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Two new *ent*-kaurane glucosides from the fruits of *Xanthium strumarium* subsp. *sibiricum*

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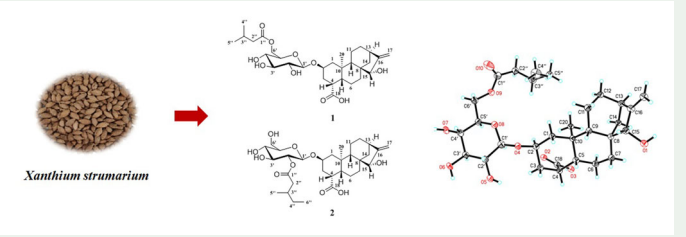
ABSTRACT

The chemical investigation of the fruits of *Xanthium strumarium* (Asteraceae) led to the isolation of two new *ent*-kauranoid glucosides named 2-*O*-(6-*O*-isocaleryl-*β*-D-glucopyranosyl) atractyligenin (**1**) and 2-*O*-(2-*O*-isovaleryl-*β*-D-glucopyranosyl) atractyligenin (**2**), together with one known compound. Their structures were established by comprehensive spectroscopic analysis coupled with single-crystal X-ray diffraction and electronic circular dichroism data. All compounds and their aglycone were evaluated for their anti-proliferative activities *in vitro* against three human cancer cell lines.



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Xanthium strumarium; *ent*-kaurane glucosides; structural elucidation

1. Introduction

The genus *Xanthium* belongs to Asteraceae family, with four species and two varieties growing in mainland China. The dry fruits of *Xanthium strumarium* subsp. *sibiricum*, known as *Xanthii fructus* in TCM, are widely used to treat headache, fever, sinusitis, chronic rhinitis and herpes (Shi et al. 2015). Previous research indicated that *Xanthium strumarium* had multiple chemical composition, mainly including sesquiterpene

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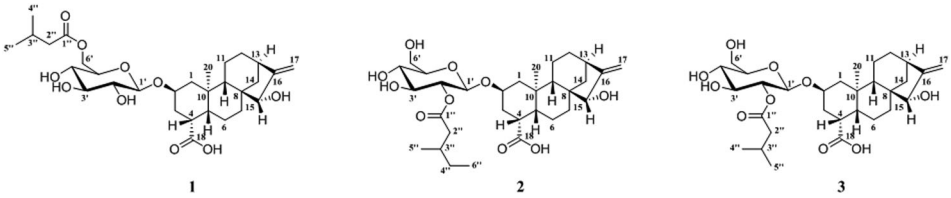

Figure 1. Chemical structures of isolated compounds **1**–**3**.

lactone, phenolic acid, thiazinedione and *ent*-kauranoid glucosides (Sonia et al. 1996; Zhang et al. 2006; Kan et al. 2011; Cheng et al. 2013; Chen et al. 2015; Yin et al. 2016; Xu et al. 2017), and these constituents showed anti-inflammatory, antibacterial, antiviral, and antitumor activities (Lin et al. 2014; Romero et al. 2015; Yeom et al. 2015; Jiang et al. 2016; 2019). As a part of our continuing studies on the bioactive constituents from *Xanthium strumarium*, 75% EtOH extract of the fruits of this species was investigated, thereby two new *ent*-kauranoid glucosides (**1** and **2**) and one known compound (**3**) were isolated and characterized, as shown in Figure 1. And their bioactivities against the human liver cancer cells, larynx cancer cells, and colon cancer cells were evaluated. Herein, the isolation and structure elucidation of two new compounds, as well as the bioactivities of all the isolated compounds are reported.

