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Selective cytotoxic activities of isolated compounds from *Impatiens chapaensis* grown in Vietnam

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ABSTRACT

This study aims to evaluate the selective cytotoxic activities against cancer stem cells (NTERA-2), mesenchymal stem cells (MSC), and normal human embryonic kidney cells (HEK) of eight isolated compounds derived from Impatiens chapaensis grown in Sapa and Ha Giang, Vietnam, including yemuoside (1), kaempferol (2), quercetin (3), phlorizin (4), spinasterol (5), spinasterone (6), 1H-indole-3-carboxylic acid (7), and arachidic acid (8). Among them, compound 2 exhibited the strongest inhibitory effect on NTERA-2 cells, with an IC_{50} value of 98.39 ± 3.29 µg/mL. Although compound 3 showed a weaker inhibitory effect compared to 2 on NTERA-2 cells (inhibition rate of 57.65%), it demonstrated greater selectivity by exhibiting lower cytotoxicity toward non-cancerous MSC and HEK cells, maintaining cell viabilities of 69.73% and 73.3%, respectively. The results of this study provide a foundation for further research aimed at applications in cancer treatment.

1. INTRODUCTION

Cancer stem cells (CSCs) are a subset of tumor cells characterized by their abilities for self-renewal and differentiation, akin to normal stem cell (Yu et al., 2012). These properties enable CSCs to drive tumor growth, metastasis, and recurrence. Notably, CSCs exhibit resistance to conventional chemotherapy and radiotherapy,

posing significant challenges in cancer treatment. The CSC hypothesis suggests that only this distinct population within a tumor can perpetuate malignancy and sustain tumor progression. Identifying and targeting CSCs are critical for developing therapies aimed at achieving more effective and lasting cancer eradication (Stopschinski et al., 2013)

Vietnam, a country rich in plant biodiversity, harbors numerous valuable natural species. Among these, the genus Impatiens has strongly attracted both phytochemists and biologists due to its widespread traditional uses in treating various ailments, including articular rheumatism, inflammation, allergies, diabetes, and cancer (Yang et al., 2001; Singh et al., 2017). Phytochemical investigations of Impatiens species have identified diverse secondary metabolites such as flavonoids, monophenols, coumarins, quinones, and triterpenoids, which served as bioactive candidates for various activities, including antimicrobial, anti-hyperglycemic, anti-inflammatory, and anti-hyaluronidase effects (Grabowska et al. 2016; Sakunphueak et al., 2012). Furthermore, the mechanisms of action of Impatiens components, such as inducing apoptosis in cancer cells and disrupting microbial biofilms, have also been investigated, revealing their potential as natural drug candidates within modern drug discovery pipelines (Lim et al., 2007; Cimmino et al., 2016). Despite the notable cytotoxic potential of Impatiens constituents against various human cancer cells, current literature on their selective cytotoxic activity toward cancer stem cells (NTERA-2) remains limited.

Considering these factors, our previous study provided an initial phytochemical analysis of *I. chapaensis* collected in Vietnam, leading to the isolation and structure elucidation of 8 compounds (1-8) (Linh et al., 2021; Linh et al., 2023). To search for promising selective cytotoxic compounds, we herein conducted an *in vitro* investigation into the cytotoxic effects of these isolated compounds against cancer stem cells (NTERA-2), and noncancer cells (MSC and HEK).

2. MATERIALS AND METHODS

2.1 Materials

I. chapaensis Tard. was collected in Lao Cai and Ha Giang districts, Vietnam in July 2025. Two voucher specimens of IC.LC.2025 and IC.HG.2025 were deposited in the Institute of Chemistry, VAST, Hanoi, Vietnam. Do Van Truong from Vietnam National Museum of Nature, VAST, Hanoi, Vietnam, identified the scientific name of plant.

Cancer stem cell line NTERA-2 (pluripotent human embryonic carcinoma), MSC (mesenchymal stem cells), and HEK (normal human embryonic kidney cells) were kindly provided by Pezzuto at Rutgers University, USA and Wongtrakoongate at Mahidol University, Thailand.

