TRITERPENOIDS FROM *SCHEFFLERA HEPTAPHYLLA* AND THEIR CYTOTOXIC ACTIVITY

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ARTICLE INFO

Received: 03/02/2026
Revised: 13/4/2026
Published: 15/4/2026

KEYWORDS

Schefflera heptaphylla
Triterpene
Lupane
Araliaceae
Cytotoxicity

ABSTRACT

Using combined chromatographic methods, three known triterpenoids: 3*α*,11*α*-dihydroxy lup-20(29)-ene-23,28-dioic acid (**1**), 3*α*-hydroxy lup-20(29)-ene-23,28-dioic acid (**2**), and 3*α*-hydroxy lup-20(29)-ene-28-oic acid (**3**) were isolated from the methanolic extract of *Schefflera heptaphylla.* Their structures were elucidated by 1D- and 2D-NMR spectroscopic analyses, HR-ESI-MS and comparison with previously reported NMR data. All compounds were evaluated for cytotoxic activity against human hepatocellular carcinoma (HepG2) and human embryonic kidney (HEK-293A) cell lines. Compounds **2** and **3** exhibited cytotoxic effects, with IC_{50} values of 32.29 ± 1.96 and 32.62 ± 2.30 µM for compound **2**, and 86.22 ± 6.27 and 80.79 ± 4.45 µM for compound **3** against HepG2 and HEK-293A cells, respectively, compared with the positive control ellipticine (IC_{50} = 0.34 ± 0.02 and 0.32 ± 0.03 µM). These research results partly demonstrate the potential for searching for triterpenoid compounds capable of inhibiting the growth of human liver cancer cell lines (HepG2) and human embryonal kidney cancer cells (HEK-293A) in particular and other cancer cell lines from *S. heptaphylla.*

CÁC HỢP CHẤT TRITERPENE TỪ LOÀI *SCHEFFLERA HEPTAPHYLLA* VÀ HOẠT TÍNH GÂY ĐỘC TẾ BÀO CỦA CHÚNG

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THÔNG TIN BÀI BÁO

Ngày nhận bài: 03/02/2026
Ngày hoàn thiện: 13/4/2026
Ngày đăng: 15/4/2026

TỪ KHÓA

Schefflera heptaphylla
Triterpene
Lupane
Araliaceae
Gây độc tế bào ung thư

TÓM TẮT

Sử dụng các phương pháp sắc ký kết hợp, ba hợp chất triterpenoid đã biết: 3*α*,11*α*-dihydroxy lup-20(29)-ene-23,28-dioic acid (**1**), 3*α*-hydroxy lup-20(29)-ene-23,28-dioic acid (**2**), và 3*α*-hydroxy lup-20(29)-ene-28-oic acid (**3**) được phân lập từ dịch chiết methanol của loài Ngũ gia bì chân chim *(Schefflera heptaphylla).* Cấu trúc hóa học của các hợp chất phân lập được xác định dựa trên phân tích phổ cộng hưởng từ hạt nhân một chiều và hai chiều (1D-, 2D-NMR), phổ khối lượng phân giải cao (HR-ESI-MS) và so sánh với các dữ liệu NMR đã được công bố trước đó. Tất cả các hợp chất phân lập được đánh giá hoạt tính gây độc tế bào trên các dòng tế bào ung thư gan người (HepG2) và tế bào ung thư thận gốc phôi người (HEK-293A). Trong đó, các hợp chất **2** và **3** thể hiện hoạt tính gây độc tế bào, với giá trị IC_{50} lần lượt là 32,29 ± 1,96 và 32,62 ± 2,30 µM đối với hợp chất **2**, và 86,22 ± 6,27 và 80,79 ± 4,45 µM đối với hợp chất **3** trên các dòng tế bào HepG2 và HEK-293A, (chất đối chứng dương ellipticine, có giá trị IC_{50} tương ứng là 0,34 ± 0,02 và 0,32 ± 0,03 µM). Những kết quả nghiên cứu này phần nào cho thấy khả năng tìm kiếm các hợp chất triterpenoid có khả năng ức chế sự phát triển các dòng tế bào ung thư thực nghiệm gan người (HepG2) và tế bào ung thư thận phôi người (HEK-293A) nói riêng và các dòng tế bào ung thư thực nghiệm khác từ loài Ngũ gia bì chân chim *(S. heptaphylla).*