2. Results and discussion

The molecular formula of compound **1** was deduced to be $C_{30}H_{46}O_{10}$ (eight indices of hydrogen deficiency) based on the pseudomolecular ion at *m/z* 565.3008 $[M\text{-}H]^-$ (calcd for 565.3013) from the HRESIMS analysis. The ^{1}H NMR data of **1** indicated the presence of three methyls [δ_H 0.95 (3H × 2, d, $J = 6.6$ Hz, 4″, 5″-CH_3) and 1.00 (3H, s, 20-CH_3)], one olefinic methylene [δ_H 5.18 (1H, br s, H-17a) and 5.08 (1H, br s, H-17b)]. Moreover, a set of signals between δ_H 3.10–4.50 in ^{1}H NMR spectrum in combination with the signal for an anomeric methine (δ_H 4.42, δ_C 103.4), indicated the presence of a sugar moiety. The coupling constant of anomeric proton signal (δ_H 4.42, d, $J = 8.0$ Hz, H-1′) indicated that the sugar was attached to aglycone via a β-linkage. The acid hydrolysis of **1** afforded D-glucose, which was identified by HPLC analysis. The ^{13}C NMR and HSQC data for **1** revealed 30 carbon resonances including two nonprotonated olefinic carbons (δ_C 160.4 and 109.2), two carbonyl carbons (δ_C 179.0 and 174.7), three methyls (δ_C 22.9, 22.9, and 17.4). Apart from aforementioned 7 carbons, the remaining 23 carbon signals were assigned to nine methylenes (one oxygenated), twelve tertiary carbons (seven oxygenated), and two quaternary carbons. The ^{1}H and ^{13}C NMR data for **1** were similar to those for previously known compound, 2-*O*-(2-*O*-Isocaleryl-β-D-glucopyranosyl)-4-*epi* atractyligenin (Liu et al. 2012), suggesting compound **1** might have a skeleton of *ent*-kaurane glucoside, which was further confirmed by ^{1}H-^{1}H COSY and HMBC experiments (Figure S1). After careful 2 D NMR data analysis, the main difference between these two compounds were the substitution position of the isobutyryl group. The key HMBC correlation from H-6′ to C-1″ (δ_C 174.7) revealed the isobutyryl group was attached to C-6′ in **1**. Therefore, the planar structure of **1** was elucidated. On biogenetic grounds, compound **1** was confirmed as an *ent*-kaurane

glycoside with the configuration of Me-20 being α-oriented. The relative configuration of **1** was deduced from coupling constants, the NOESY experiment, and X-ray diffraction, as shown in Figure S1. The NOE correlation of H-2 with Me-20 indicated that they were on the same side of ring A and H-2 was assigned to be α-oriented. The NOE correlations of H-9 with H-5 and H-15 indicated that these protons were are oriented on the same side of ring B. And the observed $^{3}J_{\text{H-2, H-1}\beta}$ value of 11.9 Hz (Brucoli et al. 2012) and the NOE correlation of H-1β with H-9 indicated that H-5, H-9 and H-15 were β-oriented. The assignment of the relative configuration of **1** was further confirmed by X-ray diffraction (Figure S2). However, due to the tiny crystal form, the flack parameter of **1** was too large, which would lead to an uncertain absolute configuration. Therefore, the olefin octant rule (Scott and Wrixon 1971) was applied to establish the absolute configuration of **1**, the absolute configuration of C-15 was assigned as *S* by the observation of a negative Cotton effect ($\Delta\varepsilon - 3.0$) at 205 nm in the electronic circular dichroism (ECD) spectrum (Figure S23) for aglycone. Finally, the absolute configuration of **1** was assigned as 2*R*, 4*R*, 5*R*, 8*R*, 9*S*, 10*R*, 13*R*, 15*S*, and named 2-*O*-(6-*O*-isocaleryl-β-D-glucopyranosyl) atractyligenin.

