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Original Article
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Veratramine Inhibits Human Non-Small Cell Lung Cancer Cell Growth by Inhibiting the Hedgehog Signaling Pathway

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Objectives: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in both males and females. Considering the growing impact of NSCLC on public health, there is an urgent need for additional treatment strategies. Veratramine, a natural steroidal alkaloid extracted from the roots of plants in the lily family, has recently garnered attention regarding its potential anti-cancer effects. However, to the best of our knowledge, the role of veratramine in the progression of lung cancer is unclear.
Methods: The various concentration of veratramine were applied to the NSCLC cell lines (A549, NCI-H358 and NCI-H1299). The cell viability, apoptosis, and the cell cycle were evaluated using CCK-8 and flow cytometry assays. Phenotype of NSCLC cells were examined using an optical microscope and ImageJ software. Protein expression in veratramine-treated NSCLC cells was measured using immunoblotting.
Results: Veratramine-treated NSCLC cells exhibited significantly reduced cell viability and migration ability. Flow cytometry (i.e., fluorescence-activated cell sorting) revealed that treatment with veratramine increased apoptosis and cell cycle delay. Immunoblotting indicated that the Hedgehog (Hh) signaling pathway was significantly downregulated via inhibiting gli1 expression. Cell cycle-related proteins in NSCLC cells were decreased by veratramine treatment.
Conclusion: Veratramine suppresses lung cancer cell growth by inhibiting the Hh signaling pathway, suggesting its potential applicability in the treatment of NSCLC.

Keywords: Hedgehog signaling pathway, lung cancer, non-small cell lung carcinoma, phytomedicine, veratramine

INTRODUCTION

Lung cancer is a type of solid tumor that originates in the respiratory system and could develop anywhere across the lungs, including the parenchyma, bronchi, and even the trachea. Both subtypes of lung cancer, i.e., non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma, are considered malignant due to their poor prognosis and high recurrence rates [1, 2]. Risk factors for lung cancer include smoking, exposure to air pollution, genetic predisposition, and exposure to asbestos,

among others [3]. According to GLOBOCAN, an estimated 2.2 million new cases and 1.8 million deaths due to lung cancer were reported in 2020, rendering it a leading cause of cancer-related deaths worldwide [4]. Among these cases, NSCLC accounts for approximately 80% of all lung cancers; thus, it is considered a major global morbidity and mortality concern. Current treatment options for NSCLC include surgery, radiation therapy, chemotherapy, and targeted therapy [5]. However, surgery would lead to a good prognosis only for early-stage NSCLC; thus, drug therapy is generally accepted as the gold standard for lung cancer treatment [6]. Extensive research has focused on screening novel therapeutic agents for NSCLC, and despite considerable advances in recent years, several challenges are yet to be addressed. Identifying novel compounds that can successfully inhibit the growth of NSCLC is thus essential.

Veratramine, a natural bioactive steroidal alkaloid isolated from plants of the lily family, can act as an antihypertensive and analgesic [7]. This compound was recently shown also to exhibit anticancer effects. For example, in a study by Yin et al. [8], veratramine substantially inhibited the proliferation of human hepatocellular carcinoma cells (HepG2), and in our previous study, we found that veratramine markedly suppresses the growth of cancer cells originating from glioma and prostate carcinoma via DNA damage-mediated ATM/ATR pathways [9, 10]. These findings encourage further investigation of the anticancer effects of veratramine.

About a quarter of drugs in the USA contain plant-derived ingredients with high medicinal potential [11]. However, most phytomedicines have not been studied yet, and research on their anticancer effects has only just begun to gain traction. For example, Gahtori et al. (2023) [12] reported that the phytomedicines can suppress cancer cell survival by delaying the cell cycle, inhibiting metastasis, and inducing cell death. Based on these findings, we hypothesized that veratramine may be a candidate for NSCLC therapy. Therefore, the present study aimed to elucidate the role and effects of veratramine in NSCLC progression in humans in vitro.

MATERIALS AND METHODS

1. Cell culture and veratramine preparation

Human lung cancer cells (A549, H358, and H1299) were obtained from the Korea Cell Line Bank. The cells were cultured in Dulbecco's Modified Eagle Medium (HyClone, USA) and RPMI-1640 medium (HyClone, USA), supplemented with 10% fetal bovine serum (FBS; Gibco, USA) and 1% penicillin/streptomycin (P/S; Gibco, USA). The cells were maintained in an incubator at 37℃ with 5% CO_2. Upon reaching 70%–80% confluency, the cells were detached using 0.05% trypsin-ethylenediaminetetraacetic acid (EDTA; Gibco) and plated for expansion and further experiments. Veratramine (ab142367; Abcam, Cambridge, MA, USA) was diluted in 100% ethanol immediately before use; otherwise, it was stored at 4℃ in the dark. Before veratramine treatment, cells were incubated for 24 h at 37℃ with 5% CO_2, followed by treatment with veratramine or vehicle (ethanol).

