

ORIGINAL RESEARCH

Echinacoside suppresses cervical cancer by inhibiting cell growth and angiogenesis

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Abstract

Background: This study aims to investigate the effects of Echinacoside (Ech) on the progression of cervical cancer (CC) and to elucidate its underlying mechanisms. **Methods:** The viability of CC cells was assessed using cell counting kit-8 (CCK-8) and colony formation assays. Wound healing and Transwell assays were conducted to evaluate CC cell motility. The effects on angiogenesis were confirmed through tube formation and immunoblot assays. Additionally, immunoblot further confirmed the mechanism. **Results:** Echinacoside significantly inhibited CC cell viability in a dose-dependent manner, reducing viability ($p < 0.001$). Colony formation was markedly suppressed, with a reduction in colony number ($p < 0.001$). Ech also decreased migration and invasion ($p < 0.01$) as measured by wound healing and Transwell assays. Furthermore, tube formation analysis showed a substantial reduction in total tube length and branch number ($p < 0.01$), indicating impaired angiogenic capacity. These effects were associated with significant downregulation of β -catenin, c-myc and Vascular Endothelial Growth Factor A (VEGFA) expression ($p < 0.05$ to $p < 0.001$). **Conclusions:** Ech inhibits growth, motility and angiogenesis in cervical cancer cells through the Wnt/ β -catenin pathway.

Keywords

Cervical cancer (CC); Echinacoside (Ech); Angiogenesis; Invasion; Wnt/ β -catenin axis

1. Introduction

Recent global cancer statistics indicate that cervical cancer (CC) is one of the leading causes of cancer-related fatalities among women, ranking fourth in both incidence and mortality worldwide [1]. In its early stages, CC often presents without symptoms; however, symptoms may arise in more advanced stages, particularly during the metastatic stage [2]. The tumor metastases continue to develop and adversely affect the survival of some patients diagnosed early [3]. Despite significant research efforts on CC, the mechanisms driving its progression remain poorly understood.

The Wnt/ β -catenin axis is essential for cancer initiation, tissue homeostasis, angiogenesis and carcinogenesis [4]. When this pathway is overactivated in cancer cells and cancer stem cells, it can lead to drug resistance and recurrence in patients undergoing conventional chemotherapy and radiation therapy [5]. During tumor angiogenesis, the overactivation of the Wnt/ β -catenin axis continuously induces the up-regulation of pro-angiogenic factors [6]. Additionally, excessive Wnt/ β -catenin axis has been associated with poorer prognoses across various types of human cancers [5, 7]. Consequently, the overactivation of the Wnt/ β -catenin axis poses significant challenges and limitations for effective tumor treatment.

Echinacoside is a natural phenylethanolic glycoside that was

first isolated from the root of Echinacea 60 years ago [8]. It is also found in Cistanche, which is commonly used in Europe to treat the common cold. Research has revealed that Ech possesses several beneficial effects, including neuroprotection, anti-aging, scavenging free radicals, vascular endothelial cells protection, the promotion of hematopoietic and other functions [9, 10]. In the context of cancer, Ech has been shown to inhibit the growth, migration, invasion and angiogenesis of ovarian cancer cells via the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway [11]. Furthermore, it suppresses breast cancer (BC) cells by targeting the Wnt/ β -catenin pathway [12]. While Ech has been found to inhibit cervical cancer (CC) cells by mitigating the PI3K/AKT pathway, its specific role in cervical cancer remains to be fully elucidated.

Recent studies have shown that the Wnt/ β -catenin pathway is aberrantly activated in cervical cancer. Consequently, targeting this pathway may offer a promising therapeutic strategy for cervical cancer [9]. Aberrant activation of the Wnt/ β -catenin pathway has been strongly linked to cervical cancer progression, metastasis and resistance to conventional therapies, highlighting its value as a promising therapeutic target. Echinacoside has demonstrated the ability to inhibit Wnt signaling in breast and colorectal cancers, suggesting its potential utility in targeting this pathway in cervical cancer as well. However, current treatment options that address this pathway

are limited. Thus, exploring natural compounds such as Ech, which may modulate this signaling axis, represents a novel and promising approach for cervical cancer treatment.

Ech has demonstrated the ability to inhibit tumor progression in various cancers; however, its effects on cervical cancer, mainly through the modulation of the Wnt/ β -catenin pathway, remain largely unexplored. In this study, we investigated the impact of Ech on the progression of CC. Our results indicated that Ech significantly suppressed the growth, motility and angiogenesis of CC cells by targeting the Wnt/ β -catenin axis. These findings suggest that Ech could serve as a promising therapeutic agent for combating this disease.

2. Materials and methods

2.1 Cell lines and culture

The following CC cell lines were utilized in this study: Hela (American Type Culture Collection (ATCC), CCL-2), Siha (ATCC, HTB-35) and Human Umbilical Vein Endothelial Cells (HUVECs) (ATCC, CRL-1730). All cells were cultured in a complete Dulbecco's Modified Eagle Medium (DMEM) medium (11965-092, Gibco, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS, 16000-044, Gibco, Thermo Fisher Scientific, Waltham, MA, USA) and 1% penicillin-streptomycin (15140-122, Gibco, Thermo Fisher Scientific, Waltham, MA, USA). Cultures were maintained in a humidified incubator at 37 °C with 5% CO₂. Experiments were performed using cells at passages 3–8. Each cell line underwent authentication through short tandem repeat (STR) profiling and was confirmed to be free of mycoplasma contamination before use.

