Four sesquiterpenoids from the vegetable raw material
*Schisandra chinensis* (Turcz.) Baill.: leaves and stems

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**ABSTRACT**

Four sesquiterpenoids A-D (1–4) were isolated from the ethanol extracts of the leaves and stems from *Schisandra chinensis*. Their structures and absolute configurations were elucidated by a combination of NMR, MS and ECD. Compounds 1–4 (10 μM) exhibited moderate hepatoprotective activities against APAP-induced LO2 cell damage with increasing cell viability by 18%, 17%, 16%, and 19% compared to the model group (bicyclol, 26%) at 10 μM, respectively. All the compounds displayed no cytotoxic activity against five human cell lines, which also suggested the safety of leaves and stems of *S. chinensis* as an edible vegetable in a degree.

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**1. Introduction**

*Schisandra chinensis* (Turcz.) Baill., a deciduous woody liana belonging to the Schisandraceae family, is widely distributed in northeastern China, Japan and Korea
Simultaneously, the woody stems and leaves of *S. chinensis* are utilized as a folk herbal medicine for the treatment of asthma, influenza, frostbite and gastrointestinal dysfunction in northeastern China (Shao 1995). In addition, the leaves of *S. chinensis* are edible as a vegetable to enhance the immune function in Northeast China. It’s reported that triterpenoids, lignans, and polysaccharides have been isolated from the woody stems and leaves of *S. chinensis* (Zheng et al. 2014; Yang et al. 2019; Zhao et al. 2020). Several studies have shown that the woody stems and leaves of *S. chinensis* possess anti-aging, anti-viral (Song et al. 2013) and antifeedant (Guo et al. 2019) activities. In order to further characterize the chemical constituents and explore their hepatoprotective activity, our teams used several chromatographic technologies to isolate four sesquiterpenoids (1–4) from the ethyl acetate extracts of the woody stems and leaves of *S. chinensis* (Figure 1). We report herein the isolation, structural elucidation and hepatoprotective activity assay of these compounds.

2. Results and discussion

2.1. Structural elucidation

Compound 1 was obtained as a colorless oil and exhibited an ion peak at *m/z* 243.1591 [M + H]⁺ (calcd for C₁₃H₂₃O₄, 243.1596) in its positive HRESIMS data, which indicated a molecular formula of C₁₃H₂₂O₄. The indices of hydrogen deficiency (IHDs) of compound 1 was 3. Based on the ¹H NMR spectroscopic data (Table S1), a set of ene proton signals at δ_H 5.71 (1H, d, J = 2.4 Hz, H-7, H-8) were observed, which were deduced to be an ethylene within Z-configuration in its sub-structures. In addition, the ¹H NMR spectrum has given three oxidized methines signals at δ_H 3.74 (1H, s, H-4), 4.04 (1H, d, J = 6.6 Hz, H-3) and 4.31 (1H, m, H-9), four methyl signals at δ_H 1.26 (3H, s, H-10), 1.10 (3H, s, H-11), 0.90 (3H, s, H-12) and 1.37 (3H, s, H-13). The ¹³C NMR spectrum data of compound 1 comprised two sp² hybridized carbon signals at δ_C 124.4 (C-7) and 136.3 (C-8), five oxidized carbon signals at δ_C 93.3 (C-6), 86.9 (C-5), 85.7 (C-3), 83.6 (C-4) and 69.2 (C-9), four methyl signals at δ_C 24.0 (C-10), 23.3 (C-11), 32.5 (C-12), 25.1 (C-13). Besides, the ¹H NMR and ¹³C NMR spectra then revealed a methylene [δ_C 45.6; δ_H 1.75 (1H, dd, J = 12.0, 6.6 Hz), 1.62 (1H, d, J = 12.0 Hz)] and a quaternary carbon (δ_C 44.0). Based on the above spectral information, the structure of 1 was speculated as a decarburized sesquiterpene with thirteen carbons, and was similar to megastagman-7-en-3,6-epoxy-5,9-diol 9-O-β-D-glucopyranoside except for a hydroxyl substituted at C-4 and desugar at C-9 (Shitamoto et al. 2010), which was confirmed by the long range correlations between δ_H 4.04 (H-4) and δ_C 85.7 (C-3), δ_H 4.04 (H-4) and δ_C 86.9 (C-5) in the HMBC spectrum. Furthermore, two key spin-spin
coupling at H-2/H-3/H-4, H-7/H-8/H-9/H-10 were observed in the $^1$H–$^1$H COSY spectrum (Figure S2), which can be further confirmed the planar structure of 1.

