



Two new lignans from the aerial parts of *Saururus chinensis* with cytotoxicity toward nasopharyngeal carcinoma

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ABSTRACT

Two new lignans (**1** and **12**), together with 15 known compounds (**2–11** and **13–17**), were isolated from the aerial parts of *Saururus chinensis* Baill. Their structures were determined through extensive spectroscopic analyses. All the isolates were evaluated for their cytotoxicity against four human nasopharyngeal carcinoma cells (HONE1, CNE1, CNE2, and SUNE1). Compound **13** showed the most potent cytotoxicity toward HONE1, SUNE1, CNE2, and CNE1 cells with IC₅₀ values of 0.76, 5.42, 5.86 and 6.28 μM, respectively. Further studies revealed that compound **13** suppressed cell growth by arresting the cell cycle at the S phase and induced cell apoptosis in the HONE1 cell line.

1. Introduction

Saururus chinensis Baill (Saururaceae), a famous medicinal perennial herbaceous plant grown in China and Korea, has been traditionally used to cure various diseases such as leproma, edema, jaundice, hypertension, gonorrhoea, and pneumonia [1]. Phytochemical studies led to the isolation of lignans [2], aristolactams [3], flavonoids [4], and furanoditerpenes [5]. Lignans are reported as the primary effective constituents of *S. chinensis*, including anti-inflammation [6], anti-oxidative activity [7], cytotoxicity [8] and inhibition of EBV [9], HIV-1 protease [10], arginase II [11], Stat3 [12], and HIF-1 [13].

Nasopharyngeal carcinoma (NPC) is characteristic of certain geographies, being prevalent in Southern China, Southeast Asia, and North Africa, with an occurrence of 50 cases per 100,000 people per year [14]. The treatment effects for NPC have been greatly improved by radiotherapy and combined chemo-radiotherapy. However, the local relapse, distant metastasis and therapeutic resistance led to high mortality of NPC patients [15]. There is an important relationship between Epstein-Barr virus (EBV) and the occurrence of NPC [16]. EBV infection is found in > 90% NPC cases in endemic area [12]. A recently proposed approach to treat EBV-positive cancers involves administration of antiviral drugs [17]. Our previous work has shown that lignans from the roots of *S. chinensis* Baill exhibited potent inhibitory effects toward EBV lytic replication [9]. Here, the anti-NPC active constituents was further investigated on the aerial parts of *S. chinensis*.

2. Results and discussion

Chromatographic separation the EtOAc extract of the aerial parts of *S. chinensis* yielded two new lignans (**1** and **12**) and 15 known compounds (**2–11** and **13–17**). The known compounds were identified as saurufurin B (**2**) [18], sauruculin I (**3**) [9], (-)-zuonin A (**4**) [19], sauchinone A (**5**) [20], 1'-*epi*-sauchinone (**6**) [20], sauchinone (**7**) [20], licarin B (**8**) [21], licarin A (**9**) [22], eupomatenoid-7 (**10**) [23], (2*R*,3*R*)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methylbenzofuran-5-aldehyde (**11**) [24], saucerneol (**13**) [25], saucerneol methyl ether (**14**) [25], (-)-(7''*R*,8''*R*)-saucerneol J (**15**) [9], 4-*O*-demethylmanassantin B (**16**) [26], and manassantin B (**17**) [27] with the reported spectral data in literature.

Compound **1** (7'-*epi*-henricine) was isolated as colorless oil. Its molecular formula was established as C₂₂H₂₆O₆ based on HRESIMS ion at *m/z* 409.1630 [M + Na]⁺ (calcd 409.1622). The NMR spectra of **1** showed signals for two aromatic rings. In the ¹H NMR signals, five protons appeared at δ_H 6.62–6.98 in the low-field. Three methoxy groups were observed at δ_H 3.88 (3H, s), 3.89 (3H, s), and 3.89 (3H, s). In addition, extra carbon signals appeared at δ_C 87.4/87.3 (C-7 and C-7'), 44.6/44.2 (C-8 and C-8'), and 13.0/12.8 (C-9 and C-9') in ¹³C NMR spectrum. The NMR spectra of compound **1** closely resembled to those of henricine [28], except for the chemical shifts at C-7/7', C-8/8', and C-9/9'. Thus compound **1** may be an epimer of henricine, which was further confirmed by 2D NMR (Fig. 2). The NOESY correlations of

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Table 1
 ^1H NMR and ^{13}C NMR data of Compounds **1** and **12**.

