydrolysis and derivatization

Compounds **1** (1.00 mg) and **2** (1.00 mg) were heated with trifluoroacetic acid (TFA) (2 M) for 6 h at 100 °C. The mixture was cooled and partitioned between CH_2Cl_2 (2 mL) and H_2O three times, and the water layer was dried under reduced pressure. At last, l-cysteine methyl ester hydrochloride (1.5 mg) and the residue of the aqueous phase were dissolved in pyridine (0.5 mL) and heated at 60 °C for 1 h, and after phenylisothiocyanate (0.5 mL) was added to the mixture and heated at 60 °C for 1 h. The solvent was analyzed by HPLC (25% CH_3CN/H_2O, flow rate = 0.8 mL/min) equipped with a diode array detector (DAD) detector (under 254 nm) using a C-18 column. Finally, the absolute configuration of the monosaccharides was confirmed by comparing the retention time with those of *D*-glucose (t_R = 14.643 min), *D*-xylose (t_R = 17.843 min) and *L*-arabinose (t_R = 17.380 min).

7*R*,8*R*-threo-4,7,9,9′-tetrahydroxy-3-methoxy-8-*O*-4′-neolignan-3′-*O*-(6-α-L-arabinofuranosyl)-β-D-glucopyranoside (**1**). a white gum, [α]20D − 44 (c = 0.30, MeOH); IR (KBr) ν_{max} 3436, 2924, 2857, 1734, 1630, 1613, 1458, 1422, 1269, 1646, 644 cm^{-1}; UV λ_{max} 280 (2.86), 224 (3.33) nm; CD (*c* 1.05×10^{-3} M, MeOH), $\Delta\varepsilon_{196\,nm}$ +6.50, $\Delta\varepsilon_{225\,nm}$ +7.00, $\Delta\varepsilon_{239\,nm}$ −10.95; HRESIMS: *m/z* 681.23541 $[M + Na]^+$, calcd. for 681.24729.

butylphenol-4′-*O*-(6-β-D-xylosyl)-β-D-glucoside (**2**). a colorless gum, [α]20D- 56 (c = 0.30, MeOH); IR (KBr) ν_{max} 3417, 2926, 2525, 1697, 1611, 1515, 1392, 1317, 1240, 1084, 822, 771, 665, 570, 515cm^{-1}; UV λ_{max} 224 (2.96) nm; HRESIMS: *m/z* 481.16779 $[M + Na]^+$, calcd. for 481.17881.

3.5. Cell viability assay

MTT colorimetric assays were performed to estimate the cytotoxic effects of compounds **1**-**4** on RAW264.7 macrophage cells. The detailed process was described previously (Guo et al. 2019).

3.6. Quantification of NO production

Griess reaction was used to measure the NO production by measuring the accumulation of nitrite. RAW264.7 macrophages (1×10^5 cells/mL) were cultured with lipopolysaccharide (LPS) at 100 ng/mL and each compound at 7.5, 15, 30 μg/mL for 24 hours. The cell-free medium without nitrite was used as the blank control, and sodium nitrite was used as the standard to calculate the concentration of nitrite in the medium. The detailed process was described previously (Guo et al. 2019).

3.7. Measurement of pro-inflammatory cytokine production

The inhibitory effects of compounds **1**-**4** on proinflammatory cytokines (IL-6 and TNF-α) were examined by cytokine analysis. The production of pro-inflammatory cytokines

in the supernatant of RAW264.7 macrophages treated with LPS (100 ng/mL) was determined by using mouse enzyme-linked immunosorbent assay (ELISA) kit. The detailed process was described previously (Guo et al. 2019).

4. Conclusions

Two new terpene glycosides along with two known analogs had been isolated from the roots of *S. officinalis*. The structures of the new compounds were elucidated using NMR and HRESIMS, as well as hydrolysis reactions. Compounds **1**-**4** exhibited anti-inflammatory properties in vitro by attenuating production of inflammatory mediators, such as NO, IL-6, and TNF-α at the concentration of 7.5 μg/mL.

Disclosure statement

There are no conflicts to declare.

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