2. Cell Counting Kit-8 analysis

To determine the anticancer effects of veratramine on cancer cells, cell viability was assessed using a Cell Counting Kit-8 (CCK-8; Dojindo, Japan). Briefly, the lung cancer cells were seeded in 96-well cell culture plates (SPL Life Sciences, Pocheon, Republic of Korea) at a density of 3×10^3 cells/well and allowed to adhere for 24 h. Next, veratramine was added in a series of concentrations (0, 0.1, 1, 2.5, 5, 7.5, 10, 25, 50, 100, 250, and 500 μM). Cell viability was assessed 24–72 h thereafter. After the cells had been cultured for specified time periods, 10 μL CCK-8 solution per 100 μL cell culture medium was added to each well. Subsequently, the cells were incubated for 1 h at 37℃ with 5% CO_2. The absorbance of each sample was determined at 480 nm using a SpectraMax iD3 microplate reader (Molecular Devices, Sunnyvale, CA, USA). IC_{50} values were calculated using GraphPad Prism 5 for Windows.

3. Soft agar assay

Briefly, 0.5% agar mixture (35 mL melted 1.25% agar solution, 35 mL 2 × cell culture medium, 18 mL FBS, and 0.9 mL P/S) was poured into each well of six-well plates to form the base layer. Then, 3×10^3 cells were resuspended in 0.3% agar solution, with or without 50 μM veratramine, and plated on the base agar layer. Thereafter, the cells were incubated at 37℃ with 5% CO_2 for 3 weeks. Images were acquired using a microscope (CKX53; Olympus) with Excope software. The average colony diameter was measured using ImageJ software (National Institutes of Health, Bethesda, Maryland, USA).

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4. Wound healing assays

Lung cancer cells were seeded in six-well plates at 100% confluence and at 37℃ with 5% CO_2 for 24 h. Next, the cells were scratched using a sterile 1000-microliter plastic pipette tip. The cell debris was washed twice using Dulbecco's phosphate-buffered saline (DPBS). The cells were then incubated in complete culture medium at 37℃ with 5% CO_2 for 24 h, with or without 50 μM veratramine. After 0 and 24 h of culturing, images of the wound closure areas were acquired using a microscope (CKX53; Olympus) with Excope software. For each NSCLC cell line, three scratched wells were used to compute the average wound closure area. The rate of wound closure area was calculated as follows: (A − B)/A × 100 (%), where A is the initial scratch wound and B is the scratch wound after 24 h. The wound closure area was measured using ImageJ software (National Institutes of Health, Bethesda, Maryland, USA).

5. Flow cytometry

Fluorescence-activated cell sorting (FACS) was performed to determine the cell cycles and apoptotic rates. Briefly, NSCLC cells (A549, H38, and H1299) were seeded at 60%–70% confluency in six-well cell culture plates (SPL Life Sciences) and incubated in complete culture medium at 37℃ with 5% CO_2 for 24 h. Next, the cells were treated with veratramine (50 μM) or a vehicle control and incubated for another 24 h at 37℃ with 5% CO_2. The cells were harvested using 0.05% trypsin-EDTA and centrifuged at 1200 rpm for 3 min. Next, the cell pellets were washed thrice with cell staining buffer (420201; BioLegend, San Diego, USA). Apoptosis was assessed using an Annexin V/propidium iodide (PI) double-staining apoptosis detection kit (640932; BioLegend), following the manufacturer's instructions. At least 5×10^3 cells were analyzed per sample using a BD Accuri C6 flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

