

**ASTILBIN FROM *Smilax glabra* Roxb. AS A PRO-APOPTOTIC AGENT:
CYTOTOXICITY IN MULTIPLE CANCER CELL LINES AND SELECTIVITY
FOR 5637 BLADDER CARCINOMA**

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ABSTRACT

This study aims to evaluate the cytotoxic and pro-apoptotic effects of astilbin, derived from *Smilax glabra* Roxb., on multiple cancer cell lines, including 5637 (human bladder carcinoma), A549 (lung carcinoma), and HeLa (cervical adenocarcinoma), with a focus on apoptosis induction in 5637 cells. Using MTT assays, we observed a dose-dependent cytotoxic effect in both A549 and 5637 cancer cell lines, with the latter showing greater sensitivity to the treatment. Additionally, astilbin demonstrated preferential toxicity toward cancer cells compared to normal HEK-293T cells. Hoechst 33342 staining revealed apoptotic nuclear changes, including chromatin condensation and nuclear fragmentation, in 5637 cells treated with astilbin at varying concentrations. Conventional PCR analysis further confirmed the upregulation of apoptotic markers, including *BAX*, *CASP8*, and *CASP3*, suggesting activation of both intrinsic and extrinsic apoptotic pathways. These findings highlight astilbin's selective anticancer properties and apoptotic mechanisms. Future studies should focus on optimizing its potency, validating these effects in *in vivo* models, and exploring its potential in combination therapies.

Keywords: 5637 bladder carcinoma, apoptosis, astilbin, anticancer, cytotoxicity, *Smilax glabra* Roxb.

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INTRODUCTION

Cancer is defined as a disease characterized by the uncontrolled proliferation of transformed cells, governed by evolutionary processes through natural selection (Brown et al., 2023). It poses a global health threat, with nearly 20 million new cases diagnosed and 9.7 million cancer-related deaths in 2022 (Bray et al., 2024). Bray et al. (2024) indicated that almost half of all new cancer cases (49.2%) and more than half of cancer deaths (56.1%) occurred in Asia in 2022, which was home to 59.2% of the world's population. In Vietnam, the number of cancer cases is projected to double from 2013 to 2025, primarily due to an ageing and growing population, along with a shift in the epidemiology from infection-related cancers to lifestyle-related cancers (Nguyen et al., 2019). These staggering figures underscore the significant impact of cancer on both families and societies.

One critical hallmark of cancer is resistance to cell death (Hanahan & Weinberg, 2011). Thus, inducing programmed cell death (PCD) represents a promising target for cancer therapy. PCD encompasses apoptotic and non-apoptotic pathways, with apoptosis, a well-characterized, energy-dependent form of cell death, being particularly relevant in cancer therapy for its ability to selectively dismantle tumor cells while preserving surrounding tissue (Wong, 2011). Apoptosis occurs via three primary pathways: the extrinsic (death receptors), intrinsic (mitochondrial), and perforin/granzyme routes, each activating a cascade involving distinct initiator caspases (e.g., Caspase -8, -9, and -10) and culminating in the activation of executioner Caspase 3, which orchestrates the characteristic morphological changes observed in apoptotic cells (Cavalcante et al., 2019; Yan et al., 2020). This tightly regulated process, which includes cellular shrinkage, chromatin condensation, and membrane blebbing, often concludes with phagocytosis of apoptotic bodies without an inflammatory response, making apoptosis an attractive target for cancer therapies (Tian et al., 2024).

Natural products, especially phytochemicals, have long served as valuable sources for drug discovery. They offer a unique advantage over synthetic compounds due to their structural diversity, high bioavailability, and generally lower toxicity profiles (Atanasov et al., 2021). In this context, astilbin, or (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-2,3-dihydrochromen-4-one, a dihydroflavonol rhamnoside derived from *Smilax glabra* Roxb. (SGR), which belongs to the Smilacaceae family and is commonly known as “Thổ phục linh”, has gained significant attention for its diverse biological activities (Yang & Zhang, 2023). Astilbin has exhibited anti-inflammatory, hepatoprotective, and neuroprotective properties (Sharma et al., 2020), and recent studies suggest it might exert anticancer effects as well. Initial research has indicated that astilbin induces cell-cycle arrest and promotes apoptosis in specific cancer cell lines, such as HepG2 (liver cancer) and MCF-7 (breast cancer), through inducing cell-cycle arrest and caspase-mediated pathways (Sa et al., 2008; Sun et al., 2018). However, astilbin's anticancer efficacy in many other cancer cell types remains unexplored.