2.2 Cytotoxic assay

The protocol used for screening and detecting syntheses was the Sulforhodamine B (SRB) colorimetric assay, which can, *in vitro*, determine the obstruction of growth in cancer cells (Skehan et al., 1990). 96 well plates were used to plant both cancer (NTERA-2) and normal cells (MSC and HEK) at the concentration of 3 $x10^4$ cells per well in 37^0C and 5% CO_2. After 24 hours, cells

were dozed with different concentrations (20 and 100 µg/mL) of tested compounds and additionally incubated for another 72 hours. Furthermore, chilled trichloroacetic acid (TCA) 20% was added to these cells and then treated with 1% (v/v) of SRB (Sigma-Aldrich) for 1 hour at ambient room temperature. The excessive SRB was rinsed with 1% (v/v) acetic acid. Lastly, the SRB-binding proteins were dissolved in a 10 mM non-buffered Trisbase solution before measuring the OD value at 515 nm with a microplate reader (BioTek EXL800). The inhibition percentage of cell growth in the presence of reagents was determined utilizing the following formula:

% Inhibition = (1 – (OD_{sample} – OD_{blank}) / ($OD_{control}$ – OD_{blank}) x 100

% Survival = (OD_{sample} – OD_{blank})/(OD_{DMSO} – OD_{blank})

3. RESULTS AND DISCUSSION

3.1 Structural elucidation

Using a column chromatographic method, five compounds (1-5) (Figure 1) were isolated from *I. chapaensis* collected in Lao Cai Province, Vietnam, while three compounds (6-8) (Figure 1) were isolated from *I. chapaensis* collected in Ha Giang Province (Linh et al., 2021; Linh et al., 2023). The chemical structures were identified as yemuoside (1), kaempferol (2), quercetin (3), phlorizin (4), spinasterol (5), spinasterone (6), 1H-indole-3-carboxylic acid (7), and arachidic acid (8) (Figure 1), using the HR ESI MS, NMR techniques and confirmed by comparison with reported data, as detailed in our previous studies (Linh et al., 2021; Linh et al., 2023).

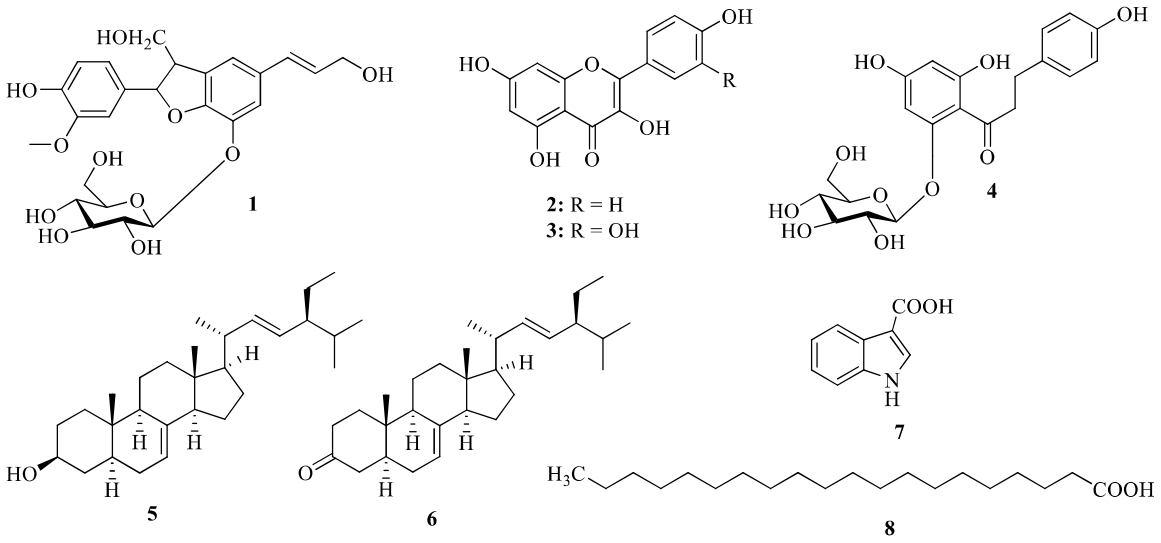

Figure 1. Structures of compounds 1-8 isolated from *I. chapaensis*

3.2 Cytotoxic activity of isolated compounds

Results from Figure 1 show that at the higher tested concentration (100 µg/mL), compounds 2 and 3 exhibited the highest inhibitory activity against NTERA-2 cells, with inhibition rates of 65.56% and 57.65%, respectively. This was followed by compounds 5 and 6, with inhibition rates of 29.12% and 21.31%, respectively, while the remaining compounds (1, 4, 7, and 8) appeared to have minimal or no inhibitory effects

on the tested cells. Regarding noncancerous cells (MSC and HEK), all tested compounds showed no significant cytotoxicity at the lower concentration (20 µg/mL), with cell survival ranging from 62.92% to 97.64% in MSCs and from 77.32% to 113.15% in HEK cells. However, at the higher concentration (100 µg/mL), compound **2** showed notable toxicity toward HEK cells, reducing their viability to 36.72%. In contrast, the remaining compounds demonstrated good safety profiles on HEK cells, with survival rates ranging from 69.38% to 119.34% at high concentration tested (100 µg/mL). These results suggested that compound **3** was a promising candidate for further investigation due to its potent inhibitory effect on NTERA-2 cancer stem cells and its low toxicity toward normal cells, even at high concentration tested (100 µg/mL).