6. Immunoblotting

To collect protein samples, human NSCLC cells (A549, H358, and H1299) were seeded in 60 mm plates. At 70%–80% confluency, the cells were washed with ice-cold DPBS and harvested using Pro-Prep™ buffer containing 1× sample buffer. The protein samples were denatured at 95℃ for 5 min, cooled on ice at 4 ℃ for 3 min, and then centrifuged at 12,000 × g for 15 s and separated by electrophoresis on a 10% polyacrylamide gel. Subsequently, the protein samples were transferred onto nitrocellulose membranes using a semi-dry western blotting system (BioRad, Hercules, CA, USA) according to the manufacturer's instructions. The transferred membranes were blocked using EveryBlot blocking buffer (BioRad) for 10 min at room temperature. Next, the membranes were incubated overnight at 4℃ with primary antibodies diluted in 5% bovine serum albumin (BSA) in tris-buffered saline with Tween-20 (TBST), including anti β-actin (1:2,000) (#MA5-15739; Thermo Fisher Scientific, Waltham, MA, USA), Shh (1:2,000) (#SC-365112; Santa Cruz Biotechnology, Santa Cruz, CA, USA), SMO (1:2,000) SC-166685, Santa Cruz Biotechnology), gli1 (1:2,000) (#SC-515751, Santa Cruz Biotechnology), CyclinD1 (1:1,000) (#2922; Cell Signaling Technology, Danvers, MA, USA), CyclinB1 (1:1,000) (#4135; Cell Signaling Technology), CDK4 (1:1,000) (#12790; Cell Signaling Technology), N-cadherin (1:1,000) (#13116; Cell Signaling Technology), Twist (1:1,000) (#90445; Cell Signaling Technology), and Snail (1:1,000) (#3879; Cell Signaling Technology). The membranes were then washed thrice using TBST and incubated with horseradish peroxidase-conjugated secondary antibodies (goat anti-rabbit and goat anti-mouse) diluted in TBST containing 5% BSA for 1 h at room temperature. The antigen-antibody complexes were detected using enhanced chemiluminescence (#1705061; BioRad). The resulting protein bands were visualized using the ChemiDoc MP imaging system (BioRad).

RESULTS

1. Veratramine significantly decreases cancer cell growth

CCK-8 analysis was performed to elucidate the anticancer effects of veratramine. Treatment with veratramine significantly suppressed the growth of human NSCLC cells (A549, H358, and H1299) in a time-dependent manner (Fig. 1A). Furthermore, the viability of NSCLC cells was reduced in a dose-dependent manner, with IC_{50} values of veratramine ranging from 51.99 μM in A549 cells (KRAS mutation) to 259.6 μM in H358 cells (KRAS mutation with p53-null) for the examined NSCLC cell lines (Fig. 1B) [13]. Wound healing and soft agar assays revealed that veratramine significantly downregulated the migration and anchorage-independent growth of human NSCLC cells (Fig. 1C-E). These results highlight the potent anticancer effects of veratramine.