Position	1 ^a		12 ^a	
	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)
1	137.0		133.3	
2	106.1	6.62, d (1.2)	108.9	6.81, d (1.7)
3	143.4		146.5	
4	134.5		144.6	
5	148.9		114.1	6.90, m
6	100.3	6.65, d (1.2)	119.2	6.76, m
7	87.4	4.49, d (6.6)	84.1	5.44, d (4.3)
8	44.6	2.29, m	44.2	2.27, m
9	13.0	1.04, d (6.8)	14.9	0.70, d (6.2)
1'	134.5		136.7	
2'	118.6	6.96, dd (8.1, 1.8)	110.1	6.92, d (1.7)
3'	110.9	6.87, d (8.1)	150.6	
4'	148.5		146.4	
5'	148.9		118.7	6.97, d (8.1)
6'	109.7	6.98, d (1.8)	118.9	6.81, m
7'	87.3	4.46, d (6.3)	83.5	5.43, d (4.7)
8'	44.2	2.29, m	44.2	2.26, m
9'	12.8	1.02, d (6.7)	14.9	0.69, overlap
1''			132.1	
2''			120.8	6.86, m
3''			146.7	
4''			145.6	
5''			113.9	6.87, m
6''			109.4	6.92, m
7''			78.5	4.62, d (8.3)
8''			83.7	4.12, m
9''			17.1	1.15, d (6.3)
OMe	55.8	3.89, s	56.0	3.88, overlap
OMe	55.9	3.89, s	56.0	3.91, overlap
OMe	56.6	3.88, s	56.1	3.86, overlap
OCH ₂ O	101.4	5.96, s		
OH				5.76, brs

^a Recorded in CDCl₃ (^1H NMR 400 MHz, ^{13}C NMR 100 MHz).

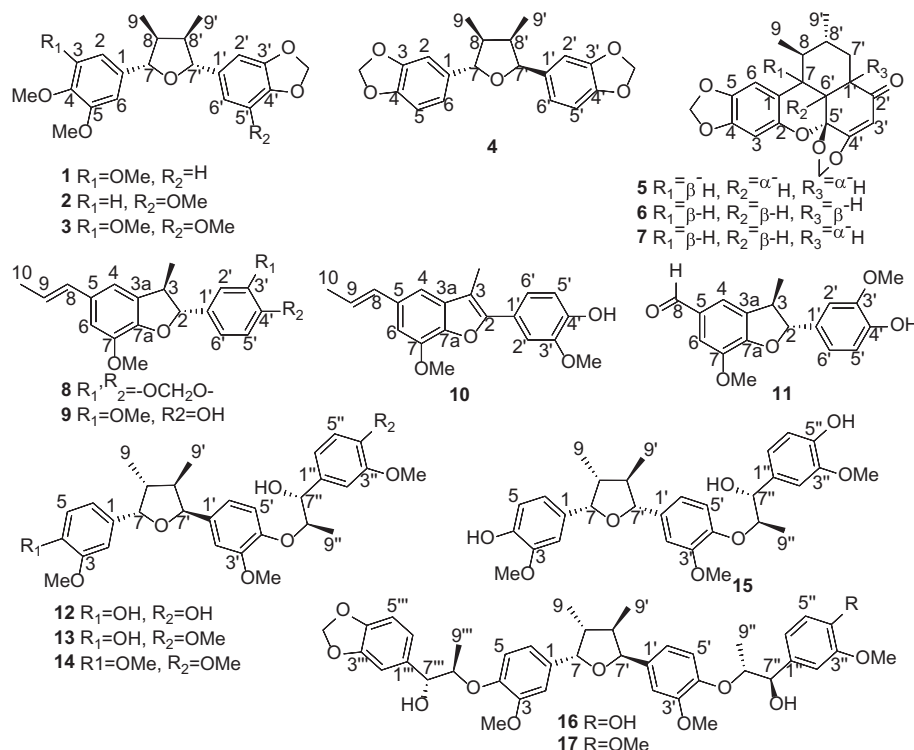


Fig. 1. Structures of compounds **1**–**17** from the aerial parts of *S. chinensis*.

