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Three new flavonoids from *Penthorum chinense* Pursh and their docking studies

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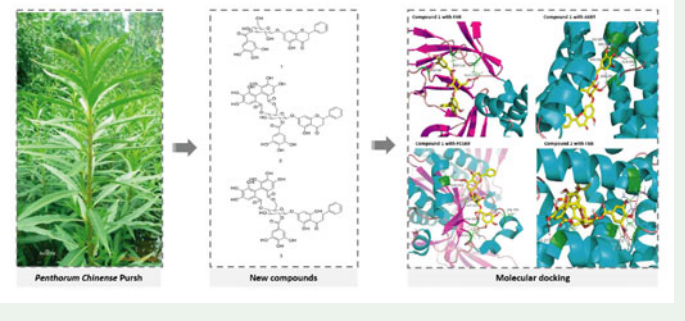
ABSTRACT

Three new flavonoids, pinocembrin-7-*O*-[3″-*O*-galloyl]-β-D-glucose (**1**), pinocembrin-7-*O*-[2″-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-D-glucose (**2**), 2′,6′-dihydroxydihydrochalcone-4′-*O*-[2″-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-D-glucopyranoside (**3**), and 12 known compounds (**4**–**15**) were isolated from *Penthorum Chinense* Pursh. The structures of all compounds were established mainly by NMR and MS experiments as well as the necessary chemical evidence. The anti-hyperlipidemic activities of the three new flavonoids were predicted by molecular docking.



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Penthorum chinense; flavonoid; molecular docking; anti-hyperlipidemic activity

1. Introduction

Penthorum chinense Pursh (Saxifragaceae), named 'GanHuang-Cao', is a traditional Chinese medicine with anti-oxidation and anti-hepatitis virus effect. It has been used as food and Chinese tea in the region of the Miao nationality for thousands of years (Wang et al. 2015). Gansu granule, prepared from the extracts of *P. chinense,* has been used in clinics to treat acute hepatitis (Zhang et al. 2013; Wang et al. 2014). Due to its

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wide pharmacological activities and clinical use, lots of bioactive constituents have been isolated from *P. chinense*, including flavonoids, triterpenoids, polyphenols, steroids and neolignans (Huang et al. 2014; Huang et al. 2018). Flavonoids are considered to be the main bioactive constituents of *P. chinense*. (Zhang et al. 2007; Huang et al. 2014; Huang et al. 2015). In our previous study, three flavonoids isolated from *P. chinense* have shown the protective effects on hepatic steatosis in HepG2 cells by activating the SIRT1/AMPK pathway (Guo et al. 2018). To seek for novel potential hypolipidemic compounds from *P. chinense*, three new flavonoid glycosides (**1–3**) along with 12 known compounds (**4–15**) have been isolated (Figure 1). In this paper, we describe the structural elucidation of these new compounds, as well as their anti-hyperlipidemic property predicted by molecular docking.

2. Results and discussion

2.1. Chemistry

Compound **1** was purified as salmon pink powder and its molecular formula was determined as $C_{28}H_{28}O_{13}$ by HR-ESI-MS spectrum (*m/z* 593.12486 $[M + Na]^+$, calcd. for

