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New α-ditetralonyl glucoside from the green walnut husk of *Juglans mandshurica*

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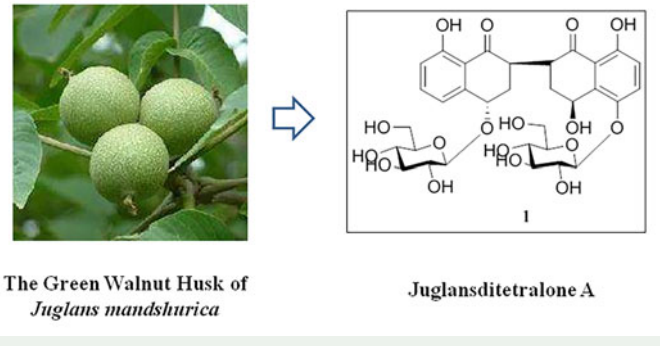
ABSTRACT

One new α-ditetralonyl glucoside (**1**), was isolated from the green walnut husk of *Juglans mandshurica* (Juglandaceae), together with twelve known compounds (**2–13**). The structure of the new compound was determined as (2*R*,4*S*,10*S*,12*S*)-2-[7-(12,13,16-trihydroxy-α-tetralonyl-13-*O*-β-D-glucopyranoside)]- 4,8-dihydroxy-α-tetralone-4-*O*-β-D-glucopyranoside (**1**), on the basis of detailed spectroscopic analyses, and acidic hydrolysis. Compounds **6**, **7** and **11** were isolated from the genus *Juglans* for the first time. Compound **1–13** showed weak cytotoxic against A549 and HeLa cell lines.



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1. Introduction

The green walnut husk of *Juglans mandshurica* Maxim. (Juglandaceae), commonly called Qinglongyi, has been used as a traditional medicine for treatment of cancer and dermatosis in China (Park et al. 2017). It has been reported that *J. mandshurica* is rich in naphthoquinones (Chen et al. 2015; Guo et al. 2015; Jin et al. 2016),

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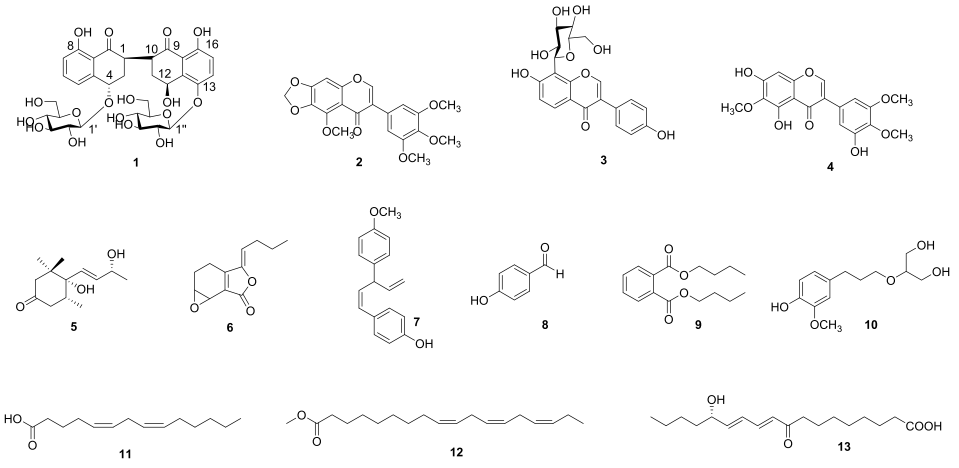

Figure 1. The structure of compounds from the green walnut husks of *J. mandshurica*.

diarylheptanoids (Jin et al. 2015; Li et al. 2017) and flavonoids (also their glycosides) (Wang et al. 2017; Xu and Bao 2014). As a continuation of our phytochemical investigations, one new α-ditetralonyl glucoside (**1**) and twelve known compounds **2**–**13** (Figure 1) were isolated from the *n*-butanol solvent fraction of the green walnut husk of *J. mandshurica*. Herein, we report the isolation, structural elucidation and cytotoxic activity of the compounds.