The stereochemistry of 1 was determined on the basis of the NOESY and circular dichroism. The NOESY correlation (Figure S2) of H$_3$-13 with H-7, H-4 established H-3, H-4, CH=CH-6 and H$_3$-13 were cofacial orientations and randomly assigned as $\beta$-oriented. Also, the coupling constant between H-3 and H-4 was 6.6 Hz, indicating that H-3 and H-4 were on the same side. The absolute configuration of the vicinal diol moiety in 1 was determined by ECD spectra of its complex with Mo$_2$(OAc)$_4$ solution (Snatzke’s method) (Frelek et al. 1999; Yan et al. 2014). According to the helicity rule relating the sign of the Cotton effect of the diagnostic O-C-C-O moiety (Tang et al. 2009), the negative Cotton effect at 310–340 nm in the ECD spectrum indicated a 5R configuration, on the contrary, which is 5S configuration. Compound 1 was confirmed by ECD spectroscopy to have a negative Cotton effect (Figure S1–S2). Therefore, the absolute configuration of C-5 was determined as R. In addition, the absolute configuration was determined by experimental and calculated ECD and assigned as (3S,4R,5R,6R)-absolute configuration (Figure S3). Therefore, the structure of compound 1 was determined to be schiterpenoid A.

Compound 2, a colorless oil, was found to have a molecular formula of C$_{15}$H$_{20}$O$_6$ as shown by its positive HRESIMS ion peak at $m/z$ 319.1152 [M+Na]$^+$ (calcd for C$_{15}$H$_{20}$NaO$_6$, 319.1158). The $^1$H NMR spectrum of 2 (Table S1) showed signals for three methyl groups at $\delta_H$ 2.34 (3H, d, $J = 0.6$ Hz, H-10), 1.06 (3H, s, H-12) and 1.32 (3H, s, H-13), two methylene groups at $\delta_H$ 1.92 (1H, m, H-2), 1.74 (1H, m, H-2), 1.86 (1H, m, H-4) and 2.29 (1H, m, H-4), an oxymethine at $\delta_H$ 3.86 (1H, m, H-3), and three olefinic protons at $\delta_H$ 6.69 (1H, d, $J = 15.6$ Hz, H-8), 6.51 (1H, d, $J = 15.6$ Hz, H-7) and 5.91 (1H, s, H-14). The $^{13}$C NMR spectrum displayed six nonprotonated carbons including an olefinic ($\delta_C$ 152.1, C-9), two carbonyls ($\delta_C$ 170.1, C-15 and 180.9, C-11), a quaternary ($\delta_C$ 53.6, C-1), and two oxygenated quaternary ($\delta_C$ 89.8, C-5 and 82.9, C-6) carbons together with nine protonated carbons. The large vicinal coupling constant (15.6 Hz) between H-7 ($\delta_H$ 6.51) and H-8 ($\delta_H$ 6.69) suggested that the olefin moiety was in the E configuration. According to the above features, the NMR spectroscopic data of 2 were very similar to those of 8’-oxo-6-hydroxy-dihydrophaseic acid (Bai et al. 2012), except for the absence of resonance for an oxygen-bearing isolated methylene group and the presence of methyl group at $\delta_H$ 2.34 (3H, d, $J = 0.6$ Hz), which indicated that a hydroxymethyl group at C-10 in 8’-oxo-6-hydroxy-dihydrophaseic acid was replaced by a methyl group in 2. It was further confirmed by HMBC correlations between the methyl proton at $\delta_H$ 2.34 and the olefinic