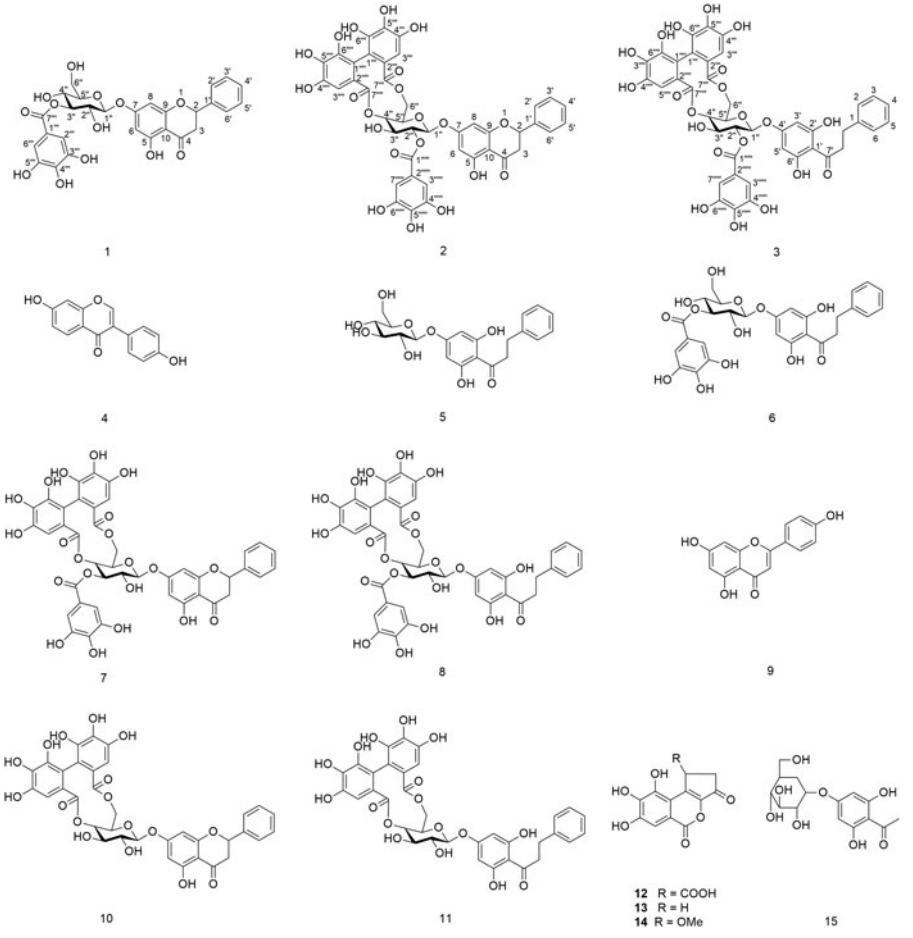

Figure 1. The structures of compounds **1**-**15**

593.12656). The UV spectrum showed absorption maximum at 280 and shoulder peak at 330 nm. The IR spectrum showed the presence of hydroxyl group (3406 cm^{-1}) and carbonyl group (1695 cm^{-1}). The flavanone skeleton was inferred by UV spectrum and the signals appearing at δ_C 197.4 (C-4) in the ^{13}C-NMR. The ^{1}H-NMR spectrum of **1** showed a mono-substituted aromatic protons at δ_H 7.44 (2H, d, $J = 7.2$ Hz, H-2′, 6′), 7.54 (2H, t, H-3′, 5′), 7.40 (1H, m, H-4′) on B-ring, together with two *meta*-coupled aromatic protons at δ_H 6.20 and 6.25 on A-ring. The resonance signals at δ_H 5.67 (1H, dd, $J = 12.8$, 2.4 Hz), 3.38 (1H, dd, $J = 16.8$, 12.8 Hz) and 2.77 (1H, dd, $J = 16.8$, 2.4 Hz) were reminiscent of the protons at the H-2 and H-3 positions in flavanone (Leu et al. 2004). The aglycone of **1** was proved to be pinocembrin (Wang et al. 2014). The ^{1}H-NMR spectrum of **1** also exhibited a series of sugar signals at δ 3.48–5.08. The ^{13}C NMR showed a sugar moiety at δ_C 99.7 (C-1″), 71.7 (C-2″), 77.8 (C-3″), 67.9 (C-4″), 77.3 (C-5″) and 60.7 (C-6″). The sugar was identified as D-glucose by acid hydrolysis. The glucopyranose moiety was determined to have a β-configuration at C-1″ with the large coupling constant of H-1″, a signal at δ_H 5.21 (d, $J = 7.2$ Hz). In HMBC spectrum, correlation between the anomeric proton H-1″ (δ_H 5.21) and C-7 (δ_C 165.5) suggested the glucosyl residue was located at the 7-*O*-position (Figure S1). In the ^{1}H-NMR spectrum, the symmetrical benzene ring at δ_H 7.00 (H-2‴ and H-6‴) suggested the presence of a galloyl group (Wang et al. 2006). In the HMBC spectrum, the galloyl group was shown to be at C-3″-*O*-position due to a down field shift of the H-3″ (δ_H 5.08) and the HMBC correlation between H-3″ (δ_H 5.08) and C-7‴ (δ_C 165.8) (Figure S1). The configuration of C-2 was inferred from the CD spectrum to 2R, which showed a positive cotton effect around 291.5 nm and a negative one around 337 nm (Pei et al. 1990). Accordingly, compound **1** was established as pinocembrin-7-*O*-[3″-*O*-galloyl]-β-D-glucose and has been named Penthorumside A.