2. Results and discussion

The 70% ethanol extract of the dried green walnut husk of *J. mandshurica* was subjected to multiple chromatographic steps over silica gel, Sephadex LH-20 and recycling preparation HPLC. Thirteen compounds were obtained, including one new compound, (2*R*,4*S*,10*S*,12*S*)-2-[7-(12,13,16-trihydroxy-α-tetralonyl-13-*O*-β-D-glucopyranoside)]-4,8-dihydroxy-α-tetralone-4-*O*-β-D-glucopyranoside (**1**) and 12 known compounds, irisfloretin (**2**) (Liu et al. 2011), puerarin (**3**) (nakamura et al. 2011), irigenin (**4**) (Ibrahim et al. 2012), 4,5-dihydroblumenol (**5**) (Xiong et al. 2017), (*Z*)-6,7-epoxyligustilide (**6**) (grech et al. 1994), 4′-*O*-methylnyasol (**7**) (Tao et al. 2011), 4-hydroxybenzaldehyde (**8**) (Hsu et al. 2009), dibutylphthalate (**9**) (Wang et al. 2012), 2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]-propane-1,3-diol (**10**) (Zhao et al. 2017), tetradeca-5,8-dienoic acid (**11**) (Alamsjah et al. 2007), linolenic acid (**12**) (Lee 2010), porrigenic acid (**13**) (Hasegawa et al. 2007). The structures of **1-13** (Figure 1) were identified by physical data analyses, including 1 D and 2 D NMR, and HRESIMS. The sugar residues were identified by GC analyses after hydrolysis.

Compound **1** was obtained as a white amorphous powder. The molecular formula of $C_{32}H_{28}O_{17}$ was determined on the basis of the HR-ESI-MS (*m/z* 735.1998, $[M + Na + H_2O]^+$). Acidic hydrolysis of **1** gave D-glucose as the monosaccharide residue. The ^{1}H NMR and ^{13}C NMR data of **1** exhibited the signals arising from two CO group at δ_C 206.4(C-9), 201.0(C-1), one benzene ring at δ_H 7.50 (1H, d, $J = 7.7$ Hz, H-7), 7.31 (1H, d, $J = 7.9$ Hz, H-6), 7.12 (1H, d, $J = 7.7$ Hz, H-5), the other benzene ring at δ_H 7.55 (1H, d, $J = 9.1$ Hz, H-14), 6.89 (1H, d, $J = 9.1$ Hz, H-15), β-glucopyranosyl moiety [anomeric H-

atom at δ_H 4.82 (1H, d, $J = 7.7$ Hz, H-1″), 4.62 (1H, d, $J = 7.7$ Hz, H-1′)] and C-atom signals at δ_C 104.5(C-1″), 103.8(C-1′), 78.3(C-3″), 78.0(C-3′/C-5′), 77.9(C-5″), 75.3(C-2″), 75.2(C-2′), 71.5(C-4″), 71.2(C-4′), 62.6(C-6″) and 62.5(C-6′). The linkage of the two sugar moieties at OH-C(4) and OH-C(12) were established from the HMBC correlations between δ_H 4.62 (1H, d, $J = 7.8$ Hz, H-1′) and δ_C 69.7(C-4), and between δ_H 4.82 (1H, d, $J = 7.8$ Hz, H-1″) and δ_C 61.2(C-12). The ^{13}C NMR spectral data combined with HSQC spectrum exhibited thirty-two carbon signals, including two carbonyl carbons [δ_C 206.5(C-9), 201.0(C-1)], twelve armomatic carbons [δ_C 159.0(C-16), 156.9(C-8), 148.8(C-13), 134.6(C-12a), 134.3(C-4a), 130.5(C-6), 129.6(C-8a), 128.4(C-14), 122.0(C-5), 119.0(C-15), 118.9(C-7), 116.1(C-16a)], two anomeric carbons [δ_C 104.5(C-1″), 103.8(C-1′)], ten oxygenated methine carbons [δ_C 78.3(C-3″), 78.0(C-3′/C-5′), 77.9(C-5″), 75.3(C-2″), 75.2(C-2′), 71.5(C-4″), 71.2(C-4′), 69.7(C-4), 61.2(C-12)], two oxygenated methylene carbons [δ_C 62.6(C-6″), 62.5(C-6′)], two sp^3 hybridized methine carbons [δ_C 34.0(C-2), 33.6(C-10)] and two sp^3 hybridized methylene carbons [δ_C 30.2(C-3), 30.0(C-11)]. These NMR characteristics resembled those observed for (4*S*)-4,8-dihydroxy-α-tetralone-4-*O*-β-D-glucopyranoside (Liu et al. 2004) and (4*S*)-4,5,8-trihydroxy-α-tetralone-5-*O*-β-D-glucopyranoside (Fujimoto et al. 1998). However, instead of a α-tetralonyl glucoside moiety in the known compounds, compound **1** had two α-tetralonyl glucoside moieties in view of the HR-ESI-MS (*m/z* 735.1998). The linkage of the two α-tetralonyl glucoside moieties at C-2 and C-9 was established from the ^{1}H-^{1}H COSY correlations between δ_H 3.15 (1H, m, H-2) and δ_H 2.51 (1H, m, H-10). The HMBC correlations also provided the linkage of the two α-tetralonyl glucoside moieties. The second α-tetralonyl glucoside moiety was located at C-2 based on HMBC correlation between H-10/H-11$_b$ and C-2. The relative configuration of compound **1** was established by NOESY spectrum (Figure S9). NOESY correlation between H-4 and H-9 suggested the β-orientation of H-4 and H-9. The absolute configuration of the saccharides was determined to be D-glucose by GC analysis of chiral derivatives in the hydrolysate of this compound. As for the absolute configuration of the chiral carton, (4*S*,12*S*)-**1** determined on the basis of negative Cotton at ca. 190-230 nm in the CD spectrum of **1** (see Figure S2) and comparison of its optical rotation ([α]20 D: -65 in MeOH) with that of literature (Machida et al. 2005).