carbons at $\delta_C$ 152.1 (C-9), 139.2 (C-8) and 122.4 (C-14). The relative configuration of 2 was deduced from a NOESY experiment, in which the correlations between H-14 and H-10 verified the conjugated diene was 8E,14Z-configuration (Bai et al. 2012). The correlation of H-3 with H$_3$-13, H$_3$-12; H-7 with H$_3$-13, H$_3$-12 established HO-3, HO-6 were cofacial orientations and randomly assigned as $\alpha$-oriented, contrarily, CH$_3$-12 and CH$_3$-13 were assigned as $\beta$-oriented. ECD calculation succeeded in establishing the absolute configuration of compound 2 as (1S,3R,5R,6S)-absolute configuration (Figure S3). Therefore, the structure of compound 2 was determined to be schiterpenoid B.
Compound 3, a colorless oil, was found to have a molecular formula of C_{13}H_{22}O_{4} as shown by its positive HRESIMS ion peak at m/z 243.1591 [M + H]^+ (calcld for C_{13}H_{23}O_{4}, 243.1596). The $^1$H NMR spectrum of 3 (Table S1) showed signals for four methyl groups at $\delta_H$ 1.28 (3H, d, $J = 6.6$ Hz, H-10), 0.90 (3H, s, H-11), 1.24 (3H, s, H-12) and 1.27 (3H, s, H-13), one methylene group at $\delta_H$ 1.90 (1H, t, $J = 12.6$ Hz, H-3) and 1.31 (1H, m, H-3), three oxymethine groups at $\delta_H$ 4.20 (1H, m, H-2), 3.58 (1H, d, $J = 2.4$ Hz, H-4) and 4.33 (1H, m, H-9), and two olefinic protons at $\delta_H$ 5.94 (1H, dd, $J = 15.6, 6.6$ Hz, H-7) and 5.77 (1H, dd, $J = 15.6, 1.2$ Hz, H-8). The $^{13}$C NMR spectrum displayed six nonprotonated carbons including a quaternary ($\delta_C$ 40.8, C-1), two oxygenated quaternary ($\delta_C$ 80.6, C-6 and 76.4, C-5) carbons and ten protonated carbons. According to the above features, the NMR spectroscopic data of 3 were very similar to those of tectoionol B (Francisco et al. 2008), the main differences included the following three aspects. Firstly, the large vicinal coupling constant (15.6 Hz) between H-7 ($\delta_H$ 5.94) and H-8 ($\delta_H$ 5.77) suggested that it had a set of trans-ene bonds in this structure (Sun et al. 2007). Secondly, a hydrogen of methylene group at C-4 in tectoionol B was replaced by a hydroxy group in 3. Even more remarkably, a double bond at C-5/C-6 in tectoionol B has been formed a ternary oxygen ring through oxidation dehydration reaction. This was further confirmed by HMBC correlations between the oxymethine proton at $\delta_H$ 3.58 and the proximal carbons at $\delta_C$ 80.6 (C-6), 76.4 (C-5), 66.6 (C-2) and 40.1 (C-3). In the NOESY spectrum, the correlations of H-2 with H-4, H-12; H-7 with H-4, H-13 established HO-2, HO-4 were cofacial orientations and randomly assigned as $\alpha$-oriented, CH$_3$-12 and CH$_3$-13 were assigned as $\beta$-oriented. The absolute configuration was determined by experimental and calculated ECD and assigned as (2$S$,4$R$,5$R$,6$S$)-absolute configuration (Figure S3). Therefore, the structure of compound 3 was determined to be schiterpenoid C.