Compound **2** was obtained as yellow powder and its molecular formula of elemental composition was determined to be $C_{42}H_{32}O_{21}$ by HR-ESI-MS spectrum (*m/z* 911.10153 $[M + K]^+$, calcd. for 911.10677). The ^{1}H and ^{13}C-NMR spectra of **2** (Table S1) are similar to those of compound **7**, Pinocembrin-7-*O*-[3″-*O*-galloyl-4″, 6″-hexahydroxydiphenoyl]-β-glucose (Wang et al. 2006), except for the connected position of one galloyl group. The sugar in **2** was considered to be linked to the C-7 of the aglycone based on the HMBC experiments. In the HMBC spectrum, the correlations from the anomeric proton H-1″ (δ_H 5.50), the H-6 (δ_H 6.17) and H-8 (δ_H 6.10) to C-7 (δ_C 164.6) were observed. Correlations between H-4″ (δ_H 4.72), H-6″ (δ_H 5.01 and δ_H 3.79) and the two carboxyl signals (δ_C 167.3 and δ_C 168.2) of HHDP were also observed, indicating that the HHDP group was connected to the C-4″/6″ position. This was consistent with the appearance of two low-field-shift signals at δ_H 4.72 (1H, m, H-4″) and 5.01 (1H, t, $J = 6.4$ Hz, H-6″) of the glucopyranosyl in the ^{1}H-NMR spectrum. The galloyl group was shown to be at C-2″ due to a downfield shift of the H-2″ (δ_H 5.06) and the HMBC correlation between the H-2″ and the C-1⁗ (δ_C 165.0) of the galloyl group (Figure S1). The CD spectrum of **2** also shows a negative cotton effect at 259.5 nm and a positive effect at 239 nm, indicating an S-configuration of the HHDP group (Wang et al. 2006; Huang et al. 2014). Thus, compound **2** was established as pinocembrin-7-*O*-[2″-*O*-galloyl-4″, 6″-hexahydroxydiphenoyl]-β-D-glucose and has been named Penthorumside B.

The molecular formula of Compound **3** was determined as $C_{42}H_{34}O_{21}$ by HR-ESI-MS spectrum (*m/z* 897.14995 $[M+Na]^+$, calcd. for 897.14848). The presence of a dihydrochalcone skeleton in the molecule could be easily deduced from the ^{1}H-NMR spectrum (Calanasan and Macleod 1998; Tanimoto et al. 2009), in which compound **3** showed the signals for a mono-substituted aromatic protons at δ_H [7.26 (H-2 and H-6), 7.23 (H-3 and H-5), 7.17 (H-4)] on A-ring, together with one singlet in the aromatic region δ_H 5.99 (s, H-3′, 5′) (She et al. 2011). The ^{13}C-NMR spectrum showed that compound **3** exhibited two methylene at δ_C 45.7 (C-β) and δ_C 30.4 (C-α). The ^{1}H and ^{13}C-NMR spectra of compound **3** are similar to those of compound **2** except for dihydrochalcone skeleton and showed signals attributed to a glucose moiety, a galloyl unit and an HHDP group. The sugar in **3** was considered to be linked to the C-4′ of the aglycone based on the HMBC experiments. The HMBC correlations from the anomeric proton H-1″ (δ_H 5.40), the H-3′ (δ_H 5.99) and H-5′ (δ_H 5.99) to C-4′ (δ_C 162.9) were observed. The correlations between H-4″ (δ_H 4.72), H-6″ (δ_H 5.03 and δ_H 3.81) and the two carboxyl signals (δ_C 167.4 and δ_C 168.2) of HHDP were also observed, indicating that the HHDP group was connected to the C-4″/6″ position. The galloyl group was linked to C-2″ via an ester bond due to the HMBC correlation between the H-2″ and the C-1‴″ (δ_C 165.1) (Figure S1). The CD spectrum showed that the absolute configurations of HHDP was S. Thus, compound **3** was established as 2′,6′-dihydroxydihydro-chalcone-4′-*O*-[2″-*O*-galloyl-4″, 6″-hexahydroxydiphenoyl]-β-D-glucopyranoside and has been named Penthorumside C.