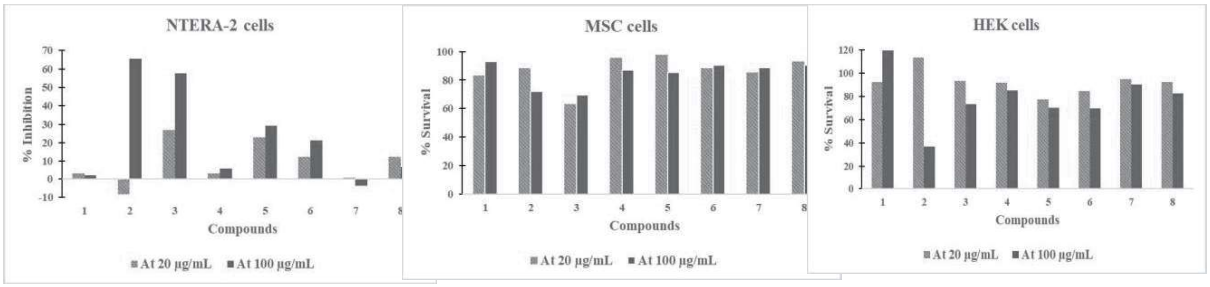

Figure 2. The cytotoxic activities of 8 compounds (1 – 8) at various concentrations (20 and 100 µg/mL)
A: Inhibition percentages of tested compounds on NTERA-2 cells; B: Survival percentage of tested compounds on Mesenchymal stem cells (MSC); C: Survival percentage of tested compounds on normal cells (HEK).

After the initial screening for cytotoxic effects, the two promising compounds (2 and 3) were further evaluated for cytotoxicity at various concentrations (0.8, 4, 20, and 100 µg/mL) to determine their IC_{50} values. Ellipticine was used as a positive control and tested at concentrations of 0.08, 0.4, 2, and 10 µg/mL. The results in Table 1 show that compound 2 exhibited a moderate inhibitory effect on NTERA-2 cells with the IC_{50} value of 98.39 ± 3.29 µg/mL, compared to ellipticine (IC_{50} 0.40 ± 0.04 µg/mL). In contrast, the IC_{50} value for compound 3 could not be determined within the tested concentration range.

Table 1. Cytotoxic activities of two compounds 2 and 3 against NTERA-2 sterm cells

Concentrations	2		3		Ellipticine*	
(µg/mL)	% Inhibition	SD	% Inhibition	SD	% Inhibition	SD
100	50.92	1.76	49.95	1.32	90.46	2.67
20	10.27	0.95	28.46	1.26	70.42	2.08
4	6.62	0.53	18.85	0.80	49.62	1.17
0.8	1.92	0.13	0.09	1.01	22.10	0.97
IC_{50}	**98.39 ± 3.29**		**> 100**		**0.40 ± 0.04**	

**Ellipticine was used as positive control and was tested at concentrations of 10-2-0.4, and 0.08 µg/mL*

Considering the structure–activity relationship, the significant inhibitory effects of compounds 2 and 3 suggested that flavonoid structures might serve as promising candidates for targeting NTERA-2 cancer stem cells. The structural differences between these two compounds implied that the presence of a hydroxyl group on the B-ring of the flavonoid skeleton could enhance safety toward non-cancerous cells (MSC and HEK). Although both flavonoids (compounds 2 and 3) were well-known for their various pharmacological properties, including antioxidant, antifungal, anti-inflammatory, antiproliferative, and anticarcinogenic activities (Wang et al., 2016; Kashafi et al., 2017), this study was the first to report their antiproliferative effects on NTERA-2 cells. The notable inhibitory activity of compound **2** against NTERA-2 cancer stem cells was consistent with previously published studies demonstrating quercetin's promising effects on other CSC lines, such as gastric and breast cancer T47D CSCs (Shen et al., 2016; Azizi et al., 2022).

4. CONCLUSION

In conclusion, this study present the initial screening of eight isolated compounds (1–8) derived from *I. chapaensis* grown in Vietnam. Among the tested compounds, 2 and 3 emerge as the most promising anticancer agents, exhibiting inhibition rates of 65.56% and 57.65%, respectively (IC_{50} value of 98.39 ± 3.29 µg/mL for 2). Notably, compound 3 shows no significant cytotoxic effects on non-cancerous MSC and HEK cells at a high concentration tested (100 µg/mL*),* suggesting its potential as a non-toxic therapeutic candidate. Future studies could focus on flavonoid structures to identify additional compounds with selective cytotoxic activity against NTERA-2 cancer stem cells.

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