Compound 4 was isolated as colorless oil and had a molecular formula of C_{14}H_{26}O_{5} based on its positive HRESIMS ion peak at m/z 297.1672 [M + Na]^+ (calcld for C_{14}H_{25}NaO_{5}, 297.1678). The $^1$H NMR spectrum of 4 (Table S1) showed signals for one methoxy group at $\delta_H$ 3.43 (3H, s), four methyl groups at $\delta_H$ 1.30 (3H, d, $J = 6.6$ Hz, H-10), 0.98 (3H, s, H-11), 1.16 (3H, s, H-12) and 1.44 (3H, s, H-13), one methylene group at $\delta_H$ 1.88 (1H, t, $J = 6.6$ Hz, H-2) and 1.27 (1H, m, H-2), three oxymethine groups at $\delta_H$ 4.17 (1H, m, H-3), 3.39 (1H, m, H-4) and 4.32 (1H, m, H-9), and two olefinic protons at $\delta_H$ 5.78 (1H, dd, $J = 16.8, 1.2$ Hz, H-7) and 6.09 (1H, dd, $J = 16.8, 6.0$ Hz, H-8). The $^{13}$C NMR spectrum displayed three nonprotonated carbons including a quaternary ($\delta_C$ 42.6, C-1), and two oxygenated quaternary ($\delta_C$ 77.4, C-5 and 87.5, C-6) carbons, together with eleven protonated carbons including a methoxy group ($\delta_C$ 55.6). According to the above features, the NMR spectroscopic data of 4 were very similar to those of 3, except for the presence of a methoxy group ($\delta_H$ 3.43, $\delta_C$ 55.6) attached to C-6, which was further confirmed by HMBC correlations between the proton at $\delta_H$ 3.43 and the carbon at $\delta_C$ 87.5 (C-6). Furthermore, two key spin-spin coupling at H-2/H-3/ H-4, H-7/H-8/H-9/H-10 were observed in the $^1$H–$^1$H COSY spectrum, which can be further confirmed the planar structure of 4 as described in Figure S1. The relative configuration of 4 was deduced from a NOESY experiment. The correlation (Figure S2) of H-3 with H$_3$-12; H-7 with H$_3$-12, H$_3$-13; H$_3$-13 with H-4 established H-3, H-4, CH$_3$O-6 and CH$_3$-13 were cofacial orientations and randomly assigned as $\beta$-oriented. The absolute
configuration was determined by experimental and calculated ECD and assigned as \((3R,4R,5R,6S)\)-absolute configuration (Figure S3). Therefore, the structure of compound 4 was determined to be schiterpenoid D.

2.2. Hepatoprotective activity

Compounds 1 – 4 were tested for their cytotoxicity against five human cell lines, LO2 (Human normal embryonic liver cells), A549 (Human lung epithelial cell line), HeLa (Human Cervical Cancer Cells), PC3 (Human prostate cancer cell) and MCF-7 (human breast cancer cell); however, they were inactive (IC\(_{50}\) > 100 \(\mu\)M), which also suggested the safety of these compounds in a degree. They were also assayed for their hepatoprotective activities against Nacetyl-p-aminophenol (APAP)-induced toxicity in LO2 cells, using the hepatoprotective activity drug bicyclol as the positive control (Li et al. 2006). Compounds 1 – 4 exhibited moderate hepatoprotective activities with increasing cell viability by 18%, 17%, 16%, and 19% compared to the model group (bicyclol, 26%) at 10 \(\mu\)M, respectively (Figure S4).

