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Original Article

Chemical constituents from the fruits of *Schisandra sphenanthera* and their cytotoxicity activity

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ABSTRACT

Schisandra sphenanthera Rehder & E.H. Wilson, Schisandraceae, is well known as a type of traditional medicine for the treatment of hepatitis, diarrhea and insomnia in Asia. It was also reported to have antiviral and anti-HIV activities. Using various chromatographic resins and isolation techniques, a new lignan (**1**), *erythro*-4-(3,4-dimethoxyphenyl)-4-hydroxy-3-methylbutan-2yl-3,4-dimethoxybenzoate, along with fifteen known compounds, were isolated from fruits of *S. sphenanthera*. The structures of the compounds were identified by extensive spectroscopic and spectrometric methods including 1D and 2D NMR and MS data. All the isolated compounds were evaluated for their cytotoxicity activity against Hela, HepG2 and HCT-116 cells. Among them, compound schisanlactone C showed significant cytotoxicity activity.

Introduction

Schisandra sphenanthera Rehder & E.H. Wilson, Schisandraceae, is widely distributed in East Asia and has been commonly used as a traditional medicine for the treatments of hepatitis, diarrhea, diabetes and insomnia (Saunders, 2000; Kuang et al., 2005; Chen, 2009). Recent studies revealed that the extract of *S. sphenanthera* showed hepatoprotective, anti-oxidant, anti-tumor and anti-HIV activities (Xu et al., 2005; Xiao et al., 2008a). In order to identify its bioactive compounds, many phytochemical investigation of various parts of the plant have been performed. Previous studies have reported that lanostane-, cycloartane- and schinortriterpenoid-*type* triterpenoids and lignans are the major components of *S. sphenanthera* (Xiao et al., 2008a; Ren et al., 2009; Zhou et al., 2009; He et al., 2010, 2012; Jiang et al., 2011; Liang et al., 2014). Some of these compounds showed significant cytotoxicity in various cell lines (Xiao et al., 2006b, 2007; He et al., 2012; Liang et al., 2014; Jiang et al., 2015). In the present study, we aimed to identify cytotoxic phytochemicals from the fruits of the *S. sphenanthera*. From this, a new lignan (**1**), *erythro*-4-(3,4-dimethoxyphenyl)-4-hydroxy-3-methlbutan-2-yl-3,4-dimethoxybenzoate, together with fifteen known compounds (**2**–**16**). These compounds were evaluated for cytotoxicity against Hela, HepG2 and HCT-116 cells.

Material and methods

General experimental procedures

All NMR spectra were recorded on an Agilent 400-MR-NMR spectrometer operated at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Data processing was carried out with the MestReNova ver. 9.0.1 program. LC-HR-ESI-MS data were obtained using an Agilent 6550 iFunnel Q-TOF system in positive mode and using YMC hydrosphere C_{18} column (4.6 mm i.d. × 250 mm, 5 μm). Data processing was carried out with Mass Hunter Data acquisition and Qualitative analysis software (Agilent). Preparative HPLC was carried out using an AGILENT 1200 HPLC system using with YMC J'sphere ODS H-80 column (20 mm i.d. × 250 mm, 4 μm). Column chromatography (CC) was performed on silica-gel (Kieselgel 60, 70-230 mesh and 230-400 mesh, Merck, Germany) or YMC RP-18 resins (150 μm, Fuji Silysia Chemical, Aichi, Japan). For thin layer chromatography (TLC), pre-coated silica-gel 60 F254 (0.25 mm, Merck) and RP-18 F254S (0.25 mm, Merck) plates were used.

Plant materials

The fruits of *Schisandra sphenanthera* Rehder & E.H.Wilson, Schisandraceae, were collected at in Kon Tum province, Vietnam, in September 2016. The sample was authenticated by Dr. Ninh Khac Ban of the Institute of Marine Biochemistry, Vietnamese Academy of Science and Technology, Vietnam. A voucher specimen (SS201609) was deposited at the Herbarium of College of