After further comprehensive analysis of its NMR spectra (see Figure S3–S8), compound **1** was identified as (2*R*,4*S*,10*S*,12*S*)-2-[7-(12,13,16-trihydroxy-α-tetralonyl-13-*O*-β-D-glucopyranoside)]- 4,8-dihydroxy-α-tetralone-4-*O*-β-D-glucopyranoside and named Juglansditetralone A.

As a unique quinone compound, naphthaquinone is widespread in the natural plant and showed a series of bioactivities (Lieberherr et al. 2017). Previous review showed that the genus *Juglans* was rich for α-tetralone (also their glycosides) (Jin, Sun, Li, Diao, Zhang, Cui, Son, Zhou and Li 2016). However, very few α-ditetralone were reported from the genus (Paedhasaradhi and Hari Babu 1978). In this study, the new compound **1** bears two α-tetralonyl glucoside moiety, which may serve as an important structural characteristic. It might be used to distinguish Juglandaceae from other genus, and is also rich in quinone.

Compound **6** was first isolated from the roots of *Angelicae sinensis*, which belongs to isobenzofuran. This structure was responsible for the various activities such as increasing coronary blood flow, relaxing smooth muscle, immunostimulating,

inhibiting platelet aggregation, preventing gynecological diseases treating menstrual disorders (Peng et al. 2008). Compound **7** was rich in *Anemarrhena asphodeloides*, which was norlignan compound. This compound may have potential to be developed as medicines for the treatment of allergies by inhibiting the activation of mast cells (Bak et al. 2016). In our research, the fatty acid (**11**) was first isolated from the species, and was also first isolated from the genus *Juglans*. Therefore, compounds **6**, **7**, **11** might serve as chemical marker from systematic opinion.

The *in vitro* cytotoxic activities of all compounds were shown in Table S1. The results showed that α-ditetralonyl glucoside (**1**), isoflavones (**2**–**4**), sesquiterpenoids (**5**–**6**), phenolic acid (**7**–**10**) and aliphatic acid (**11**–**13**) from the green walnut husk of *J. mandshurica* were all weak cytotoxic against A549 and HeLa cell lines.