3. Experimental

3.1. General experimental procedures

Optical rotations were measured with a JASCO P2000 automatic polarimeter. UV spectra were recorded on a JASCO V-650 UV spectrophotometer. 1D and 2D NMR spectra were recorded on a Bruker Avance 600 spectrometer with solvent peaks as references. HRESIMS data were obtained with an Agilent 1290 Infinity liquid chromatography system and an Agilent 6540 UHD Accurate-Mass Q-TOF mass spectrometer. High-performance liquid chromatography (HPLC) data were recorded on an Agilent 1260 instrument equipped with a photo-diode array (PDA) and a YMC C18 column (250 × 4.6 mm, 5 \(\mu\)m). Preparative HPLC was performed on Sanotac instrument China with a UV detector and a YMC C18 column (250 × 20 nm, 5 \(\mu\)m). Column chromatographic separations were carried out with silica gel (200–300 mesh, Qingdao Marine Chemical Group Corporation, Qingdao, China), MCI gel (70–150 \(\mu\)m, SEP, Beijing, China) and ODS (50 \(\mu\)m, YMC, Kyoto, Japan). TLC was conducted with glass precoated with silica gel GF254 (Yantai Chemical Industrial Institute, Yantai, China). Chromatographic grade methanol and acetonitrile were purchased from Fisher. All other solvents were of chemical grade (Da Mao Chemical Co. Ltd., Tianjin, China).

3.2. Plant material

The leaves and rattan stems from *Schisandra chinensis* (Turcz.) Baill (Magnoliaceae). ([http://www.theplantlist.org/tpl1.1/record/kew-2585428](http://www.theplantlist.org/tpl1.1/record/kew-2585428)) were collected in September 2020, from Xiuyan Manchu Autonomous County, Liaoning Province, China (coordinates: N 40°16′48.52″, E 123°16′20.11″; elevation: 49 m) and identified by Pro. Jia Jingming in Shenyang Pharmaceutical University. The specimens were deposited in the specimen room of traditional Chinese Medicine in Shenyang Pharmaceutical University (NO. YSC-2020903).
3.3. Extraction and isolation

The dry leaves and rattan stems of *S. chinensis* L (41.1 kg) were soaked by 95% ethanol aqueous solution (3 × 410 L, 3 days each) and concentrated to an ethanol odor by vacuum distillation, and then partitioned with PE, EtOAc and n-BuOH. The EtOAc extract (760.0 g) was chromatographed on a silica gel column, eluted with a gradient of CH2Cl2-MeOH (100:1–0:1) to give 7 fractions (Fr. A ~ Fr. G) based on TLC analysis. The Fr. E (62.4 g) was dealt with by an MCI column by elution with MeOH-H2O (3:7–1:0) in sequence to give fractions Fr. E1~Fr. E10. Sub-fraction Fr. E2 (2.1 g) was separated by silica gel by petroleum ether–acetone (5:1–0:1) to obtain 10 fractions, Fr. E2.1~Fr. E2.10. Afterwards, The Fr. E2.6 (89.3 mg) was separated by preparative HPLC with 25% methanol aqueous to obtain compounds 1 (2.2 mg, $t_R = 68.1$ min), 3 (3.5 mg, $t_R = 65.2$ min), 4 (2.2 mg, $t_R = 72.7$ min). The Fr. E2.8 (129.0 mg) was separated by the same chromatographic condition as sub-Fr. E2.6 to gain compound 2 (2.8 mg, $t_R = 35.8$ min).

3.3.1. Schiterpenoid A (1)

Colorless oil (MeOH); $[\alpha]_{D}^{20} = -125$ (c 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log ε): 204 (3.44) nm; $^1$H NMR (CD3OD, 600 MHz) and $^{13}$C NMR (CD3OD, 150 MHz) data (Table S1); HRESIMS $m/z$ 243.1591 [M + H]$^+$ (calcd for C13H23O4, 243.1596).

3.3.2. Schiterpenoid B (2)

Colorless oil (MeOH); $[\alpha]_{D}^{20} = -145$ (c 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log ε): 207 (3.53), 253 (3.97) nm; $^1$H NMR (CD3OD, 600 MHz) and $^{13}$C NMR (CD3OD, 150 MHz) data (Table S1); HRESIMS $m/z$ 319.1152 [M + Na]$^+$ (calcd for C15H20NaO6, 319.1158).

3.3.3. Schiterpenoid C (3)

Colorless oil (MeOH); $[\alpha]_{D}^{20} = -180$ (c 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log ε): 203 (3.35) nm; $^1$H NMR (CD3OD, 600 MHz) and $^{13}$C NMR (CD3OD, 150 MHz) data (Table S1); HRESIMS $m/z$ 243.1591 [M + H]$^+$ (calcd for C13H23O4, 243.1596).