The molecular formula of compound **2** was established as $C_{31}H_{48}O_{10}$ (eight indices of hydrogen deficiency) on the basis of HRESIMS at *m/z* 579.3161 $[M\text{-}H]^-$ (calcd for 579.3169) and ^{13}C NMR data. The ^{13}C NMR and HSQC spectra indicated the presence of 31 carbons, including two nonprotonated olefinic carbons (δ_C 160.4 and 109.1), two carbonyl carbons (δ_C 178.9 and 174.1), three methyls (δ_C 19.3, 17.3 and 11.8), and the remaining 24 carbon signals were assigned to ten methylenes (one oxygenated), twelve tertiary carbons (seven oxygenated), and two quaternary carbons. These data of **2** were reminiscent of those **1**, especially the typical signals related to the skeleton of *ent*-kaurane diterpenoid [$\delta_{C/H}$ 17.3/0.99 (C-20), 74.1/4.23 (C-2), 83.6/3.76 (C-15), 109.1/5.18, 5.07 (C-17), 178.9 (C-18)] and a set of sugar signals (δ_H 3.10–4.70), suggesting the same skeleton of the two compounds with *ent*-kaurane glycoside. Careful analyses of the ^{1}H and ^{13}C NMR data resulted that these signals of compound **2** were very similar to those of fructusnoid D (Cheng et al. 2019) except for the chemical shifts of C-3′, suggested that **2** might be a 3′-desulfated analogue of fructusnoid D, which was further confirmed by ^{1}H-^{1}H COSY and HMBC experiments (Figure S1). According to the aforementioned data, the planar structure of **2** was elucidated. In the NOESY spectrum of **2** showed the same NOE correlations as **1**, suggesting the relative configuration of **2** was consistent with that of **1**. Therefore, the absolute configuration of **2** was assigned as 2*R*, 4*R*, 5*R*, 8*R*, 9*S*, 10*R*, 13*R*, 15*S* by displaying a negative Cotton effect ($\Delta\varepsilon - 3.9$) at 205 nm in the electronic circular dichroism (ECD) spectrum (Figure S23) for aglycone, and named as 2-*O*-(2-*O*-isovaleryl-β-D-glucopyranosyl) atractyligenin.

Apart from compounds **1** and **2**, one known compound was identified as 3′, 4′-desulfated atractyloside (**3**) by comparing ^{1}H and ^{13}C NMR data with the literatures (Cheng et al. 2019).

The cytotoxic effect of compounds **1**–**3** and their aglycone on HepG2 cells, HCT 116 cells and Hep-2 cells were investigated. However, none of the isolates obtained showed cytotoxic activities against the studied cell lines (Figure S25).

3. Experimental

3.1. General experimental procedures

Silica gel (100–200 mesh and 200–300 mesh, Qingdao Haiyang Chemical Co., LTD), Sephadex LH-20 (Pharmacia, Sweden) and ODS-A-HG (50 μm) (YMC Group, Japan) were used for column chromatography. IR spectroscopic data were measured on a Bruker IFS 55 spectrometer with KBr pellets. UV spectra were recorded on a Shimadzu UV 2201 spectrophotometer. Optical rotation was obtained in CH_3OH at 20 °C, using a AUTOPOLV polarimeter (Rudolph, USA). The CD was recorded on a JASCO J-1500 spectropolarimeter. ^1H and ^{13}C NMR spectra were obtained on Bruker Avance III 600 MHz (600 MHz for ^1H and 150 MHz for ^{13}C) spectrometers. HRESIMS was performed on an Waters Xevo G-2-S UPLC-Q/TOF MS (Waters, USA). Preparative HPLC (LC-6AD) was performed on CAPCELL PAK C-18 column (5 μm, 10 × 250 mm) with SPD-20A. All reagents were HPLC or analytical grade and were purchased from Tianjin Damao Chemical Company.

3.2. Plant material

The fruits of *Xanthium strumarium* subsp. *sibiricum* were purchased from Tong Ren Tang Co., Ltd. and then identified by Professor Lijuan Zhang, Tianjin University of Traditional Chinese Medicine. A voucher specimen (herbarium No. 20151015) has been deposited in the lab.

3.3. Extraction and isolation

The dry fruits of *Xanthium strumarium* subsp. *sibiricum* (29 kg) were extracted with 75% ethanol (3 × 300 L, each 2 h) and sequentially with petroleum ether and ethyl acetate saturated with water, successively. The ethyl acetate layer (890 g) was subjected to passage over a silica gel chromatography column, eluted with a gradient of CH_2Cl_2/MeOH (from 100:1 to 0:1), to obtain eight fractions, Fr.1–Fr.8. Fr.4 (30 g) was subjected to ODS column to afford five fractions, Fr.41–Fr.45. Fr.41 (3 g) was separated on sephadex LH-20 column chromatography that eluting with MeOH to yield six fractions, Fr.411–Fr.416. Fr.411 (600 mg) was subjected to silica gel chromatography column that using a gradient of CH_2Cl_2/MeOH/H_2O (from 100:3:1 to 10:3:1) to give three fractions, Fr.4111–Fr.4113. Fr.4112 (100 mg) was purified by semi-preparative HPLC (ACN/H_2O 30%) to afford **1** (t_R = 19.0 min; 10 mg) and **2** (t_R = 25.6 min; 5 mg). Fr.4113 (80 mg) was purified with HPLC (ACN/H_2O 30%) to yield **3** (t_R = 24.8 min; 8 mg).