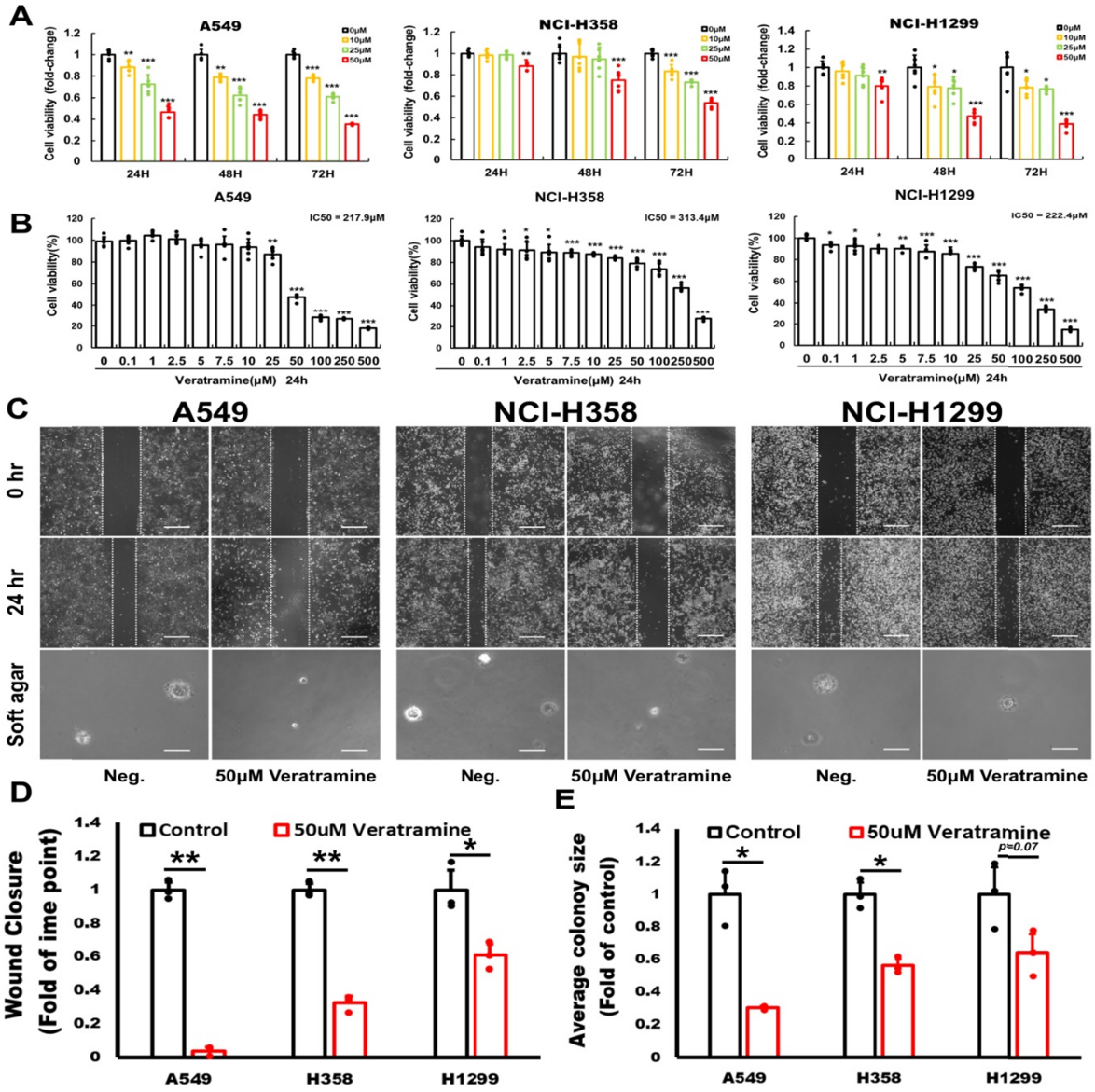

Figure 1. Veratramine significantly attenuated malignant lesions of NSCLC. (A) Time- and dose-dependent CCK-8 analysis of NSCLC cells. (B) IC_{50} values of the cancer cells. Treatment with veratramine significantly inhibited NSCLC cell growth. (C-E) Representative images and quantitative graphs of wound healing and soft agar assays of NSCLC cells. Treatment with veratramine significantly inhibited NSCLC cell regeneration and anchorage-independent growth rate. Data are presented as the mean ± standard deviation (SD). *p < 0.05, **p < 0.01, ***p < 0.001. n = 6 (A, B) and n = 3 (C, D). Scale bars = 400 μm for wound healing assay and 400 μm for soft agar. CCK-8, cell counting kit 8; NSCLC, non-small cell lung carcinoma.

2. Veratramine induces apoptosis in NSCLC cells

We measured the rates of apoptosis in veratramine-treated NSCLC cells, and according to FACS results, veratramine significantly increased the apoptosis of these cancer cells. Specifically, early and late apoptotic phases were significantly pronounced in A549 cells (Fig. 2A, B). However, results differed for the anti-apoptotic protein p53-null NSCLC cell lines (H358 and H1299) (Fig. 2C-F) [13]. Collectively, these results suggest that veratramine induces apoptosis in human NSCLC cells.

3. Veratramine induces cell cycle arrest in NSCLC cells

FACS analysis was performed to determine whether veratramine delays cell cycle progression in NSCLC. The results of PI cell cycle analysis revealed that veratramine treatment

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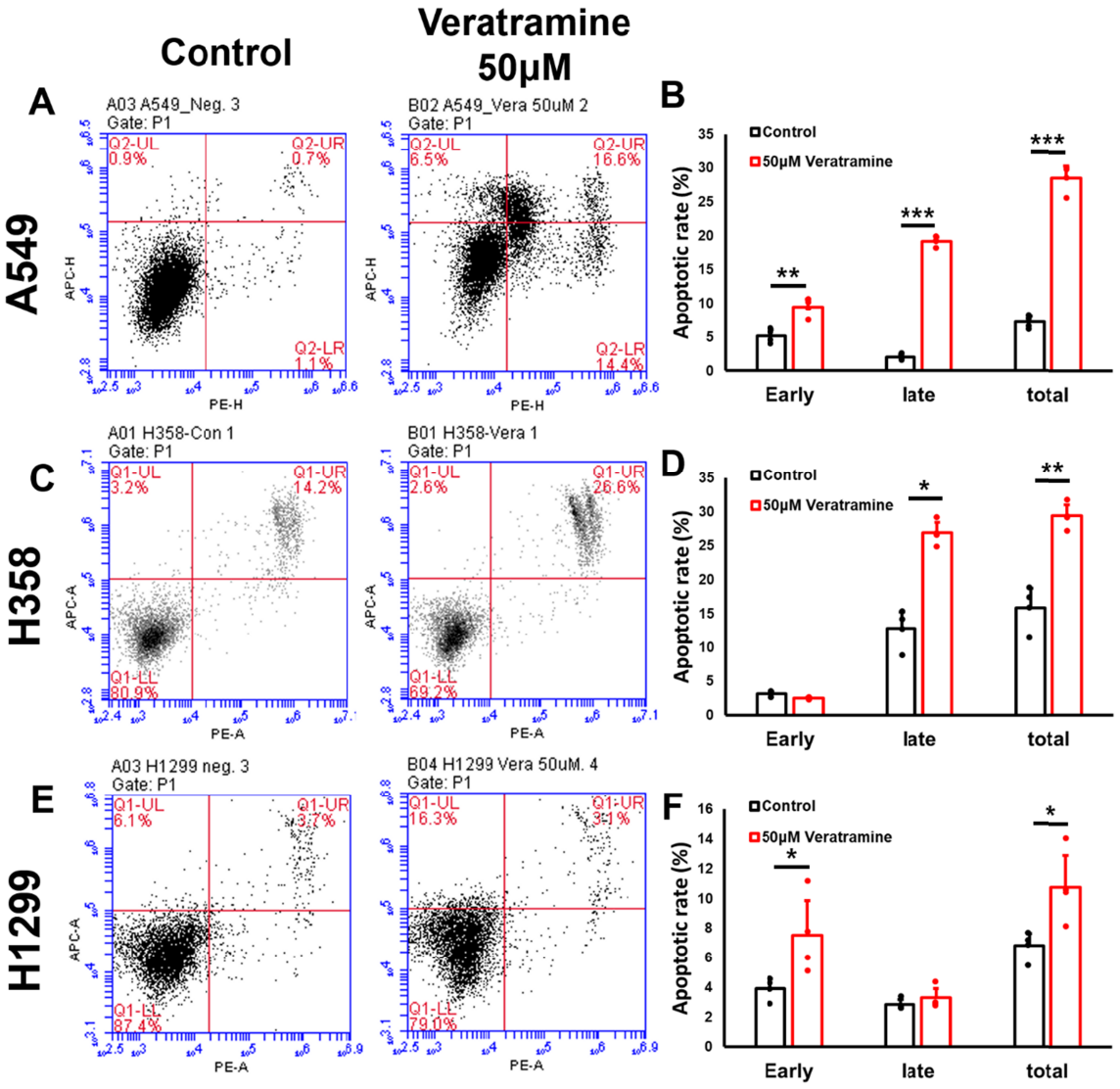