H₃–9/H-7', H₃–9'/H-7, and H-7/H-7' indicated that H₃–9, H₃–9', H-7, and H-7' are β-oriented. In our previous research [9], we summarized the chemical shifts of C-7/7', C-8/8', and C-9/9' for different configurations of tetrahydrofuran ring [9]. In compound **1**, the carbon signals for C-7/7', C-8/8', and C-9/9' are 87.4/87.3, 44.6/44.2, and 13.0/12.8 (Table 1). Hence, the absolute configuration of compound **1** was assigned as 7*S*, 7'*R*, 8*S*, and 8'*R* Fig. 1.

The molecular formula of **12** (8,7',8'-*epi*-saucerneol C) was determined as C₃₀H₃₆O₈ by HRESIMS. In the ^1H NMR spectrum, nine protons at δ_{H} 6.76–6.97 in the low-field region could be attributed to three 1,3,4-trisubstituted aromatic rings. The NMR data of compound **12** exhibited strong similarities to those of saucerneol C [29], which suggested **12** may be an epimer of saucerneol C. The HMBC spectrum (Fig. 3) confirmed that its planar structure was identical to that of saucerneol C. The NOESY correlations of H-7'/H-8/H-9' and H-7'/H-8'/H-9 confirmed the relative configurations of H-7' and H-8' protons in an α-orientation and the H-7 and H-8 protons in a β-orientation. The chemical shifts of C-7/7', C-8/8', and C-9/9' indicated the absolute configurations were 7*S*, 8*R*, 7'*S*, and 8'*R* [9]. Similarities of C-7''/8'' *threo* configuration ($J_{7'',8''} = 8.3$ Hz) between compounds **12**, **13**, and saucerneol C demonstrated that they have the same relative configurations of C-7''/8''. Thus, the configuration of compound **12** was determined to be 7*S*, 8*R*, 7'*S*, 8'*R*, 7''*R*, and 8''*R*.

All the isolates were evaluated for their cytotoxicity against four NPC cells as shown in Table 2. Among them, compound **13** showed the most potent cytotoxicity against HONE1 human NPC cells (IC₅₀ = 0.76 μM), which is better than the positive control cisplatin (IC₅₀ = 8.00 μM) in HONE1 cells. It disturbed cell cycle progression and resulted in an increasing number of cells in the S phase region in HONE1 cells (Fig. 4). Moreover, compound **13** decreased the expression level of protein CDK2 and Cyclin D1 which closely related to the S phase progression (Fig. 5). Annexin V-FITC/PI double staining analysis was carried out to detect cell apoptosis. Flow cytometry analysis revealed that compound **13** dose-dependently induced cell apoptosis in HONE1 cells through down regulation of the apoptotic protein poly ADP-ribose polymerase (PARP) (Fig. 5). In conclusion, these findings

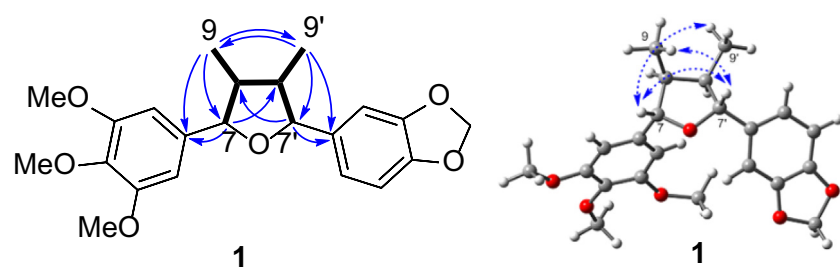


Fig. 2. Key $^1\text{H} - ^1\text{H}$ COSY (—), HMBC (—), and NOESY (—) correlations of compound 1.