To address this gap, the present research aims to investigate the anticancer activities of astilbin derived from SGR on multiple cancer cell lines, namely 5637 (human bladder carcinoma), A549 (lung carcinoma), and HeLa (cervical adenocarcinoma). These findings are anticipated to provide foundational insights into astilbin's anticancer potential, positioning it as a candidate for further development in natural product-based cancer therapies.

MATERIALS AND METHODS

Preparation of astilbin

Astilbin (96% purity) was extracted and purified from SGR by Assoc. Prof. Nguyen Thi Mai Phuong, Institute of Biology, Vietnam Academy of Science and Technology, as described previously (Nguyen et al., 2020) and was dissolved in dimethyl sulfoxide (DMSO) 100% to create a stock solution of 50 mg/mL, stored at -20 °C. Working

concentrations were prepared by diluting the stock solution in cell culture medium.

Cell lines and culture conditions

Human cancer cell lines 5637 (bladder carcinoma), HeLa (cervical adenocarcinoma) and A549 (lung carcinoma) were obtained from the American Type Culture Collection (ATCC; Manassas, VA, USA). HEK-293T cells (human embryonic kidney, used as a normal control cell line) were also sourced from ATCC.

5637 cells were cultured in Gibco™ Roswell Park Memorial Institute 1640 Medium (1X) containing L-glutamine (Invitrogen Corp., Carlsbad, CA, USA) supplemented with 10% (v/v) Fetal Bovine Serum (FBS) (Invitrogen Corp., Carlsbad, CA, USA) and 1% (v/v) Antibiotic-Antimycotic 100X (Invitrogen Corp., Carlsbad, CA, USA). HeLa, A549 and HEK-293T cells were cultured in Dulbecco's Modified Eagle Medium (1X) (Invitrogen Corp., Carlsbad, CA, USA) composed of 10% (v/v) FBS and 1% (v/v) antibiotic-antimycotic 100X. Cells were maintained in a humidified incubator (Eppendorf CellXpert C170) at 37 °C with 5% CO₂ and subcultured every 2–3 days upon reaching approximately 80% confluence.

Cell viability assay

Cells were seeded into 96-well cell culture plates (Biologix Europe GmbH, Germany) at a density of 2×10^4 cells/200 µL/well and allowed to adhere overnight. After 24 hours, astilbin was added to the cells in serial concentrations (0, 10, 25, 50, 100 and 200 µg/mL) and incubated for 48 hours. Following treatment, 10% (v/v) of 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide reagent (MTT, SERVA Electrophoresis GmbH, Heidelberg, Germany) (final concentration, 0.5 mg/mL) was added to each well, and plates were incubated at 37 °C for an additional 4 hours in the dark. The resulting formazan crystals were dissolved in 200 µL of absolute isopropyl alcohol (Xilong Scientific Co., Ltd., China), and absorbance was measured at 570 nm using Synergy HTX Multi-mode Reader (BioTek, Vermont, USA).

Hoechst 33342 staining for apoptosis detection in 5637 cells

5637 cells were seeded into 60 × 15 mm cell culture dishes (Biologix Europe GmbH, Germany) at a density of 1×10^5 cells/dish in complete medium and allowed to adhere for 24 hours. Then, cells were treated with astilbin at varying concentrations (0, 10, 25, 50, 100 and 200 µg/mL) for 48 hours. After treatment, cells were washed twice with phosphate-buffered saline and stained with Hoechst 33342 (Thermo Fisher Scientific, MA, USA) dye following the manufacturer's instructions. Stained cells were then visualized under an Eclipse Ni-U microscope with Intensilight C-HGFI Epi-fluorescence Illuminator and a color DS-Ri2 Camera (Nikon, Tokyo, Japan) at 20X objective to observe nuclear condensation and fragmentation.

RNA extraction and cDNA synthesis

Total RNA was extracted from astilbin untreated and treated 5637 cells using TRIzol from TaKaRa RNAiso Plus (Takara Bio Inc., Japan), following the manufacturer's protocol. RNA quality and concentration were determined using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, MA, USA). First-strand cDNA was synthesized using 1 µg of total RNA with the HiScript III All-in-one RT SuperMix Perfect for qPCR (Nanjing Vazyme Biotech Co., Ltd, China), and was subsequently stored at -20 °C until use.