3. Experimental

3.1. General experimental procedures

The NMR spectra were measured in methanol-d_4, on a Bruker ARX-400 or AV600 instrument with TMS as an internal standard. CD spectrum was tested using JASCO pu-2080 spectrometer. IR spectra were taken on a Bruker IFS-55 infrared spectrophotometer with a KBr disk. Optical rotations were measured on a Peking-Elmer 241 MC Spectropolarimeter at 20 °C. ESI-MS spectra were recorded on Waters Quattro micro API LC/MS/MS spectrometer (Waters, USA). HPLC was performed on JAI LC9103 Recycling preparative HPLC (Japan Analytical Industries, Japan) equipped with JAIGEL-ODS-AP-P column and JAIGEL-GS310 column using a JAI refractive index detector and a JAI UV-3702 detector with MultiChro 2000 workstation.

3.2. Plant material

The green walnut husks of *J. mandshurica* were collected in October 2014 at Yichun, Heilongjiang, China, and authenticated by Engineer Wei Sun (The Traditional Chinese Medicine, Shenyang pharmaceutical University). A voucher specimen has been deposited in our laboratory (voucher No. HTQ-2014-001).

3.3. Extraction and isolation

The green walnut husk of *J. mandshurica* (20 kg) were extracted with 70% (v/v) aqueous ethanol. The 70% EtOH extract (1 kg) was successively partitioned with EtOAc and *n*-BuOH. The *n*-BuOH soluble fraction (120 g) was subjected to silica gel chromatography, eluting with a gradients of CH_2Cl_2-MeOH (1:0–0:1) to give seven fractions (Fr. A to Fr. G). Fraction A was then subjected to HPLC with MeOH-H_2O (90: 10) as eluent and each subfraction was further purified on recycling preparation HPLC with MeOH-H_2O (90:10) to yield **9** (28.4 mg), **11** (12.6 mg), **12** (5.6 mg) and **13** (8.1 mg). Fraction B was subjected to recycling preparation HPLC with MeOH-H_2O (85:15) as eluent to obtain compound **5** (4.8 mg), **6** (15.3 mg), **7** (5.5 mg), **8** (5.6 mg) and **10** (8.2 mg). Fraction D was further purified to recycling preparation HPLC with MeOH-H_2O (45:55) to yield **1** (25.3 mg), **2** (12.9 mg), **3** (15.4 mg) and **4** (5.7 mg).

3.3.1. (2R,4S,10S,12S)-2-[7-(12,13,16-trihydroxy-α-tetralonyl-13-O-β-D-glucopyranoside)]-4,8-dihydroxy-α-tetralone-4-O-β-D-glucopyranoside (1)

White amorphous power, [α]20 D -65 (c, 0.1, MeOH); HR-ESI-MS: *m/z* 735.1998 $[M + Na + H_2O]^+$ (calcd for $C_{32}H_{30}O_{18}Na$ 735.2003). ^{1}H NMR (600 MHz, methanol-d_4) δ 7.55 (1H, d, $J = 9.1$ Hz, H-14), 7.50 (1H, d, $J = 7.7$ Hz, H-7), 7.31 (1H, d, $J = 7.9$ Hz, H-6), 7.12 (1H, d, $J = 7.7$ Hz, H-5), 6.89 (1H, d, $J = 9.1$ Hz, H-15), 5.44 (1H, d, $J = 3.2$ Hz, H-4), 5.38 (1H, d, $J = 3.2$ Hz, H-12), 4.82 (1H, d, $J = 7.7$ Hz, H-1″), 4.62 (1H, d, $J = 7.7$ Hz, H-1′), 3.94 (1H, dd, $J = 5.0$, 1.6 Hz, H-6″$_a$), 3.92 (1H, dd, $J = 5.0$, 1.6 Hz, H-6′$_a$), 3.75 (1H, dd, $J = 5.0$, 1.6 Hz, H-6″$_b$), 3.94 (1H, dd, $J = 5.0$, 1.6 Hz, H-6′$_b$), 3.55 (1H, t, $J = 9.2$ Hz, H-2″), 3.40 (1H, m, H-3′), 3.34 (1H, m, H-4′), 3.33 (1H, m, H-5′), 3.32 (1H, m, H-3″), 3.31 (1H, m, H-4″), 3.30 (1H, m, H-5″), 3.21 (1H, m, H-2′), 3.15 (1H, m, H-2), 2.57 (1H, m, H-11$_a$), 2.51 (1H, m, H-10), 3.24 (2H, m, H-3), 2.21 (1H, m, H-11$_b$).^{13}C NMR (101 MHz, Methanol-d_4) δ 206.4(C-9), 201.0(C-1), 159.0(C-16), 156.9(C-8), 148.8(C-13), 134.6(C-12a), 134.3(C-4a), 130.5(C-6), 129.6(C-8a), 128.4(C-14), 122.0(C-5), 119.0(C-15), 118.9(C-7), 116.1(C-16a), 104.5(C-1″), 103.8(C-1′), 78.3(C-3″), 78.0(C-3′/C-5′), 77.9(C-5″), 75.3(C-2″), 75.2(C-2′), 71.5(C-4″), 71.2(C-4′), 69.7(C-4), 62.6(C-6″), 62.5(C-6′), 61.2(C-12), 34.0(C-2), 33.6(C-10), 30.2(C-3), 30.0(C-11).