DOI: https://doi.org/10.34238/tnu-jst.14720

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1. Introduction

Schefflera heptaphylla is a flowering plant species belonging to the family Araliaceae and is native to China, Vietnam, Japan, Cambodia, and Malaysia... This woody species prefers moist and sunny habitats and typically grows along streams or forest edges, reaching heights of 5–10 m [1]. *S. heptaphylla* is a rare and valuable medicinal plant widely used in folk medicine. The bark of this plant is used to treat colds, fever, bone pain, and sore throats [1]. Previous phytochemical studies have indicated that triterpenoids are the main chemical components of this plant, such as: taraxerone, 3-epi-taraxerol, aleuritolic acid, heptursosides A–D, heptoleosides A–D, heptdamoside A, asiaticoside D, 3-*epi*-betulinic acid 3-*O*-sulfate, 3*α*-hydroxy-lup-20(29)-en-23,28-dioic acid, betulinic acid 3-O-sulfate [2] - [7]. In addition, this plant also contains several caffeoylquinic acid derivatives, such as: 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, and 3-O-caffeoylquinic acid [8]. This species is known for its many interesting pharmacological effects and biological activities. Specifically, this species has a blood clotting effect [5]; antiviral activity against RSV [8]; cytotoxic [8], [9]; anti-inflammatory [3], [4], [10], [11], and antinociceptive activities [7]. Owing to these pharmacological properties, *S. heptaphylla* has attracted considerable scientific interest as a promising source of bioactive compounds.

In this study, we report on the isolation and structural determination of three triterpenoid compounds: 3*α*,11*α*-dihydroxy lup-20(29)-ene-23,28-dioic acid (1), 3*α*-hydroxy lup-20(29)-ene-23,28-dioic acid (2), and 3*α*-hydroxy lup-20(29)-ene-28-oic acid (3) from *S. heptaphylla* and evaluate their cytotoxic activity against human hepatocellular carcinoma (HepG2) and human embryonic kidney (HEK-293A) cell lines.

2. Materials and methods

2.1. General experimental procedures

All NMR spectra were recorded on a Bruker Avance III^{TM} 600 MHz spectrometer. Column chromatography (CC) was performed using silica gel (Kieselgel 60, 63-200 μm, Merck) or RP-18 resin (30–50 μm, Fuji Silysia Chemical Ltd.) or Sephadex LH-20. Thin-layer chromatography (TLC) was conducted on pre-coated silica-gel 60 F_{254} (0.20 mm, Merck) and RP-18 $F_{254}S$ (Merck) plates. Spots were visualized by spraying with a 10% sulfuric acid solution in methanol, followed by heating at 100°C.

2.2. Plant identification

The *Schefflera heptaphylla* (L.) Frodin was collected in Son La, Vietnam in September 2024, and identified by Dr. Tran Thi Phuong Anh, Graduate University of Science and Technology, VAST, Hanoi, Vietnam. A voucher specimen (SH-2024) was deposited at the Center for High Technology Research and Development, VAST, Hanoi, Vietnam.

2.3. Extraction and isolation

The aerial parts of *S. heptaphylla* (5.0 kg) were harvested, washed, dried, ground, and then ultrasonically extracted with methanol solvent (3 × 15 L, 3 h each at 45 °C). The extract was filtered, the solvent was removed under reduced pressure, and a methanolic extract (350.0 g) was obtained. The extract was suspended in water and successively partitioned with organic solvents to yield dichloromethane (SH1A), ethyl acetate (SH1B), and water (SH1C) fractions.