Conventional PCR and gel electrophoresis

Conventional PCR was performed using synthesized cDNA as a template on a ProFlex PCR System (ThermoFisher Scientific, USA). Primer sequences for 18S rRNA, BAX, CASP8, and CASP3 were indicated in Table 1. PCR reactions were carried out in a 15 µL reaction mixture containing 2 µL of cDNA at a concentration of 200 ng/µL, 7.5 µL of 2x Taq Master Mix (dye plus) (Vazyme Biotech Co., Ltd, China), and 0.25 µL of each primer. Amplification conditions were as follows: initial denaturation at 95 °C for 5 minutes, followed by 35 cycles of denaturation at 95 °C for 30 seconds, annealing at the specific primer annealing temperature for 30 seconds, and

72 °C for 40 seconds, with a final extension at 72 °C for 8 minutes. PCR products were separated on a 2% agarose gel electrophoresis stained with RedSafe. Bands were visualized under UV light using the UVP GelStudio

imaging system (Analytik Jena, Germany). Band intensities were quantified using ImageJ software, and the expression levels were normalized to 18S rRNA. Densitometric data are presented as mean $\pm$ SD.

Table 1. Primer sequences of study genes

Genes	Primer sequences	Length
18S rRNA	F: 5' CAGCCACCCGAGATTGAGCA 3'	251 bp
	R: 5' TAGTAGCGACGGGCGGGTG 3'	
Bcl-2-associated X protein (BAX)	F: 5' CCTGTGCACCAAGGTGCCGGAAGT 3'	113 bp
	R: 5' CCACCCTGGTCTTGGATCCAGCCC 3'	
Caspase 8 (CASP8)	F: 5' AAGCAAACCTCGGGGATACT 3'	114 bp
	R: 5' TGCATCCAAGTGTGTTCCAT 3'	
Caspase 3 (CASP3)	F: 5' TGACAGCCAGTGAGACTTGG 3'	111 bp
	R: 5' GACTCTAGACGGCATCCAGC 3'	

Statistical analysis

The data are expressed as the mean $\pm$ SD from at least three independent experiments. Differences between groups were analyzed using a Student's t-test and one-way ANOVA by GraphPad Prism 9.5.0.

RESULTS

Cytotoxicity of astilbin on multiple cell lines

The viability of HEK-293T cell line and human cancer cells (including HeLa, A549, and 5637) after being treated with different concentrations of astilbin compound for 48 hours was indicated using the MTT assay (Fig. 1).

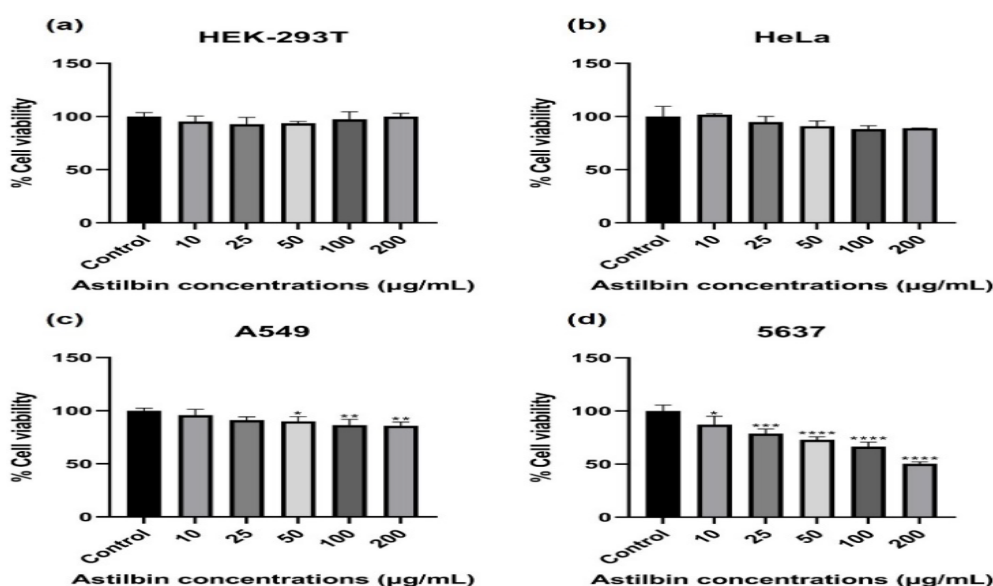


Figure 1. Cell viability of HEK-293T and human cancer cell lines after being treated with astilbin at increasing concentrations (0, 10, 25, 50, 100 and 200 µg/mL), including (a) HEK-293T; (b) HeLa; (c) A549; and (d) 5637. Each concentration of treatment was compared to the control sample and the data was analyzed using one-way ANOVA. Results are presented as mean $\pm$ SD, * $p \leq 0.05$, ** $p \leq 0.01$; *** $p \leq 0.001$; **** $p \leq 0.0001$ (n = 3)