3.4. Physical and spectroscopic data of isolated compounds

2-*O*-(6-*O*-isocaleryl-β-D-glucopyranosyl) atractyligenin (**1**): Initially obtained as white amorphous powder, by recrystallization in CH_2Cl_2/MeOH (1:1), the colorless needles were obtained; mp 172.7–173.2 °C; $[\alpha]_D^{25}$ + 30.3 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3628, 2923, 1717, 1650 cm^{-1}; UV (MeOH) λ_{max} log(ε) 202 (2.73) nm; HRESIMS *m/z* 565.3008 [M-H]$^-$ (calcd 565.3013); ^1H NMR (600 MHz, CD_3OD): δ 2.31 (1H, dd, *J* = 12.0, 3.7 Hz, H-1α), 0.80

(1H, dd, $J = 12.0$, 11.9 Hz, H-1β), 4.23 (1H, m, H-2), 2.47 (1H, m, H-3), 1.34 (1H, m, H-3), 2.67 (1H, m, H-4), 1.49 (1H, m, H-5), 1.93 (1H, m, H-6), 1.64 (1H, m, H-6), 1.69 (1H, m, H-7), 1.45 (1H, m, H-7), 1.06 (1H, br d, $J = 7.6$ Hz, H-9), 1.62 (1H, m, H-11), 1.48 (1H, m, H-11), 1.63 (1H, m, H-12), 1.47 (1H, m, H-12), 2.71 (1H, m, H-13), 1.87 (1H, br d, $J = 11.6$, H-14), 1.40 (1H, dd, $J = 11.6$, 5.0 Hz, H-14), 3.76 (1H, s, H-15), 5.18 (1H, br s, H-17a), 5.08 (1H, br s, H-17b), 1.00 (3H, s, H-20), 4.42 (1H, d, $J = 8.0$ Hz, H-1′), 3.12 (1H, dd, $J = 9.0$, 8.0 Hz, H-2′), 3.35 (1H, dd, $J = 9.3$, 9.0 Hz, H-3′), 3.25 (1H, t, $J = 9.3$ Hz, H-4′), 3.47 (1H, ddd, $J = 9.3$, 6.5, 1.6 Hz, H-5′), 4.46 (1H, dd, $J = 11.7$, 1.6 Hz, H-6′), 4.13 (1H, dd, $J = 11.7$, 6.5 Hz, H-6′), 2.21 (2H, d, $J = 7.6$ Hz, H-2″), 2.07 (1H, m, H-3″), 0.95 (3H, d, $J = 6.6$ Hz, H-4″), 0.95 (3H, d, $J = 6.6$ Hz, H-5″); ^{13}C NMR (150 MHz, CD_3OD): δ 49.0 (C-1), 74.3 (C-2), 35.7 (C-3), 44.8 (C-4), 50.5 (C-5), 26.7 (C-6), 36.3 (C-7), 48.9 (C-8), 54.5 (C-9), 41.9 (C-10), 19.4 (C-11), 33.8 (C-12), 43.8 (C-13), 37.3 (C-14), 83.6 (C-15), 160.4 (C-16), 109.2 (C-17), 179.0 (C-18), 17.4 (C-20), 103.4 (C-1′), 75.2 (C-2′), 78.0 (C-3′), 71.9 (C-4′), 75.3 (C-5′), 64.7 (C-6′), 174.7 (C-1″), 44.3 (C-2″), 27.0 (C-3″), 22.9 (C-4″), 22.9 (C-5″).