The SH1B fraction was subjected to silica gel column chromatography and eluted with a gradient of CH_2Cl_2/MeOH (100/0–0/1, v/v) to obtain five fractions, SH2A-SH2E. Fraction SH2C (5.6 g) was separated by RP-18 column chromatography using MeOH/water (2.5/1, v/v) to yield four fractions, SH3A-SH3D. Fraction SH3B (0.5 g) was purified by silica gel column chromatography eluted with CH_2Cl_2/acetone (5/1, v/v) to give compounds **1** (12.0 mg) and **2** (8.0

mg). Compound **3** (4.0 mg) was isolated from SH3D fraction by silica gel column chromatography using *n*-hexane/acetone (2/1, v/v).

3*α*,11*α*-dihydroxy lup-20(29)-ene-23,28-dioic acid (**1**): white amorphous powder; $C_{30}H_{46}O_6$; HR-ESI-MS *m/z* 503.3367 $[M+H]^+$ (calcd. for $C_{30}H_{47}O_6^+$ 503.3373), *m/z* 525.3182 $[M+Na]^+$ (calcd. for $C_{30}H_{46}O_6Na^+$ 525.3192); ^1H- (C_5D_5N, 600 MHz) and ^{13}C-NMR (C_5D_5N, 150 MHz) data, (see Table 1).

3α-hydroxy lup-20(29)-ene-23,28-dioic acid (**2**): white amorphous powder; $C_{30}H_{46}O_5$; HR-ESI-MS *m/z* 487.3418 $[M+H]^+$ (calcd. for $C_{30}H_{47}O_5^+$ 487.3423), *m/z* 509.3236 $[M+Na]^+$ (calcd. for $C_{30}H_{46}O_5Na^+$ 509.3243); ^1H- (C_5D_5N, 600 MHz) and ^{13}C-NMR (C_5D_5N, 150 MHz), (see Table 1).

3α-hydroxy lup-20(29)-ene-28-oic acid (**3**): white amorphous powder; $C_{30}H_{48}O_3$; HR-ESI-MS *m/z* 501.3595 $[M+HCOO]^-$ (calcd. for $C_{31}H_{49}O_5^+$ 501.3580); ^1H- (C_5D_5N, 600 MHz) and ^{13}C-NMR (C_5D_5N, 150 MHz), (see Table 1).

Table 1. *The ^1H- and ^{13}C-NMR data of compounds **1–3***

No	1		2		3	
	δ_C	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)
1	35.2	2.31 (m)/3.08 (m)	32.8	1.39 (m)/1.73 (m)	34.2	1.35 (m)/1.67 (m)
2	26.4	1.87 (m)/2.12 (m)	25.8	1.83 (m)/1.96 (m)	23.3	1.85 (m)/2.73 (m)
3	72.6	4.22 (m)	72.6	4.18 (br s)	82.4	4.65 (br s)
4	52.5	-	51.7	-	37.8	-
5	44.9	2.62 (d, 12.0)	44.7	2.45 (d, 11.4)	50.4	1.50 (m)
6	21.9	1.58 (m)/1.78 (m)	21.5	1.47 (m)/1.75 (m)	18.3	1.22 (m)/1.39 (m)
7	35.7	1.33 (m)/1.80 (m)	34.4	1.28 (m)/1.72 (m)	34.5	1.26 (m)/1.39 (m)
8	42.7	-	41.5	-	41.2	-
9	56.3	1.95 (br d, 10.8)	50.7	1.60 (m)	50.5	1.41 (m)
10	39.4	-	37.3	-	37.4	-
11	69.7	4.22 (m)	20.8	1.17 (m)/1.40 (m)	20.9	1.11 (m)/1.35 (m)
12	38.1	1.59 (m)/2.40 (m)	25.8	1.06 (m)/1.83 (m)	25.9	1.11 (m)/1.86 (m)
13	37.5	2.87 (m)	38.4	2.62 (m)	38.5	2.64 (m)
14	43.2	-	42.7	-	42.8	-
15	30.0	1.15 (m)/1.71 (m)	29.9	1.10 (m)/1.73 (m)	30.2	1.18 (m)/1.78 (m)
16	32.7	1.46 (m)/2.53 (m)	30.9	1.41 (m)/2.12 (m)	32.8	1.47 (m)/2.53 (m)
17	56.4	-	56.3	-	56.5	-
18	49.3	1.70 (m)	49.5	1.62 (m)	49.6	1.71 (m)
19	47.4	3.45 (m)	47.5	3.40 (m)	47.7	3.46 (m)
20	150.7	-	151.1	-	151.3	-
21	31.1	1.44 (m)/2.16 (m)	32.5	1.42 (m)/2.48 (m)	31.1	1.47 (m)/2.18 (m)
22	37.3	1.50 (m)/2.17 (m)	37.2	1.48 (m)/2.12 (m)	37.4	1.53 (m)/2.18 (m)
23	179.5	-	179.4	-	29.0	1.37 (s)
24	18.2	1.47 (s)	17.7	1.35 (s)	22.3	0.81 (s)
25	17.1	1.27 (s)	16.5	0.84 (s)	16.3	0.74 (s)
26	17.9	1.11 (s)	16.5	1.01 (s)	16.3	0.99 (s)
27	14.6	0.95 (s)	14.6	0.86 (s)	15.0	0.90 (s)
28	178.7	-	178.6	-	178.7	-
29	110.0	4.61 (s)/4.82 (s)	109.7	4.70 (s)/4.84 (s)	109.8	4.75 (s)/4.90 (s)
30	19.4	1.65 (s)	19.2	1.70 (s)	19.4	1.79 (s)