Figure 2. Veratramine treatment induced apoptosis in NSCLC cells. (A, B) FACS analysis showed that veratramine increased the proportions of early and late apoptotic A549 cells. (C-F) Veratramine-treated H358 and H1299 cells also exhibited increased proportions of early (H1299) and late (H358) apoptotic cells. Data are presented as the mean ± standard deviation (SD). *p < 0.05, **p < 0.01, ***p < 0.001. n = 4 (A-F). FACS, fluorescence-activated cell sorting; NSCLC, non-small cell lung carcinoma.

significantly delays cell cycle progression. Specifically, a delay in the G0/G1 phase was observed in A549 cells (Fig. 3A, B), and a delay in the G2/M phase was observed in the H358 and H1299 cells (Fig. 3C-F). These results indicate that veratramine arrests cancer cell growth by delaying cell division.

4. Veratramine significantly downregulates the Hh signaling pathway

Immunoblotting was performed to determine the mechanism by which veratramine suppresses the growth of NSCLC cells. Considering that veratramine is a cyclopamine analogue, which is a known inhibitor of the Hh signaling pathway, we assessed the expression levels of Hh signaling-related proteins including Smoothened (SMO), sonic hedgehog signaling molecule (Shh), and glioma-associated oncogene homolog (gli1) [14]. The Hh signaling pathway was significantly downregulated in veratramine-treated NSCLC cells compared with that in controls. Treatment with veratramine decreased SMO and Shh expression in all examined NSCLC cell lines (SMO: A549 and H1299 cells; Shh: H1299 cells), except for H358 cells. Similarly, gli1 was downregulated in all NSCLC cell lines (Fig. 4A). Con-