As can be seen in Figure 1A, astilbin had no cytotoxic effects on the viability of HEK-293T cells at all tested concentrations (10, 25, 50, 100, and 200 $\mu\text{g/mL}$). Similarly, the cell viability of HeLa cells at all concentrations was not significantly affected by astilbin (Fig. 1B). However, the cell viability of A549 presented a slight decrease from $90.07 \pm 4.37\%$ to $85.87 \pm 3.43\%$ (from 50 $\mu\text{g/mL}$ to 200 $\mu\text{g/mL}$, respectively) (Fig. 1C). Notably, astilbin showed the strongest effect on the 5637 cells, with cell viability significantly reduced to approximately $49.7\% \pm 1.83$ at 200 $\mu\text{g/mL}$, as shown in Figure 1D. Overall, these results indicate that astilbin has the most potential anticancer activity against the 5637 cancer cell line.

Astilbin induced apoptosis in human bladder carcinoma (5637)

To investigate whether the cytotoxic effects of astilbin on 5637 cell lines were attributed to the induction of apoptosis, Hoechst 33342 staining was performed. As shown in Figure 2, cells treated with higher concentrations of astilbin displayed classic apoptotic features, including chromatin condensation and nuclear fragmentation, as compared to the untreated control, which showed uniformly round nuclei. These nuclear morphology changes suggest that astilbin promoted apoptotic cell death in 5637 cells.

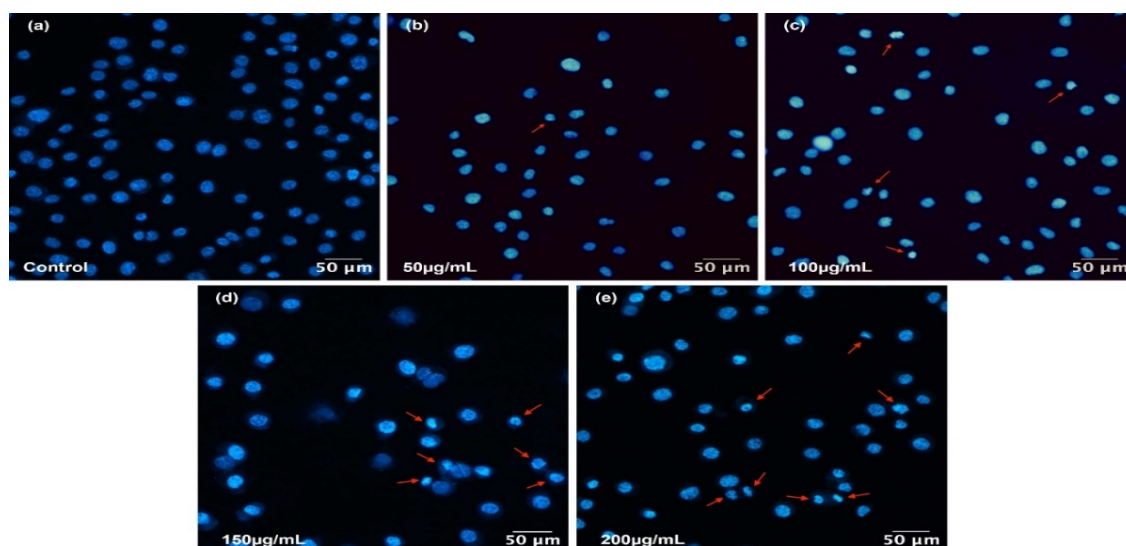


Figure 2. Induction of apoptosis in 5637 bladder carcinoma cells treated with astilbin at concentrations of (b) 50; (c) 100; (d) 150; (e) 200 $\mu\text{g/mL}$ for 48 hours as detected by Hoechst 33342 staining. Untreated cells were used as a control (a). Representative images show apoptotic features, including chromatin condensation and nuclear fragmentation, which are absent in untreated cells ($n = 3$)

Astilbin modulated the expression of genes associated with apoptosis

To examine the expression of key apoptosis-related genes in cancer, polymerase chain reactions were conducted. Three target apoptotic markers were assessed, including *BAX*, *CASP8*, and *CASP3*. The 18S rRNA housekeeping gene served as a reference for RNA integrity (Fig. 3).