3.3.4. Schiterpenoid D (4)

Colorless oil (MeOH); $[\alpha]_{D}^{20} = -159$ (c 0.1, MeOH); UV (MeOH) $\lambda_{max}$ (log ε): 204 (3.44) nm; $^1$H NMR (CD3OD, 600 MHz) and $^{13}$C NMR (CD3OD, 150 MHz) data (Table S1); HRESIMS $m/z$ 297.1672 [M + Na]$^+$ (calcd for C14H26NaO5, 297.1678).

3.4. Mo2(OAc)4 induced electronic circular dichroism

According to the published procedure (Gao et al. 2021), about 1:1.2 mixture of diol-to-Mo2(OAc)4 for compound 1 was prepared at the concentration of 1.0 mg/mL. Soon after mixing, the first ECD spectrum was recorded immediately, and its evolution was monitored until stationary (about 15 min after mixing). The inherent ECD of the diol was subtracted. The diagnostic band at around 310 nm in the induced ECD spectra were correlated to the absolute configuration of 1,2-diol unit.
3.5. ECD calculations

The ECD spectra were calculated according to the reported methods (Jiang et al. 2017; Zhang et al. 2019). Compounds 1–4 were calculated via density functional theory (DFT) and time-dependent DFT (TDDFT) using ORCA. The structure at the HF/6-31G level in the gas phase was optimized. Next, the corresponding minimum geometries were further optimized at the B3LYP/6-31 + G (d, p) level in the gas phase. The ECD spectra were calculated at the B3LYP/6-31+ + G (2d, 2p) level in MeOH. The computational ECD data were fitted in the SpecDis software package. The computational data were fitted in the GraphPad Prism 7.0.

3.6. Cytotoxicity assay

Compounds 1–4 were tested for cytotoxicity against human cancer cells lines MCF-7 (Michigan Cancer Foundation-7, breast), PC3 (Human prostatic cancer cell), A549 (lung) and HeLa (cervical) using MTT cell viability assay (Shima et al. 2021). First, cellular suspensions (1 × 10^5 cells/mL) were cultured in 96-well plates and exposed to different concentrations of compounds (1–200 μg/mL), using three wells for each concentration. The plates were incubated at 37 °C in 5% CO2 for 48 h. Then, 200 μL of MTT solution was added and the cells were further cultured for 4 h. The absorbance of each well was measured at 490 nm by using a microplate reader.

3.7. Hepatoprotective activity assay

Human LO2 (Human normal embryonic liver cells) cells were cultured in 1640 medium supplemented with 10% fetal calf serum at 37 °C in a humidified atmosphere of 5% CO2 + 95% air. The MTT assay was used to assess the cytotoxicity of test samples. The cells were seeded in 96-well multiplate. After an overnight incubation at 37 °C with 5% CO2, 10 μM test samples and APAP (final concentration of 8 mM) were added into the wells and incubated for another 16 h. Then, 200 μL of 0.5 mg/mL MTT was added to each well after the withdrawal of the culture medium and incubated for an additional 4 h. The resulting formazan was dissolved in 150 μL of DMSO after aspiration of the culture medium. The plates were placed on a plate shaker for 30 min and read immediately at 490 nm using a microplate reader.

4. Conclusions

This chemical investigation of the leaves and stems of S. chinensis identified four sesquiterpenoids. The hepatoprotective effects of compounds 1–4 against N-acetyl-p-aminophenol (APAP)-induced toxicity in LO2 cells were evaluated in vitro using a MTT assay, and compounds 1–4 displayed moderate hepatoprotective activities comparable to bicyclol (positive drugs). Additionally, compounds 1–4 showed no cytotoxic effects against five human cell lines, as demonstrated by MTT assays.
Disclosure statement

No potential conflict of interest was reported by the authors.

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