2.4. Cytotoxic assay

The cytotoxicity of the tested compounds was evaluated against two human cancer cell lines, LNCaP (prostate carcinoma) and SK-LU-1 (lung adenocarcinoma), using the Sulforhodamine B (SRB) assay [12], [13]. Cells were obtained from the American Type Culture Collection

(Manassas, VA, USA) and cultured in DMEM. Cells were trypsinized, counted, and seeded into 96-well plates (190 µL/well). Test samples were dissolved in 100% DMSO to obtain 20 mM stocks and diluted in serum-free medium directly on the plate to generate four serial concentrations. Diluted samples (10 µL) were added to the wells. Wells containing medium + 1% DMSO served as the day-0 control. After 1 h, day-0 wells were fixed with 20% TCA, and the remaining wells were incubated for 72 h. Cells were then fixed with 20% TCA for 1 h, stained with SRB for 30 min at 37 °C, washed with 1% acetic acid, air-dried, and the bound dye was solubilized in 10 mM Tris base. Absorbance was measured at 540 nm using a microplate reader. Cell growth inhibition was calculated as:

$$\%\text{Inhibition} = 100\% - \frac{OD(sample) - OD(day\ 0)}{OD(DMSO) - OD(day\ 0)} \quad (1)$$

3. Results and discussion

Compound **1** was obtained as a white amorphous powder. The molecular formula of compound **1** was $C_{30}H_{46}O_6$ as deduced by the pseudo molecular ion peaks on the HR-ESI-MS (*m/z* 503.3367 $[M+H]^+$ (calcd. for $C_{30}H_{47}O_6^+$ 503.3373), *m/z* 525.3182 $[M+Na]^+$ (calcd. for $C_{30}H_{46}O_6Na^+$ 525.3192). The ^{1}H-NMR spectrum of compound **1** showed signals of five tertiary methyl groups (δ_H 0.95, 1.11, 1.27, 1.47, and 1.65; each 3H, s); two olefinic protons (δ_H 4.61 and 4.62; each 1H, s); two oxygenated methine protons [4.22 (2H, m)]. The ^{13}C-NMR and HSQC spectra of **1** showed the signals of 30 carbons, including 8 non-protonated carbons (δ_C 39.4, 42.7, 43.2, 52.5, 56.4, 150.7, 178.7, and 179.5), 7 methines (δ_C 37.5, 44.9, 47.4, 49.3, 56.3, 69.7, and 72.6), 10 methylenes (δ_C 21.9, 26.4, 30.0, 31.1, 32.7, 35.2, 35.7, 37.3, 38.1, and 110.0), and 5 methyl groups (δ_C 14.6, 17.1, 17.9, 18.2, and 19.4). Analysis of the ^{1}H- and ^{13}C-NMR data suggested that compound **1** possessed a lupane-type triterpenoid skeleton, similar to 3α,11α-dihydroxy lup-20(29)-ene-23,28-dioic acid [14] (Figure 1). The HMBC correlations between H-24 (δ_H 1.47) and C-3 (δ_C 72.6)/C-4 (δ_C 52.5)/C-5 (δ_C 44.9)/C-23 (δ_C 179.5), H-9 (δ_H 1.95) and C-11 (δ_C 69.7), H-18 (δ_H 1.70) and C-17 (δ_C 56.4)/C-19 (δ_C 47.4)/C-20 (δ_C 150.7)/C-28 (δ_C 178.7), and H-30 (δ_H 1.65) and C-19 (δ_C 47.4)/C-20 (δ_C 150.7)/C-29 (δ_C 110.0) confirmed the positions of hydroxyl groups at C-3 and C-11, carboxylic acid groups at C-23 and C-28, and an olefinic bond at C-20/C-29 (Figure 2). Based on the above data, the structure of **1** was determined as 3α,11α-dihydroxy lup-20(29)-ene-23,28-dioic acid.