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Extraction and isolation

Dried fruits of *S. sphenanthera* (8 kg) were extracted with MeOH (5 l × 3 times) under sonication for 4 h to yield an extract (1.5 kg), which was then suspended in H_2O and successively partitioned using hexane, CH_2Cl_2 and EtOAc to obtain hexane (310 g), CH_2Cl_2 (150 g), EtOAc (17 g), and H_2O (910 g). Then the extracts were dry down *in vacuo*. The CH_2Cl_2 fraction (150 g) was subject to a silica gel column chromatography and eluting with a gradient of hexane:acetone (5:1 → 1:1, v/v) yielding three fractions: SS3A, SS3B and SS3C. The SS3B fraction was chromatographed on silica gel column eluting with a gradient of CH_2Cl_2:MeOH (24:1 → 1:1, v/v) yielding three fractions: SS4D, SS4E and SS4F. The SS4D fraction was chromatographed on a silica gel column eluting with hexane:EtOAc (1.5:1, v/v) yielding six fractions: SS4D1 to SS4D6. The combined SS4D3 and SS4D4 fractions were chromatographed on a YMC RP-18 column eluting with MeOH:H_2O (3.5:1, v/v) yielding four sub-fractions (F1: 62.6 mg, F2: 153.4 mg, F3: 92.3 mg, F4: 95.1 mg). The F1 was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 42% aq. MeCN, and a flow rate of 4 ml/min yielding *p*-hydroxy benzaldehyde (**2**, 8.4 mg, 0.00056%), vanillin (**3**, 8.9 mg, 0.00059%), coniferaldehyde (**4**, 6.6 mg, 0.00044%). The combined SS4D5 and SS4D6 fractions were chromatographed on a YMC RP-18 column eluting with MeOH:water (3:1, v/v) yielding four sub-fractions (F5: 111.5 mg, F6: 222.2 mg, F7: 27.5 mg, F8: 91.9 mg). The F5 fraction was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 50% aq. MeCN, and a flow rate of 4 ml/min to yield arisantetralone A (**5**, 15.5 mg, 0.0010%), and 3',4'-dimethoxybenzoic acid (3",4"-dimethoxyphenyl)-2-methyl-3-oxobutyl ester (**10**, 10 mg, 0.00066%). The F6 fraction was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 50% aq. MeCN, and a flow rate of 4 ml/min yielding gomisin S (**8**, 5 mg, 0.00033%), arisantetralone C (**6**, 3.6 mg, 0.00024%), 4-(3,4-dimethoxyphenyl)-4-hydroxy-3-methylbutan-2yl-3,4-dimethoxybenzoate (**1**, 3.1 mg, 0.00020%), schizandrin (**7**, 3.9 mg, 0.00026%), and gomisin D (**9**, 3.2 mg, 0.21%). The F7 fraction was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 50% aq. MeCN, and a flow rate of 4 ml/min yielding schisanlactone C (**11**, 11.8 mg, 0.00078%). The SS3C fraction was chromatographed on silica gel column eluting with CH_2Cl_2:MeOH (12:1, v/v) yielding five fractions, SS4G, SS4H, SS4I, SS4J and SS4K. The SS4I fraction was chromatographed on a YMC RP-18 column eluting with MeOH:water (1.4:1, v/v) yielding six sub-fractions (F8: 180 mg, F9: 33.8 mg, F10: 35.6 mg, F11: 40.7 mg, F12: 61.7 mg, F13: 484.8 mg). The F9 fraction was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 40% aq. MeCN, and a flow rate of 4 ml/min yielding henridilactone A (**15**, 7.5 mg, 0.0005%), lancifodilactone L (**12**, 11.4 mg, 0.00076%). The F10 fraction was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 50% aq. MeCN, and a flow rate of 4 ml/min yielding schirubridilactone E (**14**, 7.3 mg, 0.00048%). The SS4J fraction was chromatographed on YMC RP-18 column eluting with MeOH:water (1.3:1, v/v) to give four sub-fractions (F14: 141 mg, F15: 117 mg, F16: 269 mg, F17: 526 mg). The F15 fraction was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 51% aq. MeCN, and a flow rate of 4 ml/min yielding micrandilactone F (**16**, 6.5 mg, 0.00043%). The fraction SS4K was chromatographed on HPLC using J'sphere ODS H-80, 250 mm × 80 mm column, 50% aq. MeCN, and a flow rate of 4 ml/min yielding 20-hydroxymicrandilactone D (**13**, 694 mg, 0.046%).

Table 1
^1H and ^{13}C NMR data of compound **1**.