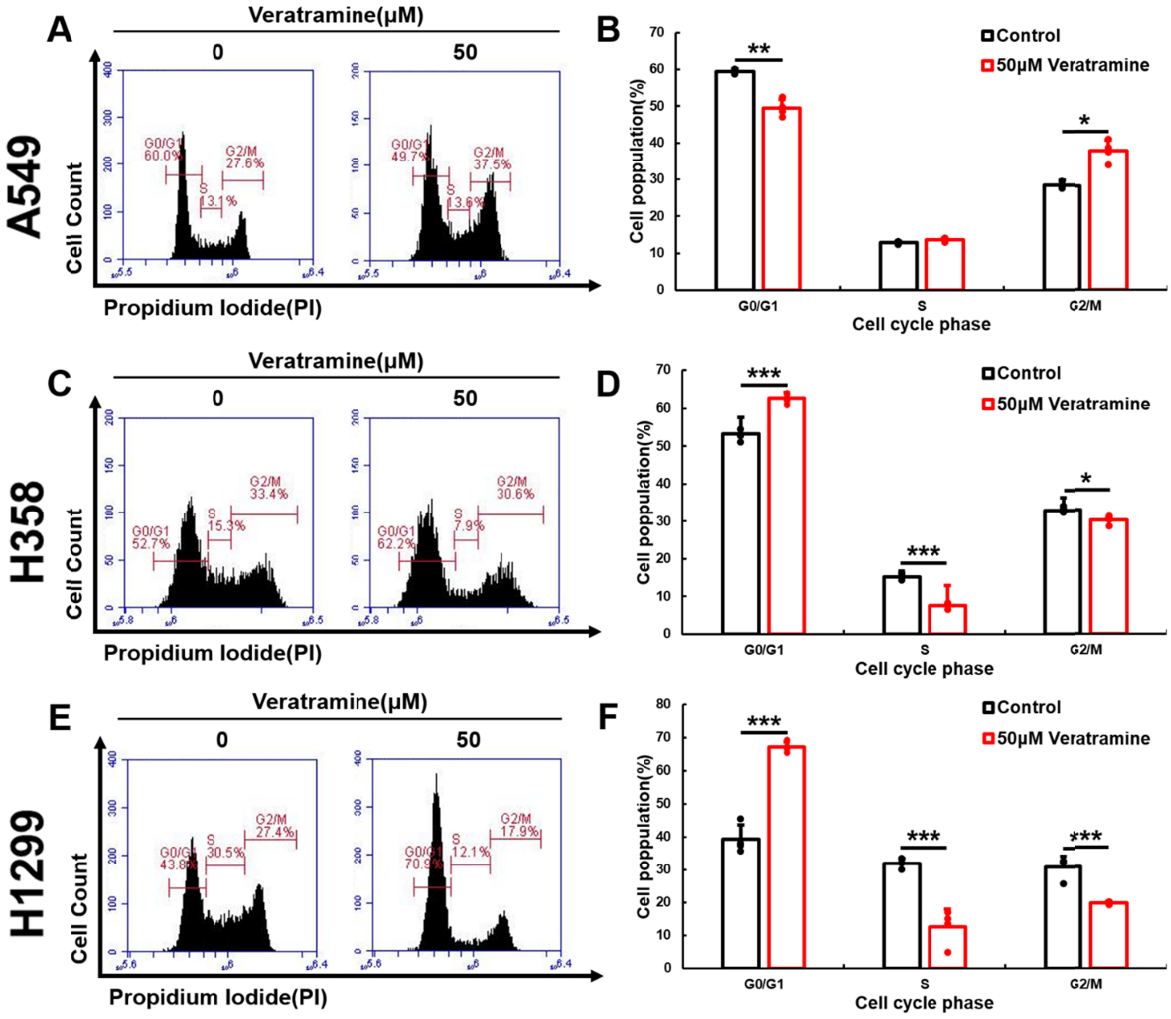

Figure 3. Veratramine treatment delayed cell cycle progression. (A, B) PI FACS analysis confirmed that veratramine-treated A549 cells mainly exhibited early-stage cell cycle delay (G0/G1). (C-F) PI FACS analysis confirmed that veratramine-treated H358 and H1299 cells mainly exhibited late-stage cell cycle delay. Data are presented as the mean ± standard deviation (SD). *p < 0.05, **p < 0.01, ***p < 0.001. n = 4 (A-F). FACS, fluorescence-activated cell sorting; NSCLC, non-small cell lung carcinoma; PI, propidium iodide.

sidering that gli1 plays a crucial role in NSCLC progression as a transcription factor of the Hh signaling pathway, these results suggest that veratramine significantly inhibits Hh signaling by downregulating gli1 expression. Additionally, immunoblotting revealed that the expression of cell cycle- and epithelial-mesenchymal transition (EMT)-related proteins (e.g., Cyclin D1, Cyclin B1, CDK4, N-cadherin, Twist, and Snail), downstream targets of the Hh signaling pathway, was significantly suppressed in veratramine-treated NSCLC cells (Fig. 4B, 4C). The results thus suggest that the anticancer effects of veratramine could be attributed to the inhibition of gli1 expression and downregulation of the Hh signaling pathway (Fig. 4D).

DISCUSSION

The rise in NSCLC-related mortality in recent years has put a spotlight on this subtype of cancer [4]. Among effective strategies to treat NSCLC, chemotherapy remains the primary treatment option [15]. Chemotherapy, which involves the use of cytotoxic drugs to kill rapidly proliferating cancer cells, offers several clinical benefits, but because these cytotoxic drugs are often non-selective, normal healthy cells are also affected [16]. Therefore, the search for novel drug candidates continues and has gained momentum in recent years.