Densitometric quantification confirmed a gradual increase in the expression levels of *BAX*, *CASP8*, and *CASP3* with increasing concentrations of astilbin (50; 100; 150; 200 $\mu\text{g/mL}$), as shown in Figures 3b-d. Among them, only the 200 $\mu\text{g/mL}$ treated group showed a statistically significant increase in the expression of *BAX* and *CASP3* when compared to the untreated

control. While *CASP8* expression also increased in a dose-dependent manner, the change did not reach statistical significance at any concentration tested.

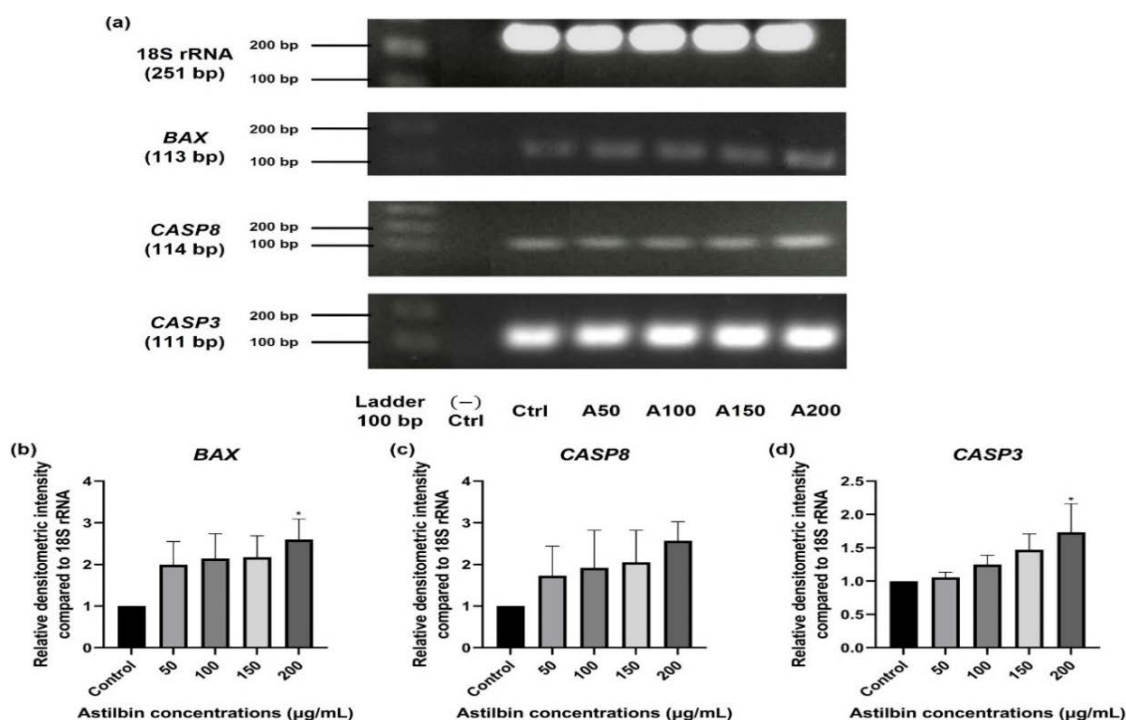


Figure 3. Conventional PCR analysis of 18S rRNA (251 bp), BAX (113 bp), CASP8 (114 bp), and CASP3 (111 bp) following the treatment with astilbin at increasing concentrations (0, 10, 25, 50, 100 and 200 μg/mL). HyperLadder™ 100bp (Cat. No. BIO-33029, Bioline, Meridian Bioscience Inc.) was used to assess the PCR product size. (a) Representative agarose gel images showing PCR amplification of target genes. (b-d) Quantitative densitometric analysis of PCR band intensities normalized to 18S rRNA. Each treatment concentration was compared to the control. Statistical significance was determined using one-way ANOVA. Data are presented as mean ± SD, * $p \leq 0.05$ ($n = 3$)

DISCUSSION

Astilbin has demonstrated a range of beneficial physiological and pharmacological properties in various studies. These include potent anti-inflammatory activity, hepatoprotective effects, neuroprotective effects, as well as antioxidant, antibacterial, and anti-diabetic properties (Sharma et al., 2020). Up to the present, astilbin and its plant origin have been shown to possess anticancer activities on certain cancer cell lines. Sa et al. (2008) showed that extracts of SGR, a plant source of astilbin, inhibits the growth of HepG2 and Hep3B cells by inducing cell-cycle arrest at the S phase or S/G2 transition and promoting apoptosis.