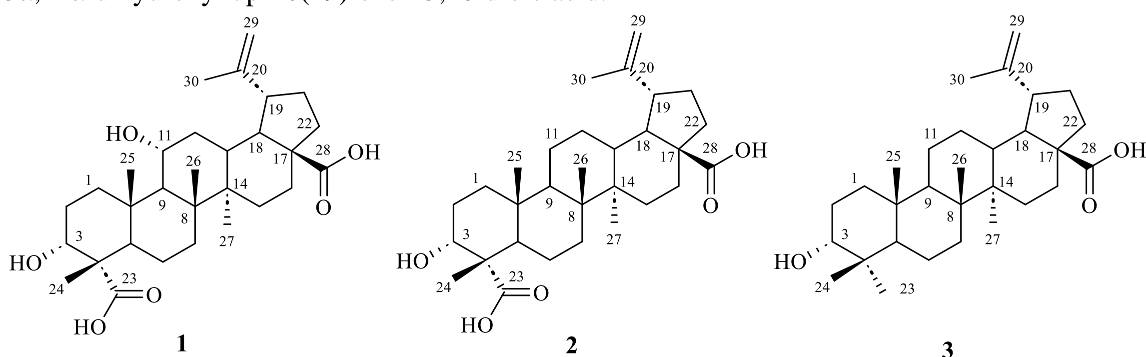

Figure 1. *The chemical structures of compounds 1–3*

Compound **2** was isolated as a white amorphous powder. The molecular formula of compound **2** was $C_{30}H_{46}O_5$ as determined by its HR-ESI-MS (*m/z* 487.3418 $[M+H]^+$, calcd. for $C_{30}H_{47}O_5^+$ 487.3423, *m/z* 509.3236 $[M+Na]^+$, calcd. for $C_{30}H_{46}O_5Na^+$ 509.3243). The NMR spectroscopic data of compound **2** were similar to those of compound **1**, except for the absence of a hydroxyl group at C-11. This structural difference was indicated by the upfield shift of the methylene

carbon and proton signals at C-11 (δ_C 20.8, δ_H 1.17 and 1.40) and was further confirmed by HMBC correlations from H-11 (δ_H 1.17/1.40) to C-9 (δ_C 50.7)/C-10 (δ_C 37.3) (Figure 2). On the basis of these spectroscopic data and comparison with previously reported literature data [15], compound **2** was identified as 3α-hydroxy lup-20(29)-ene-23,28-dioic acid.