According to Bellusci et al. [17] and Wang et al. [18], lung embryogenesis and regeneration depend closely on the Hh

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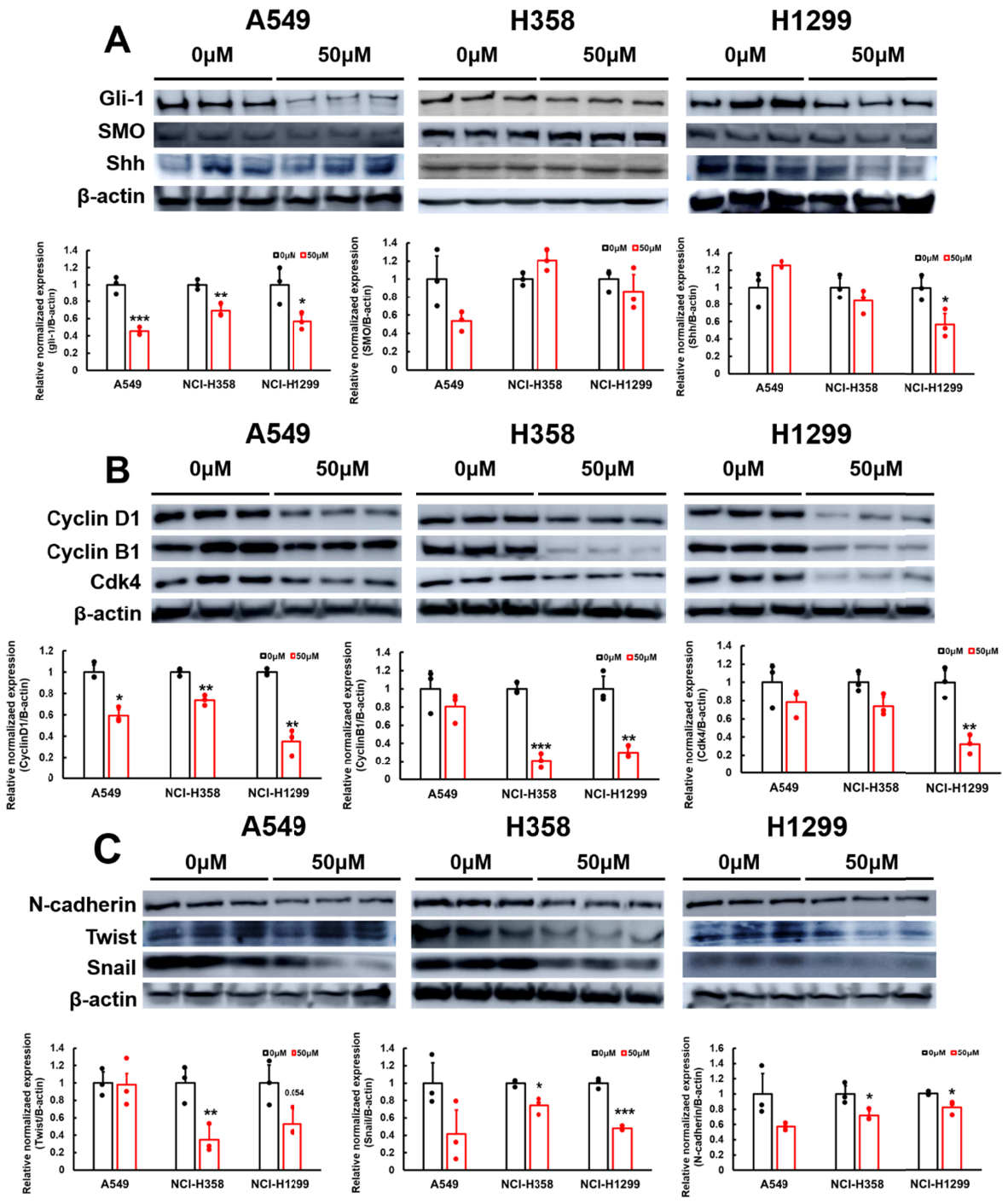

Figure 4. Veratramine treatment significantly inhibited the Hedgehog (Hh) signaling pathway in NSCLC cells. (A) Protein expression levels of Hh signaling-mediated proteins in NSCLC cells. (B) Protein expression levels of cell cycle-related proteins in NSCLC cells. (C) Protein expression levels of EMT-related proteins in NSCLC cells. (D) Schematic representation of the anticancer effects of veratramine in NSCLC. Veratramine arrests the growth of NSCLC cells by inhibiting the Hh signaling pathway. The figure was created using BioRender. Data are presented as the mean ± standard deviation (SD). *p < 0.05, **p < 0.01, ***p < 0.001. NSCLC, non-small cell lung carcinoma.