3.4. Acid hydrolysis of compound 1

Compound (4 mg) was treated with 1 M HCl (4 mL) at 90 °C for 2 h. Then the reaction mixture was extracted with $CHCl_3$ (3 × 5 mL). The aqueous layer was collected and the water was evaporated under vacuum with the repeated addition of MeOH to remove the solvent completely. The residue was redissolved in anhydrous pyridine (2 mL) and mixed with a pyridine solution of L-cysteine methyl ester hydrochloride (2 mL). After the mixed solution was heated at 60 °C for 1 h, trimethylchlorosilane (0.5 mL) was added and the resulting mixture was stirred at 60 °C for another 30 min. Then the solution was concentrated to dryness and taken up in water (3 × 1 mL), followed by extraction with n-hexane (3 × 1 mL). The supernatant was analyzed by GC. Separations were carried out on HP-5 columns (320 μm × 30 cm, 0.25 μm). Highly pure N_2 was employed as a carrier gas (1.0 mL/min), and the FID detector operated at 280 °C (column temperature 160–200 °C). The retention times of the monosaccharide derivatives were as follows: and D-glucose (14.43 min).

3.5. Cytotoxicity

Human lung cancer cells (A549) and human cervical carcinoma cancer cells (HeLa) was provided by the American Type Culture Collection (ATCC). The cells were cultured in medium (RPMI1640 for A549 and DMEM for HeLa) supplemented with 10% heat-inactivated fetal bovine serum (FBS) and antibiotics antimycotics (PSF; 100 units/mL penicillin G sodium, 100 μg/mL streptomycin, and 250 ng/mL amphotericin B). The cells were incubated at 37 °C and 5% CO_2 in a humidified atmosphere. Etoposide (Sigma, purity > 98%) was used as a positive control. Cell viability was determined by the sulforhodamine B (SRB) protein staining method. Cells were seeded in 96-well plates and incubated for 24 h, and were fixed (for zero day controls) or treated with test compounds for 72 h. All compounds were solved in DMSO (final concentration of 0.1%[v/v]), stored at −20 °C and diluted to desired concentration (0.01, 0.1, 1, 10, 100 μM) in normal saline immediately prior to each experiment. Each

concentration was tested thrice. At least three experiments were performed. After incubation, cells were fixed with 10% trichloroacetic acid (TCA), dried and stained in 0.4% sulforhodamine B (SRB) in 1% acetic acid solution. Unbound dye was washed and stained cells were dried and dissolved in 10 mM Tris (pH 10.0). Absorbance was measured at 515 nm and cell proliferation was determined as follows: cell proliferation (%) = (average absorbance$_{compound}$ − average absorbance$_{zero\ day}$)/(average absorbance$_{control}$ − average absorbance $_{zero\ day}$) × 100%. GI_{50} values were calculated by non-linear regression analysis using the Table Curve 2 D software (Version 5.01, Systat Software Inc., CA).

4. Conclusion

A new α-diteralonyl glucoside (**1**) along with twelve known compounds were isolated from 70% EtOH extract from the green walnut husk of *J. mandshurica*. Compound **1–13** showed weak cytotoxic against A549 and HeLa cell lines. In this contribution, our findings would both enrich chemical context of genus *Juglans* and expand the variety of tetralonyl glucosides.

Disclosure statement

No potential conflict of interest was reported by the authors.

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