Compound **3** was obtained as a white amorphous powder. Its molecular formula was determined to be $C_{30}H_{48}O_3$ based on HR-ESI-MS data (*m/z* 501.3595 $[M+HCOO]^-$, calcd. for $C_{31}H_{49}O_5^+$ 501.3580). The ^{1}H- and ^{13}C-NMR spectra of compound **3** were similar to those of compound **2**, except that the carboxylic acid group at C-4 was replaced by a methyl group, as indicated by signals at δ_C 29.0 (C-23) and δ_H 1.37 (s). This structural difference was further confirmed by HSQC and HMBC experiments. In the HMBC spectrum, correlations were observed between H-24 (δ_H 0.81) and C-3 (δ_C 82.4)/C-4 (δ_C 37.8)/C-5 (δ_C 50.4)/C-23 (δ_C 29.0) (Figure 2). On the basis of these spectroscopic data, compound **3** was identified as 3α-hydroxy lup-20(29)-ene-28-oic acid [16].

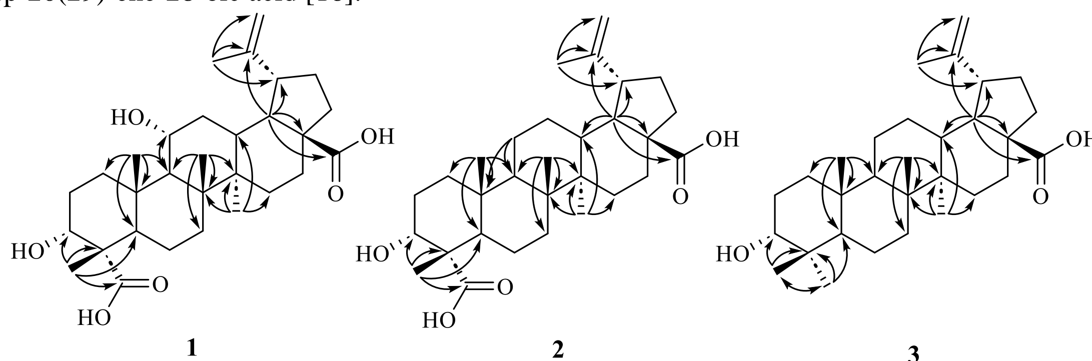

Figure 2. *The main HMBC interaction of compounds* **1** - **3**

All compounds isolated from *S. heptaphylla* were screened for cytotoxic activity against human hepatocellular carcinoma (HepG2) and human embryonic kidney (HEK-293A) cell lines at a concentration of 100 µM. As a result, compounds **2** and **3** exhibited cytotoxic activity with inhibition rates greater than 50%. Therefore, these compounds were further evaluated at various concentrations (100, 20, 4, and 0.8 µM) to determine their IC_{50} values. Ellipticine, an anticancer agent, was used as a positive control and exhibited cytotoxic activity with IC_{50} values of 0.34 ± 0.02 µM against HepG2 cells and 0.32 ± 0.03 µM against HEK-293A cells. Compound **2** showed significant cytotoxic activity against HepG2 and HEK-293A cell lines, with IC_{50} values of 32.29 ± 1.96 and 32.62 ± 2.30 µM, respectively. Compound **3** also exhibited cytotoxic activity against HepG2 and HEK-293A cells, with IC_{50} values of 86.22 ± 6.27 and 80.79 ± 4.45 µM, respectively.

The cytotoxic activity of compounds **1** and **2** on HepG2 have been previously reported by Dong Li Li and co-workers, and the results obtained in the present study are consistent with their published findings [17]. This is the first time compounds **1** and **2** have been studied for their cytotoxic activity on HEK-293A cell lines. This is the first time compound **3** has been studied for its cytotoxic activity on HepG2 and HEK-293A cell lines.

4. Conclusions

Three known compounds (**1**-**3**) were isolated from *S. heptaphylla*. Their chemical structures were elucidated by HR-ESI-MS, 1D- and 2D NMR spectra in comparison with the reported data. Compounds **2** and **3** exhibited cytotoxic effects, with IC_{50} values of 32.29 ± 1.96 and 32.62 ± 2.30 µM for compound **2**, and 86.22 ± 6.27 and 80.79 ± 4.45 µM for compound **3** against HepG2 and HEK-293A cells, respectively.

Acknowledgments

This research was supported by the Vietnam Academy of Science and Technology (VAST) under grant number KHCBSS.02/24-25.

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