Pos.	δ_C [a,b]	δ_H [a,c] (*J* in Hz)	HMBC (^1H ^{13}C)
1	124.4	–	–
2	113.3	7.43 (d, 2.0)	4, 6, 7
3	150.0	–	–
4	154.9	–	–
5	112.0	6.92 (d, 8.5)	1, 3
6	124.8	7.54 (dd, 2.0, 8.5)	2, 4, 7
7	167.4	–	–
8	73.4	5.27 (q, 6.3)	7, 9, 8′, 9′
9	15.7	1.24 (d, 6.4)	8, 8′
1′	137.4	–	–
2′	111.5	6.82 (d, 1.8)	4′, 6′, 7′
3′	150.3	–	–
4′	149.9	–	–
5′	112.6	6.79 (d, 8.2)	1′, 3′
6′	120.6	6.76 (dd, 1.8, 8.2)	2′, 4′
7′	76.5	4.44 (d, 7.7)	8, 1′, 2′, 6′, 8′, 9′
8′	45.2	2.22 (m)	8, 9, 7′, 9′
9′	11.3	0.74 (d, 7.0)	8, 7′, 8′
3-OMe	56.5	3.77 (s)	3
4-OMe	56.6	3.80 (s)	4
3′-OMe	56.5	3.70 (s)	3′
4′-OMe	56.4	3.69 (s)	4′

Assignments were done by HSQC, HMBC and COSY experiment.
[a] Measured in CD_3OD.
[b] 100 MHz.
[c] 400 MHz.

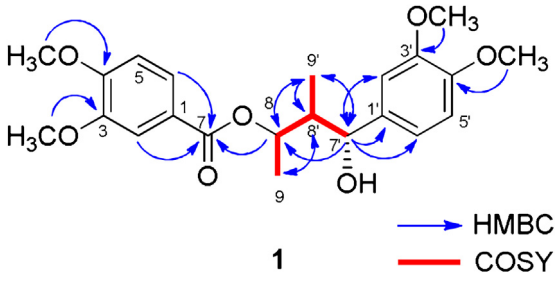


Fig. 1. Key HBMC and COSY correlation of compound **1**.

Cytotoxicity assay

Hela, HepG2 and HCT-116 cells were purchased from Korea Cell Bank (Seoul, Korea). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma, St Louis, MO) supplemented with 10% heat-inactivated fetal bovine serum (FBS, Gibco BRL, Gaithersburg, MD, USA), containing 100 IU/mL penicillin and 100 mg/mL streptomycin at 37 °C and 5% CO_2. For the measurement of cytotoxicity, the compounds to be tested were dissolved in dimethyl sulfoxide (DMSO) as a stock solution at 100 μM concentration and stored in aliquots at −20 °C. Hela, HepG2 and HCT-116 cells were seeded in 96-well plates at a density of 5×10^4 cells/ml and incubated for 24 h. Cells was treated with the compounds at the concentration of 10 and 20 μM for 24 h. Measurement of cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT, Sigma Chemical Co., St. Louis, MO, USA) assay, based on the conversion of MTT to formazan crystals by mitochondrial enzyme. MTT was added to each well and incubated for 2 h. The medium was removed followed by adding 200 μl of DMSO to dissolve the formazan crystals. The absorbance was determined with microplate reader at 450 nm.

Result and discussion

The methanol extract of the fruits of *S. sphenanthera* was suspended in H_2O and partitioned with hexane, $CHCl_3$ and EtOAc.

Using various chromatographic resins and isolation techniques, a new lignan (**1**) along with fifteen known compounds were isolated. All the structures were elucidated by extensive spectroscopic and spectrometric methods including 1D and 2D NMR and HR-ESI-MS analysis. The known compounds were compared with those reported.