Similarly, Sun et al. (2018) reported that astilbin exhibits pro-apoptotic properties in MCF-7 and MDA-MB-231 cells through modulation of the caspase-dependent pathway. However, the anti-cancer effect of astilbin in other cancer cell types remains untested. Therefore, this study aims to investigate the cytotoxic and pro-apoptotic effects of astilbin, a dihydroflavonol rhamnosid, derived from SGR on multiple cancer cell lines, including 5637, A549 and HeLa.

Astilbin showed dose-dependent cytotoxicity in 5637 and A549 cancer cell lines, as indicated by MTT assay results. Between them, 5637 cells exhibited more

pronounced sensitivity, where the cell viability decreased to approximately $49.7 \pm 1.83\%$ at the highest concentration (200 $\mu\text{g/mL}$). Meanwhile, astilbin did not exhibit cytotoxic effect on normal HEK-293T cells at all tested concentrations, indicating astilbin's preferential toxicity toward cancer cells and its potential as a selective anticancer agent.

Hoechst staining was used as an assessment of the potential of astilbin to induce early apoptotic changes in 5637 cells without causing excessive cell death that could obscure specific apoptotic characteristics, such as nuclear condensation and fragmentation. In our study, astilbin treatment enabled us to observe potential pro-apoptotic effects in a dose-dependent manner and provide insight into astilbin's apoptotic induction, which is critical for evaluating its mechanistic role.

Bcl-2-associated X protein, or BAX, a pro-apoptotic member of the Bcl-2 family, is a key regulator of mitochondrial-mediated apoptosis (Cavalcante et al., 2019). The increase in BAX expression at higher concentrations of astilbin suggests that this compound may promote apoptotic signalling through mitochondrial pathways. CASP3, an executioner caspase (Cavalcante et al., 2019), also exhibits increased band intensity, further supporting the notion that astilbin may trigger apoptosis in 5637 bladder cancer cells. Notably, statistically significant upregulation was observed only for BAX and CASP3 at the highest concentration (200 $\mu\text{g/mL}$), which coincides with the MTT assay result where only $49.7 \pm 1.83\%$ of 5637 cells remained viable at this concentration. This supports the conclusion that astilbin induces apoptotic cell death in 5637 bladder carcinoma at high concentration and higher exposure may be necessary to induce a robust apoptotic response.

Although CASP8, a critical initiator caspase in the extrinsic apoptosis pathway (Cavalcante et al., 2019), also increased with dose, it did not reach statistical significance. This may reflect a more sensitive activation of the intrinsic apoptotic pathway, as indicated by significant upregulation of BAX and

CASP3. Another possible explanation for the lack of statistically significant change in CASP8 expression is that, as proposed in a previous study (Muzio et al., 1998), only a small amount of active CASP8 may be required to effectively transmit Fas-mediated apoptotic signals, provided that it reaches the activation threshold necessary to trigger CASP3. This implies that even if CASP8 expression is modest or not statistically increased, its biological function could still be fulfilled in initiating apoptosis.

However, at this stage, it is premature to draw any firm conclusions based solely on the current set of experiments. mRNA expression level testing via conventional PCR alone may not fully reflect the functional activation of apoptotic pathways, which often rely on post-translational processing of caspases (Zamaraev et al., 2017). Therefore, further validation using quantitative PCR (qPCR), western blotting, caspase activity assays, or protein-level quantification is necessary to confirm these findings and delineate the precise apoptotic mechanisms involved.

CONCLUSION

Our study demonstrates that astilbin, isolated from *S. glabra* Robx., exerts dose-dependent cytotoxicity on selected cancer cell lines, A549 and 5637. Among them, 5637 bladder carcinoma exhibits the highest sensitivity to astilbin's anticancer effects, primarily mediated through activation of the pro-apoptotic pathway. Further studies are needed to validate its mechanisms *in vitro* and its potential *in vivo*.

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