The known compounds were identified as daidzein (**4**) (Diao et al. 2011), 2′,6′-dihydroxydihydrochalcone-4′-*O*-β-D-glucopyranoside (**5**) (Williams 1979), 2′,6′-dihydroxydihydro-chalcone-4′-*O*-[3″-*O*-galloyl]-β-D-glucopyranoside (**6**) (Ohtani et al. 2000), pinocembrin-7-*O*-[3″-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-D-glucose (**7**) (Wang et al. 2006), 2′,6′-dihydroxydihydro-chalcone-4′-*O*-[3″-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-D-glucopyranoside (**8**) (Ohtani et al. 2000), kaempferol (**9**) (Sloley et al. 2000), pinocembrin-7-*O*-[4″,6″-hexahydroxydiphenoyl]-β-D-glucose (**10**) (Hegde et al. 2003), thonningianin B (**11**) (Ohtani et al. 2000), brervifolincaboxylic acid (**12**) (Yan et al. 1996), brevifolin (**13**) (Guo et al. 1987), methyl brevifolincarboxylate (**14**) (Yao and Zuo 1993), 2,6-dihydroxyacetophenon-4-*O*-β-D-glucoside (**15**) (Chosson et al. 1998). Among them, compound **4** was isolated from this genus for the first time.

2.2. Molecular modeling

Molecular docking study was performed to investigate the interactions between four anti-hyperlipidemic targets including FXR, AMPK, PCSK9, ASBT and the three new flavonoids (**1**–**3**). The docking score and binding mode were evaluated with docking studies (Table S2, Figure S22). The phenolic hydroxyl (Ph-O-H, H-bond acceptor) groups in galloyl or HHDP showed strong hydrogen bond interactions with amino acid residue (H-bond donor) in all the three ligands. In compound **1**, H-bond interaction was observed at oxygen atom (2″-O-H or 6″-O-H) of the glucopyranosyl unit with amino acid residue. In compound **2**, H-bond interactions were also observed at position of oxygen atom (5-O-H) in the A-ring or the carbonyl (C = O) group in the C-ring with amino acid residue.

In compound **3**, H-bond interactions was observed in the oxygen atom of the 6′-OH and 7′ C = O, respectively (Figure S22). Compounds **2** and **3** showed higher docking scores for binding with FXR (10.5725 and 9.8215) than the co-crystallized ligand 1 (4-({(2S)-2-[2-(4-chlorophenyl)-5,6-difluoro-1H-benzimidazol-1-yl]-2-cyclo-hexylacetyl}amino)-3-methylbenzoic acid, $C_{29}H_{26}ClF_2N_3O_3$), indicating their effects by activating hepatic FXR to maintain bile acid (BA) homeostasis and thus regulating lipid metabolism. Compound **1** showed better binding action with AMPK, ASBT and PCSK9 (5.2458, 7.0601 and 3. 7019, respectively) than compounds **2** and **3**. Further investigations are in progress on enzyme inhibitory activity and cytotoxicity to validate these results.

3. Experimental

3.1. General experimental procedures

IR and UV spectra were measured on Thermo Nicolet iS5 spectrophotometer (Tewksbury, MA, US) and Agilent 8453 UV-visible Spectroscopy System (Agilent, Mississauga, Ontario, Canada), respectively. The NMR spectra including ^{1}H, ^{13}C and 2D-NMR were recorded on a Bruker Avance II spectrometer (Bruker Co., Karlsruhe, Germany) operating at 800 MHz for ^{1}H- and 200 MHz for ^{13}C- in DMSO-d_6 and the chemical shifts were expressed in δ values (ppm). CD spectra were obtained using a JASCO J-810 Circular Dichroism Chiroptical spectrometer (JASCO, Tokyo, Japan). The HR-ESI-MS data were measured on FT-ICR-MS (Bruker Co., Karlsruhe, Germany) in *m/z*. MCI gel (CHP20/P120, Mitsubishi Chemical Co., Japan) was used for column chromatography. HPLC was carried on Shimadzu LC-6A (Kyoto, Japan) and the detector was Shimadzu SPD-10A. A semi-preparative RP-HPLC column (Hibar Purospher STAR® RP-18e Semi-Prep 5 μm, 10 × 250 mm, Merck & Co., Inc., NJ, USA) was employed for the isolation.

3.2. Plant materials

P. chinense was provided by Sichuan New Lotus Traditional Chinese Herb Limited Company, Chengdu, Sichuan, in January 2012 and authenticated by Zhang Li Senior Engineer of this company. A voucher specimen (No. 111138) was deposited at School of Traditional Chinese Medicine, Capital Medical University, China.