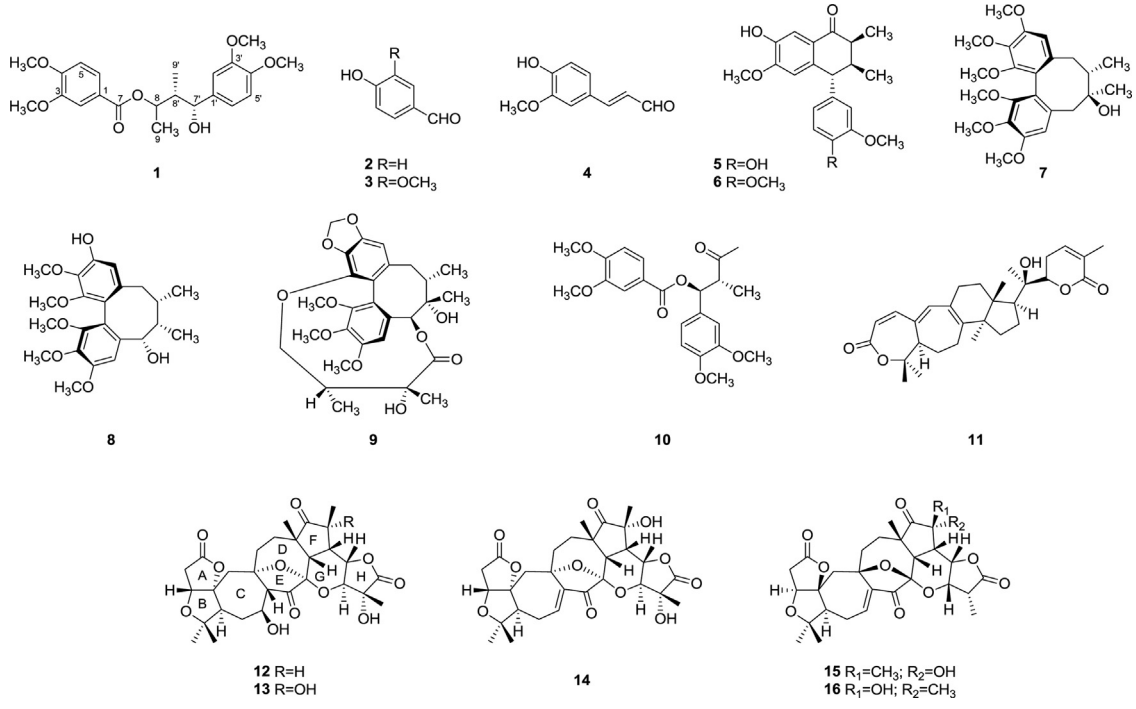
Compound **1** was obtained as white amorphous powder and its molecular formula was determined as $C_{22}H_{28}O_7$ by HR-ESI-MS $[M+Na]^+$ ion at *m/z* 427.1718 (calcd for $[C_{22}H_{28}O_7Na]^+$, 427.1727). The ^1H NMR spectrum showed two ABX-type aromatic rings at δ_H 6.92 (1H, d, *J* 8.5 Hz), 7.43 (1H, d, *J* 2.0 Hz) and 7.54 (1H, dd, *J* 2.0, 8.5 Hz) and at δ_H 6.76 (1H, dd, *J* 1.8, 8.2 Hz), 6.79 (1H, d, *J* 8.2 Hz) and 6.82 (1H, d, *J* 1.8 Hz), respectively (Table 1). In addition, it revealed signals due to two methyl proton signals at δ_H 0.74 (3H, d, *J* 7.0 Hz) and 1.24 (3H, d, *J* 6.4 Hz) and three methine protons at δ_H 2.22 (1H, m), 4.44 (1H, d, *J* 7.7 Hz), and 5.27 (1H, p, *J* 6.3 Hz). The ^{13}C-NMR spectrum indicated that compound **1** contains two aromatic rings (two veratryls), one carbonyl carbon at δ_C 167.4, three methine carbons (two oxygenated) at δ_C 45.2, 73.4 and 76.5 and two methyl carbons at δ_C 11.3 and 15.7 (Table 1). The HMBC showed that the correlations between H-2, H-6, H-8 and a carbonyl group C-7 and between H-7′ and C-8/C-1′/C-2′/C-6′. Furthermore, the COSY experiment established the location of a methyl group at C-9 by establishing the spin system of $(CH_3)CH—CH(CH_3)—CH—$ (Fig. 1). The 1D and 2D NMR spectra of compound **1** showed a typical backbone signal for a 8-8′-lignan. From all the above evidence, the planar structure of compound **1** was established as 4-(3,4-dimethoxyphenyl)-4-hydroxy-3-methlbutan-2-yl-3,4-dimethoxybenzoate, and it was similar to that of 3′,4′-dimethoxybenzoic acid (3′,4′-dimethoxyphenyl)-2-methyl-3-oxobutyl ester (**10**); unfortunately the absolute configuration was not determined (Li et al., 2013). The relative configuration between H-7′ and H-8′ was established as *erythro* due to the smaller coupling constant between H-7′ and H-8′ (*J* 7.7 Hz) (Lopez et al.,1995; Yu et al. 2014). Consequently, the structure of compound **1** was determined as *erythro*-4-(3,4-dimethoxyphenyl)-4-hydroxy-3-methlbutan-2-yl-3,4-dimethoxybenzoate.