2-*O*-(2-*O*-isovaleryl-β-D-glucopyranosyl) atractyligenin (**2**): white amorphous powder; $[\alpha]_D^{25}$ + 28.9 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3628, 2921, 1716, 1650 cm^{-1}; UV (MeOH) λ_{max} log(ε) 201 (2.85) nm; HRESIMS *m/z* 579.3161 [M-H]$^-$ (calcd 579.3169); ^{1}H NMR (600 MHz, CD_3OD): δ 2.30 (1H, dd, $J = 12.0$, 3.6 Hz, H-1α), 0.75 (1H, t, $J = 12.0$ Hz, H-1β), 4.23 (1H, m, H-2), 2.40 (1H, m, H-3), 1.20 (1H, m, H-3), 2.66 (1H, m, H-4), 1.45 (1H, m, H-5), 1.92 (1H, m, H-6), 1.64 (1H, m, H-6), 1.68 (1H, m, H-7), 1.44 (1H, m, H-7), 1.05 (1H, br d, $J = 7.5$ Hz, H-9), 1.62 (1H, m, H-11), 1.47 (1H, m, H-11), 1.63 (1H, m, H-12), 1.47 (1H, m, H-12), 2.70 (1H, m, H-13), 1.87 (1H, m, H-14), 1.39 (1H, m, H-14), 3.76 (1H, s, H-15), 5.18 (1H, br s, H-17a), 5.07 (1H, br s, H-17b), 0.99 (3H, s, H-20), 4.60 (1H, d, $J = 8.0$ Hz, H-1′), 4.68 (1H, dd, $J = 9.0$, 8.0 Hz, H-2′), 3.50 (1H, dd, $J = 9.2$, 9.0 Hz, H-3′), 3.38 (1H, dd, $J = 9.5$, 9.2 Hz, H-4′), 3.32 (1H, ddd, $J = 9.5$, 5.3, 1.3 Hz, H-5′), 3.85 (1H, dd, $J = 12.0$, 1.3 Hz, H-6′), 3.69 (1H, dd, $J = 12.0$, 5.3 Hz, H-6′), 2.37 (1H, dd, $J = 14.8$, 6.2 Hz, H-2″), 2.17 (1H, dd, $J = 14.8$, 8.0 Hz, H-2″), 1.88 (1H, m, H-3″), 1.43 (1H, m, H-4″), 1.24 (1H, m, H-4″), 0.97 (3H, d, $J = 6.7$ Hz, H-5″), 0.91 (3H, t, $J = 7.4$ Hz, H-6″); ^{13}C NMR (150 MHz, CD_3OD): δ 48.8 (C-1), 74.1 (C-2), 35.8 (C-3), 44.7 (C-4), 50.6 (C-5), 26.7 (C-6), 36.3 (C-7), 49.0 (C-8), 54.5 (C-9), 41.9 (C-10), 19.8 (C-11), 33.7 (C-12), 43.8 (C-13), 37.3 (C-14), 83.6 (C-15), 160.4 (C-16), 109.1 (C-17), 178.9 (C-18), 17.3 (C-20), 101.1 (C-1′), 75.2 (C-2′), 76.4 (C-3′), 71.8 (C-4′), 78.0 (C-5′), 62.7 (C-6′), 174.1 (C-1″), 42.6 (C-2″), 33.3 (C-3″), 30.5 (C-4″), 19.3 (C-5″), 11.8 (C-6″).

3.5. Acid hydrolysis of 1 and 2

Each compounds (2.0 mg) was heated in 3 M CF_3COOH (3.0 mL) for 3 h in a water bath. Each mixture was extracted three times with EtOAc. The aqueous layer was evaporated to dryness with ethanol in vacuo until neutral. The residue was dissolved in pyridine (1.0 mL), and then added the L-cysteine methyl ester (1.0 mg) and o-tolyisothiocyanate (1.0 mL) for derivatization. The reaction mixture was centrifuged and precipitate was removed. Then the solution was analyzed by Water e2695 HPLC system (CAPCELL PAK C-18 column), eluting with A (0.1% formic acid): B (acetonitrile) = 83: 17 (v/v) at 1.0 mL/min. The column temperature was set at 30 °C and the

effluent was monitored at 250 nm. The D-glucose (t_R = 44.2 min) was determined by comparing with the standard sugar (Figure S24).

3.6. Cell viability assay

HepG2 cells, Hep-2 cells, and HCT 116 cells were seeded onto a 96-well culture plates at a density of 5×10^3 cells/well for 24 h respectively, and then treated with various concentration of the tested compounds (3.125, 6.25, 12.5, 25, and 50 μM). After 48 h, the cell viability was conducted by MTT assay as previously described (Kang et al. 2010; Fan et al. 2018).

3.7. X-ray crystallographic experiment

CCDC 1993831 contains the supplementary crystallographic data for this paper. The detailed experimental procedures and crystal data were described in the Supplementary Material.

Disclosure statement

No potential conflict of interest was reported by the authors.

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