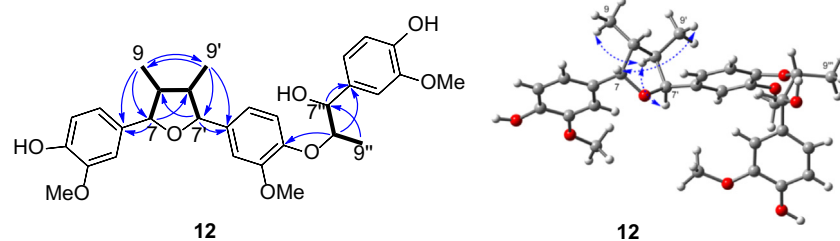


Fig. 3. Key $^1\text{H} - ^1\text{H}$ COSY (—), HMBC (—), and NOESY (—) correlations of compound 12.

Table 2
Cytotoxicity of the isolated 17 lignans from the aerial parts of *S. chinensis*.

Comps	Inhibition ratio (%) ^a			
	CNE1	CNE2	SUNE1	HONE1
1	22.7	NA ^b	NA	55.0
2	15.7	6.0	18.0	47.0
3	80.7	42.7	55.3	50.0
4	NA	NA	NA	22.7
5	NA	NA	NA	9.5
6	NA	NA	NA	22.0
7	NA ^b	NA	NA	NA
8	NA	NA	NA	NA
9	NA	NA	NA	13.0
10	21.0	NA	19.3	36.0
11	NA	NA	NA	24.5
12	95.0	31.3	31.6	50.3
13	79.7	69.2	55.8	90.8
14	49.7	17.1	15.2	38.3
15	57.3	27.7	25.7	51.3
16	52.3	26.3	53.1	42.7
17	70.5	30.7	46.7	23.7
Cisplatin ^c	76.3	82.4	92.3	72.7

^a Inhibition ratio is expressed as the mean values of three experiments at 10 μM .

^b NA means no active; ^cCisplatin was used as positive control.

suggested that compound 13 showed anti-tumor activity through inhibiting the growth of cells and inducing apoptosis in HONE1 cells.

3. Experimental section

3.1. General experimental procedures

Optical rotations data were obtained with the Anton Paar MCP 200 automatic polarimeter. UV spectra were recorded using a Shimadzu UV-2450 spectrophotometer. ECD spectra were acquired on an Applied Photophysics Chirascan spectrometer. IR spectra were determined from KBr pellets on a Fourier transformation infra-red spectrometer coupled with infra-red microscope. The ^1H (400 MHz), ^{13}C (100 MHz), and 2D NMR spectra were obtained on a Bruker AM-400 NMR spectrometer with TMS as an internal reference. HRESIMS were acquired on a Shimadzu LCMS-IT-TOF, and the ESIMS data were measured on an Agilent 1200 series LC-MS/MS system. RP-C₁₈ silica gel (Fuji, 40–75 μm), MCI gel (CHP20P, 75–150 μm , Mitsubishi Chemical

Corporation, Tokyo, Japan), silica gel (200–300 Mesh Marine Chemical Ltd., Qingdao, People's Republic of China), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden) were used for column chromatography (CC). Preparative and semi-preparative HPLC separations were carried out on a LC-20AT Shimadzu liquid chromatography system with a YMC ODS-A column (250 \times 4.6 mm, 5 μm) connected with an SPD-M20A diode array detector. TLC analysis was carried out on silica gel plates (Marine Chemical Ltd., Qingdao, China). Fractions were monitored by TLC and visualized by heating plates sprayed with 5% H_2SO_4 in EtOH. The human nasopharyngeal carcinoma cell lines (HONE1, SUNE1, CNE1, CNE2) were maintained in RPMI 1640 medium (Thermo Fisher Scientific, America) supplementing 10% fetal bovine serum (FBS) (Gibco, South America) and 10,000 U/mL penicillin, and 10,000 $\mu\text{g}/\text{mL}$ streptomycin (Hyclone, America). MTT (Sigama, America) assay was detected by Microplate reader (Molecular devices, Flex Station 3, America). Cell apoptosis assay, testing by Annexin V-FITC Apoptosis Detection Kit (Yeasen, China) and cell cycle assay, detecting with Cell Cycle and Apoptosis Analysis Kit (Yeasen, China) were analyzed on Flow cytometry (Beckman Coulter, FC500, America).