signaling pathway. Their findings suggest that the Hh signaling pathway plays a crucial role in the survival and proliferation of lung cancer cells. Similarly, Giroux-Leprieur et al. [19] suggested that the Hh signaling pathway is associated with NSCLC oncogenesis. Therefore, numerous studies have focused on the malignant effects of the Hh signaling pathway in NSCLC. For

instance, Chen et al. [20] demonstrated that gli1 expression and Hh signaling are closely associated with the epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor resistance. Ma et al. [21] suggested that the Hh signaling is associated with EMT and cancer cell cycle and modulates the tumor microenvironment through a paracrine mechanism. Collectively, these findings suggest that suppressing the Hh signaling pathway may represent a promising strategy for treating NSCLC. In the present study, veratramine treatment suppressed the Hh signaling pathway and significantly inhibited human NSCLC cell growth by arresting the cell cycle and decreasing the expression of EMT marker proteins (Fig. 4). Considering that the cell lines used in this study were isolated from patients with malignant NSCLC and had several gene mutations such as KRAS and p53, these findings indicate that veratramine may be an effective treatment for malignant lung cancers. We previously demonstrated the safety of veratramine in mice [10]. Taken together, these findings suggest that veratramine is a promising therapeutic option for lung cancer in humans.

In recent years, targeted drugs capable of inhibiting cancer cell oncogenes have emerged as popular treatment options for cancer owing to their high efficacy and favorable safety profile, especially compared to chemotherapy [22]. However, prolonged administration of targeted drugs often leads to target site mutations, causing drug resistance [23]. Resistant tumor cells eventually replace sensitive cells and result in cancer relapses and metastases [24]. Therefore, combination therapy targeting resistant cells has gained importance [25]. Consistently, multiple rounds of low-dose therapy using a combination of specific target inhibitors with other drugs represent an effective alternative therapeutic strategy for patients with NSCLC [26]. In this context, it becomes important to identify novel drug candidates with therapeutic mechanisms that are distinct from those of conventional drugs. In the current study, veratramine substantially inhibited the Hh signaling pathway by downregulating gli1 expression. Given that the Hh signaling pathway is closely related to cancer cell survival, veratramine could be used in combination with other anticancer drugs [27].

Taken together, our study demonstrated the inhibitory effects of veratramine on NSCLC cell growth. Nevertheless, some limitations of our study must be considered. First, the H358 cell line, which harbors both KRAS and p53 mutations, exhibited significantly increased late apoptosis compared with the H1299 cell line, which only possesses a p53 mutation (Fig. 2). Considering the balance between pro-survival and pro-apoptotic signals in cancer cells, our data suggest that the oncogenic shock due to veratramine treatment may explain the acute apoptotic pattern of H358 cells compared with that of H1299 cells [28]. Moreover, the p53 WT NSCLC cell line (A549) also exhibited apoptotic patterns different from those of other NSCLC cell lines such as H358 and H1299 (Fig. 3). However, the precise relationship between specific cancer gene mutations (e.g., KRAS and p53) and the effects of veratramine treatment remains elusive. Second, we did not study the effect of combining veratramine with commercial drugs. Finally, the potential adverse effects of veratramine, such as hypotension and tremors, in patients with NSCLC and normal lung epithelial cells, were not investigated. Therefore, we plan to elucidate the effects of veratramine on mutant NSCLC cells further, evaluate the efficacy of co-treatment strategies, and investigate the potential adverse effects of veratramine.

In the present study, veratramine significantly inhibited the growth of NSCLC cells by suppressing the Hh signaling pathway. Considering that the Hh signaling pathway is closely related to malignancies and cancer gene mutations, these data indicate that veratramine may be a promising candidate for NSCLC therapy owing to its capacity to block the Hh signaling pathway. To the best of our knowledge, this study is the first to report the anti-NSCLC effects of veratramine mediated via inhibition of Hh signaling. We believe that our research will improve our understanding of the role and future perspective of veratramine in NSCLC.

CONCLUSION

In the present study, veratramine significantly inhibited the growth of NSCLC cells by suppressing the Hh signaling pathway. Considering that the Hh signaling pathway is closely related to malignancies and cancer gene mutations, these data indicate that veratramine may be a promising candidate for NSCLC therapy owing to its capacity to block the Hh signaling pathway. To the best of our knowledge, this study is the first to report the anti-NSCLC effects of veratramine mediated via inhibition of Hh signaling. We believe that our research will improve our understanding of the role and future perspective of veratramine in NSCLC.

AUTHORS' CONTRIBUTIONS

S.W.L. and H.Y.K.; Conceptualization, Investigation, validation, Writing - Original Draft. W.S.K.; Investigation, Software.

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S.M.B., J.K.P., S.P., and J.E.H.: Validation, Data curation, Visualization. A.J., E.S., C.K., and L.J. Data curation, Resources. S.K.C. and S.H.; Supervision, Project administration, Funding acquisition, Writing - Review & Editing.

ETHICAL APPROVAL

Not applicable.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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