3.3. Extraction and isolation

The extract (1 kg) was prepared from the dry aerial parts of *P. chinense* (8 kg) by the same method as descripted in the previous study (Wang et al. 2014). The extract was fractionated by MCI column chromatography, eluted with the EtOH-H_2O (20:80, 40:60, 60:40, 85:15) gradient to provide four fractions (Frs I-IV), respectively. The residue in Fr. III were combined (50 g) and subjected to the silica gel column by elution with CH_2Cl_2: MeOH (99:1–88:12), which afforded Fr.1-39. The sub-fraction Fr. III-Fr. 33 (1 g) was dissolved in methanol and isolated by semi-preparative HPLC using ACN (A)-H_2O (B) (0–10 min 20%A, 10–50 min 20%–50%A, 50–60 min 50%A, v/v, 200 μL × 30 runs) to afford compound 1 (25.0 mg, t_R 45.2 min), compound 5 (29.7 mg, t_R 45.9 min), compound 2 (10.3 mg, t_R 46.7 min), compound 3 (7.4 mg, t_R 51.2 min) and compound 6

(7.4 mg, t_R 50.3 min). Fr. III-Fr. 36 (1 g) was isolated by semipreparative HPLC using the same elution condition as Fr. III-Fr. 33 to afford compound 7 (34.9 mg, t_R 50.8 min) and compound 8 (38.1 mg, t_R 55.0 min). Fr. III-Fr. 1 (0.6 g), was separated by semipreparative HPLC using MeOH-H_2O (60:40, v/v) to yield compound 4 (5 mg) and compound 9 (10 mg). Fr. III-Fr.24 (0.6 g) and Fr. III-Fr.29 (0.5 g) were separated by semipreparative HPLC using MeOH-H_2O (60:40, v/v) to yield compound 10 (8 mg) and compound 11 (5 mg), respectively. The residue in Fr. I were combined (50 g) and isolated by C_{18} column chromatography (MeOH: H_2O, 20:80–100:0), which afforded Fr.1-20. Fr. I-Fr. 5 (1.1 g) was subjected to semipreparative HPLC using ACN-H_2O (23:67, v/v) to yield compound 12 (25.0 mg, t_R 7.0 min), compound 13 (10.5 mg, t_R 13.0 min) and compound 14 (5.9 mg, t_R 15.5 min). Fr. I-Fr.10 ~ 16 were combined and subjected to semipreparative HPLC using MeOH-H_2O (30:70, v/v) to yield compound 15 (20 mg, t_R 16.0 min).

Pinocembrin-7-*O*-[3″-*O*-galloyl]-β-D-glucose (**1**): Salmon pink powder; HR-ESI-MS *m/z* 593.12486 $[M + Na]^+$ (calcd. for $C_{28}H_{26}O_{13}Na$: 593.12656); ^{1}H- and ^{13}C-NMR data, see Table S1.

Pinocembrin-7-*O*-[2″-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-D-glucose (**2**): Yellow powder; HR-ESI-MS *m/z* 911.10153 $[M + K]^+$ (calcd. For $C_{42}H_{32}O_{21}K$: 911.10677); ^{1}H- and ^{13}C-NMR data, see Table S1.

2′,6′-dihydroxydihydrochalcone-4′-*O*-[2″-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-D-glucopyranoside (**3**): Yellow solid; HR-ESI-MS, at *m/z* 897.14995 $[M + Na]^+$ (calcd. for $C_{42}H_{34}O_{21}Na$: 897.14848); ^{1}H- and ^{13}C-NMR data, see Table S1.

3.4. Acid hydrolysis of 1–3 and sugar analysis

The acid hydrolysis tests of compounds **1**–**3** were performed as described in the supplementary material. The monosaccharide composition was determined by a PMP derivatization method by HPLC. The absolute configuration of the sugar is determined by comparing the retention time (t_R) of the derivative of the sugar with the derivative of the monosaccharide reference prepared in the same manner. The t_R values of D-glucose was 17.4 min.

3.5. Molecular docking

The docking studies of the three compounds were performed with energy-metabolism-related molecular targets, including FXR (Protein Data Bank identifier (PDB ID): 3OLF), AMPK (PDB ID: 4ZHX), ASBT (PDB ID: 3ZUX) PCSK9 (PDB ID: 4OV6). The virtual screening and ligand-receptor interaction were evaluated using the same method as previously reported (Guo et al. 2018). The docking studies of the co-crystallized ligands and the targets were also done.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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