3.1.1. Plant material

The aerial parts of *Saururus chinensis* (Lour.) Baill (10.0 kg) were purchased from Guangzhou Zhong Zhi Yuan Traditional Chinese Medicine co., LTD, and identified by Dr. Chunyan Han from the Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (160401) was deposited at the School of Pharmaceutical Sciences, Sun Yat-sen University.

3.1.2. Extraction and isolation

The air-dried and powdered aerial parts of *S. chinensis* (Lour.) Baill (10.0 kg) were extracted with 95% EtOH (3 \times 30 L) at room temperature for two days to obtain an extract, which was partitioned with EtOAc (4 \times 4 L) and H₂O. The EtOAc fraction (500 g) was subjected to silica gel column chromatography (CC) using petroleum ether/EtOAc to afford Fr.1–Fr.10. Fr.2 was separated using silica gel columns eluting with petroleum ether/acetone and further purified by preparative HPLC (80% CH₃OH/H₂O) to afford 4 (130 mg) and 8 (1.59 g). Fr.3 was separated using various columns and further purified by semi-preparative HPLC to afford 5 (44 mg) and 7 (6 g). Fr.4 was separated using various columns and further purified by semi-preparative HPLC to afford 6 (25 mg), 9 (577 mg), 10 (5 mg) and 11 (40 mg). Fr.5 was separated using various columns and further purified by semi-preparative HPLC to afford 1 (38 mg) and 3 (271 mg). Fr.8 was purified by various

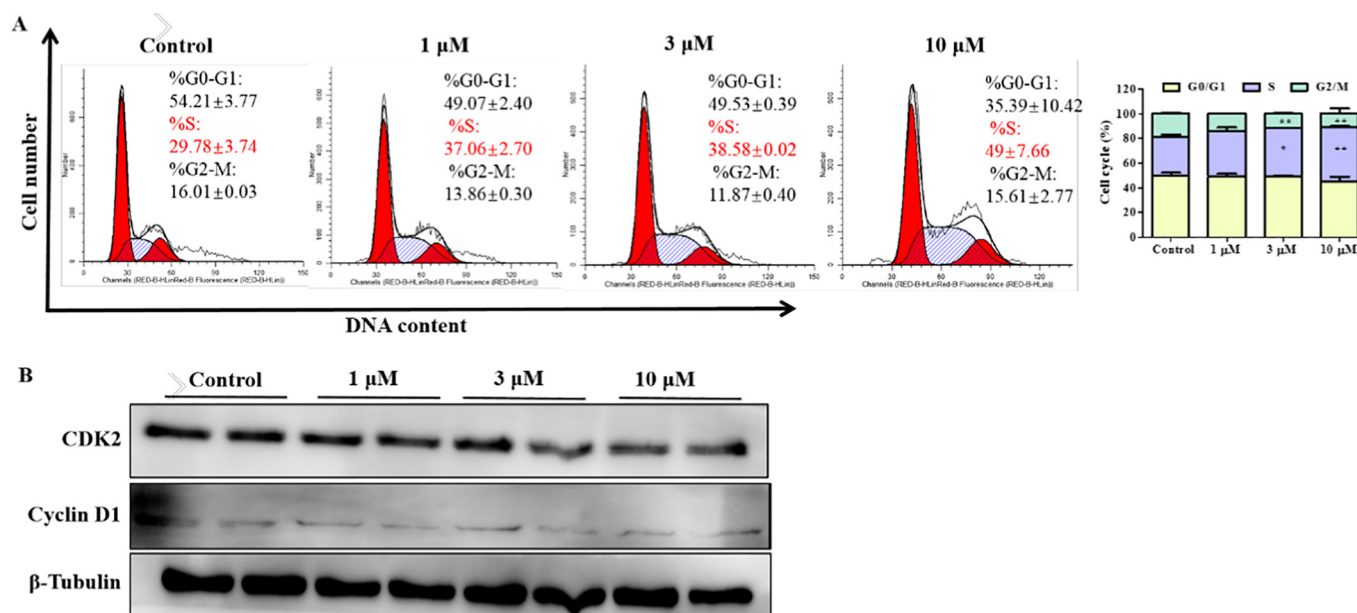


Fig. 4. Compound 13 arrested HONE1 cells at S phase. (A) HONE1 cells were treated with 13 (0, 1, 3 and 10 μM) for 24 h, and stained with PI, then analyzed by flow cytometry to determine cell-cycle phases and distribution of cells (%). (B) Western blot analysis of cell cycle regulatory protein. (**P* < .05, ***P* < .01 vs control group).