The known compounds, *p*-hydroxy benzaldehyde (**2**) (Kim et al., 2003), vanillin (**3**) (Pouységu et al., 2010), coniferaldehyde (**4**) (Carpinella et al., 2003), arisantetralone A, C (**5 - 6**) (Cheng et al., 2009), schizandrin (**7**) (Ikeya et al., 1988b), gomisin S (**8**) (Ikeya et al., 1988a), gomisin D (**9**) (Ikeya et al., 1976), 3′,4′-dimethoxybenzoic acid (3′′,4′′-dimethoxyphenyl)-2-methyl-3-oxobutyl ester (**10**) (Li et al., 2013), schisanlactone C (**11**) (Liu and Huang, 1984), lancifodilactone L (**12**) (Xiao et al., 2006a), 20-hydroxymicrandilactone D (**13**) (Xiao et al., 2010a), schirubridilactone E (**14**) (Xiao et al., 2010b), henridilactone A (**15**) (Li et al., 2004) and micrandilactone F (**16**) (Li et al., 2005) were identified by comparison of their NMR and MS data with those reported in the literature.

All the isolated compounds were tested for their cytotoxicity in Hela, HepG2 and HCT-116 cells (Table 1S). Among these, **11** showed the most potent cytotoxic activity with IC_{50} values of 15.7 ± 1.6, 18.7 ± 0.9 and 14.8 ± 1.1 μM against Hela, HepG2 and HCT-116 cells, respectively. In previous studies, schisanartane-*type* nortriterpenoids isolated from *Schisandra* genus such as rubrifloradilactone C, schigrandilactones A and B, exhibited cytotoxicity in KB, MDA-MB 231, K562 and C8166 cancer cell lines (Xiao et al., 2008b, 2009; Gao et al., 2013). However, those compounds are structurally different from the nortriterpenoids that has been isolated in this study. For example, rubrifloradilactone C forms the same planar substructure of rings A–F as those of **12**–**16** but a five-membered α-oxo-β-methyl-γ-lactone ring moiety was attached to C-22, while schigrandilactones A and B have spirocyclic moiety (ring H) in their structures. In this study, compound **11** was the only cycloartane-*type* triterpene and showed significant cytotoxicity. In line with this, cycloartane-*type* triterpene such as schispenadilactone B, henrischinin A and B isolated from Schisandrae species showed significant cytotoxic activity against HL-60 cell line (Xue et al., 2011; Liang et al., 2014). Especially, both henrischinins A and B are biogenetically related to schisanlactone A and B which structurally similar to compound **11** as well (Xue et al., 2011).

Conclusion

Herein, we detailed the phytochemical study of the fruits of *S. sphenanthera* and resulted in the isolation of a novel lignan (**1**), *erythro*-4-(3,4-dimethoxyphenyl)-4-hydroxy-3-methylbutan-2yl-3,4-dimethoxybenzoate, as well as fifteen previously reported



compounds (**2**–**16**). All the isolated compounds were tested for their cytotoxicity against Hela, HepG2 and HCT-116 cells. Among them, compound **11** exhibited significant cytotoxicity activity against all three cells.

Authors' contributions

HJK, SP, GY, JP, YO and MO contributed laboratory experiments. NXN contributed to collect plant sample. YNK and EJJ performed cytotoxicity assay. HJK contributed to isolated and purified compounds, analyse the NMR data and prepared the manuscript. SHK supervised the laboratory work and reviewed the manuscript. All the authors have read the final manuscript and approved the submission.

Ethical disclosures

Protection of human and animal subjects

The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data

The authors declare that no patient data appear in this article.

Right to privacy and informed consent

The authors declare that no patient data appear in this article.

Conflict of interest

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjp.2019.05.006.

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