columns and further purified by HPLC to afford 2 (8 mg), 3 (5 mg), 12 (45 mg), 13 (412 mg), 14 (58 mg), 15 (6 mg), 16 (109 mg), and 17 (1.0 g).

3.1.3. Spectroscopic data

7'-*epi*-henricine (1): Colorless oil; [α]_D²⁵ + 17.0 (*c* 0.1, MeOH); UV(MeOH) λ_{max} (log ε) 280 (2.76) nm; IR (KBr) ν_{max} 2956, 2836, 1635, 1515, 1454, 1133, 1037 and 798 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRESIMS: *m/z* 409.1630 [M + Na]⁺ (calcd 409.1622).

8,7',8'-*epi*-saucerneol C (12): White powder; [α]_D²⁵ + 12.0 (*c* 0.1, MeOH); UV(MeOH) λ_{max} (log ε) 204 (3.96), 232 (3.40) 280 (3.00) nm; IR (KBr) ν_{max} 3432, 2964, 1606, 1513, 12,682, 1035 and 738 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRESIMS: *m/z* 547.2286 [M + Na]⁺ (calcd 547.2302).

3.2. Biological activity assay

3.2.1. Cells cultures and cytotoxicity assay

The poorly differentiated human nasopharyngeal carcinoma (HONE1 and CNE2), the highly metastatic human nasopharyngeal carcinoma (SUNE1) and the highly differentiated human nasopharyngeal carcinoma (CNE1) cell lines were obtained from the Cancer Center of Sun Yat-sen University and cultured in RPMI 1640 medium with 10% Fetal bovine serum (v/v) and supplementary 1% (v/v) penicillin/streptomycin at 37 °C in a humidified atmosphere with 5% CO₂. For cytotoxicity assay, the cells were seeded at 2000–3000 cells/well in 96 well plates for 24 h, then supernatant was removed. Next the indicated concentrations of test compounds were added and cultured for 48 h in triplicate. Two days later, MTT solution (20 μL, 5 mg/mL) was added to each well and incubated for another 4 h (RPMI 1640 medium with MTT as blank), after which the formazan crystals were dissolved with 150 μL DMSO, and then detected by microplate spectrophotometer

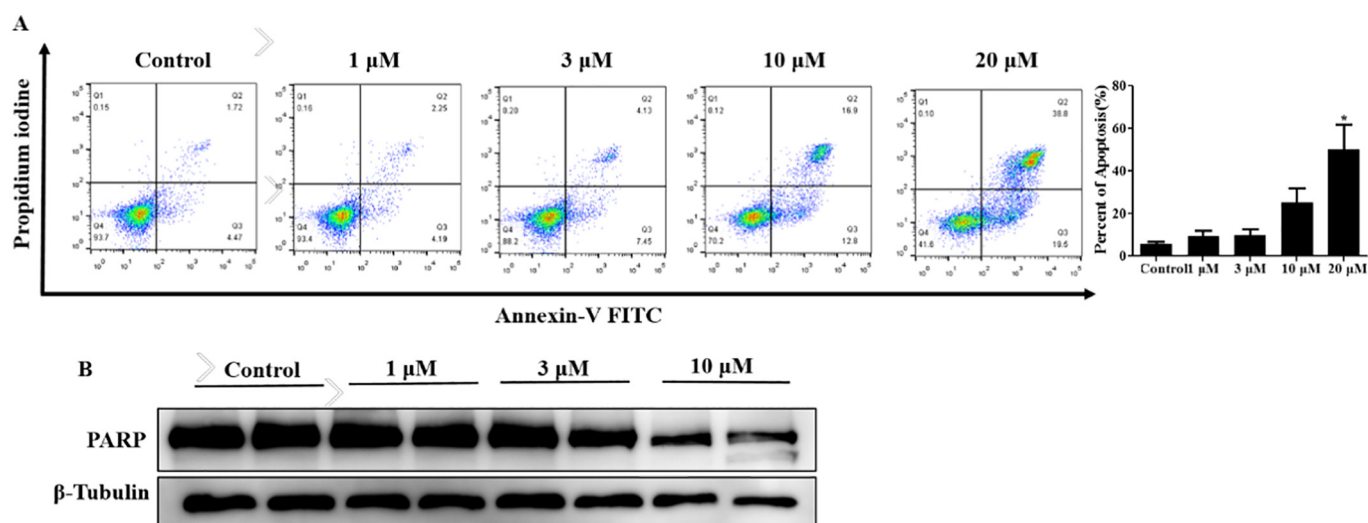


Fig. 5. Compound 13 caused apoptosis in HONE1 cells. (A) Cells were treated with compound 13 (0, 1, 3, 10 and 20 μM) for 24 h, and stained with Annexin-V FITC/PI before analyzing by flow cytometry to evaluate apoptosis ratio. (B) Western blot analysis of apoptotic protein. (**P* < .05 vs control group)

at 492 nm. All data was calculated on GraphPad Prism software version 5.

3.2.2. Cell cycle and cell apoptosis assay

HONE1 cells were seeded in 6 well plates at a density of 5×10^5 cells/well overnight. After 24 h treatment with various concentrations of compound **13** (0, 1, 3 and $10 \mu\text{M}$), HONE1 cells were collected and stained with Annexin V-FITC/PI according to the manufacturer's method then analyzed by flow cytometry (10,000 events). Results were analyzed by FlowJo VX software. To assay the cellular DNA content in HONE1 cells, cells were harvested and fixed with 1 mL ice-cold 70% (v/v) EtOH for > 4 h at 4°C . After permeabilization, cells were resuspended in staining buffer containing RNase A and PI for 30 min in the dark at 37°C and then evaluated by flow cytometry (10,000 events). Data analysis was performed on Modfit software.

3.2.3. Western blot analysis

Vehicle or indicated concentrations of compound **13** treated cells were lysed on ice with lysis buffer for 15 min, then cells were centrifuged at $13,000 \text{ g}$ at 4°C for 15 min. The protein concentration in the supernatant was detected by BCA kit (ThermoFisher Scientific, America) according to the manufacturer's method. Equal amounts of proteins ($40 \mu\text{g}$) were loaded on 12% SDS-PAGE gels then transferred to PVDF membrane (Milipore, America). After which membranes were blocked with 5% (W/V) skim milk for 1 h at room temperature and incubated with specific primary antibodies against CDK2, Cyclin D1, PARP and β -Tubulin (CST, America) and secondary antibodies (CST, America) (1:1000 for primary antibodies and 1:3000 for secondary antibodies). Finally protein signals were captured using the Tanon-5200 image system.

3.3. Statistical analysis

All data was obtained from three independent experiments. Statistical analysis was analyzed by Student's *t*-test. A $P < .05$ was considered to be statistically significant. All statistical analysis was performed on GraphPad Prism software version 5.

4. Conclusions

Seventeen lignans, including two new compounds (**1** and **12**), were isolated from the aerial parts of *S. chinensis*. All the isolates were evaluated for their cytotoxicity toward four NPC cell lines. Among them, compound **13** showed the most potent cytotoxicity toward HONE1, SUNE1, CNE2, and CNE1 cells with IC_{50} values of 0.76, 5.42, 5.86 and $6.28 \mu\text{M}$, respectively. Further studies revealed that compound **13** suppressed cells growth by arresting cell cycle at S phases and induced cells apoptosis in HONE1 cells. Here, compound **13** is a sesquiolignans with cytotoxicity against four NPC cells, while compound **17**, as a dineolignans, showed most potent anti-EBV activity in our previous report [9]. These results may suggest that the plant of *S. chinensis* may be a promising anti-NPC agent for its different type lignans having varied activity against EBV and NPC cells.

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fitote.2019.104344>.

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