2.2 Reagents

Ech was purchased from Sigma-Aldrich (82962-5MG). It was dissolved in Dimethyl sulfoxide (DMSO) and subsequently diluted in culture medium to achieve final concentrations of 25 μ M, 50 μ M and 100 μ M. These concentrations (25–100 μ M) were selected based on prior reports indicating effective anti-tumor activity of Ech *in vitro* [11, 12]. For all *in vitro* assays, the cells were treated with Ech for 24 or 72 h, based on the specific experimental design: 24 h for wound healing, Transwell, tube formation and Western blot assays; 72 h for CCK-8 and colony formation assays. The cells were treated with Ech in complete medium containing 10% fetal bovine serum (FBS). A vehicle control group (cells treated with equivalent volume of DMSO) was included in all experiments for comparison with Ech-treated groups. The final concentration of DMSO in all treatment and vehicle control groups was kept below 0.1% to avoid any nonspecific cytotoxic effects.

2.3 Antibodies

The following primary antibodies were used: β -catenin (Abcam, ab32572, 1:1000, Cambridge, UK); c-myc (Abcam, ab32072, 1:1000, Cambridge, UK); VEGFA (Abcam, ab46154, 1:1000, Cambridge, UK); β -actin (Abcam, ab8226, 1:5000, Cambridge, UK). The secondary antibodies used were Horseradish peroxidase (HRP)-conjugated anti-

rabbit Immunoglobulin G (IgG) (Abcam, ab6721, 1:5000, Cambridge, UK) and anti-mouse IgG (Abcam, ab6728, 1:5000, Cambridge, UK).

2.4 Cell growth assay

Cell viability was assessed using the CCK-8 assay (Dojindo, CK04), with absorbance measured at 450 nm using a microplate reader (Varioscan, SCANLAB, Waltham, MA, USA). Following 72 h of treatment with 100 μ M Ech in complete media, residual adherent cells were not detached or dead, indicating their viability, though their proliferation may have been inhibited. The cells were treated with Ech continuously for 72 h without media change. Fresh media was not added during the treatment period to maintain the consistency of Ech exposure to the cells throughout the experiment.

2.5 Colony formation assay

Cells (10³ per well) were seeded in 6-well plates and cultured in complete media for 14 days. After 30 minutes of fixation with 4% paraformaldehyde (PFA) (Sigma, 158127, St. Louis, MO, USA), colonies were stained with 0.1% crystal violet (Sigma, C3886, St. Louis, MO, USA). The medium was changed every three days, and the drug was replenished at each medium change to ensure consistent and sustained exposure to Ech. After fixation and staining, colonies containing more than 50 cells were counted manually using a light microscope (ZSM710, ZEISS, Oberkochen, BW, Germany).

2.6 Wound healing

A wound was created by scraping a pipette tip. Following this, the wells were washed with phosphate-buffered saline (PBS) to remove any remaining cells. The cells (10⁵ per well) were then treated with varying concentrations of Ech (25 μ M, 50 μ M, 100 μ M) in a serum-free medium. Wound closure was monitored at 0 h and 24 h using a light microscope (Olympus, CKX53). The wound area was measured at both time points using ImageJ software (NIH), and the percentage of wound closure was calculated.

2.7 Transwell assay

Transwell chambers (Corning, 3422) coated with Matrigel (100 μ L, 1:10) were used to evaluate cell invasion. Cells (5 $\times$ 10⁴) were seeded in the upper chamber with serum-free medium, while the lower chamber contained complete medium. After 24 h of incubation, the cells that migrated to the bottom were stained with 0.1% crystal violet. The number of invaded cells was manually counted in five random fields under a light microscope, and the average was used for quantification.

2.8 Tube formation assay

HUVECs (5 $\times$ 10⁴ cells) were plated in 96-well plates coated with Matrigel (50 μ L/well) in complete media. To investigate the effects of Ech on angiogenesis, HUVECs were cultured in conditioned media collected from Hela and Siha cells that had been treated with Ech (25 μ M, 50 μ M or 100 μ M) for 24 h.

After 6 h, tube formation was visualized and captured using a microscope (Olympus, CKX53). The total number of tube branches and total tube length were quantified using ImageJ software with the “Angiogenesis Analyzer” plugin.

2.9 Western blot analysis

30 μ g of total protein was loaded per lane to ensure consistency across samples. Proteins were separated using Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and subsequently transferred to Polyvinylidene Difluoride (PVDF) membranes. The membranes were blocked with 5% non-fat milk in PBS for 1 h and then incubated with antibodies overnight at 4 °C. After washing, the membranes were incubated with HRP-conjugated secondary antibodies for 1 h. Protein bands were visualized using enhanced chemiluminescence (ECL) reagent (32106, Thermo Fisher, Waltham, MA, USA) and imaged with an Imaging System (ChemiDoc™ MP, Bio-Rad, Hercules, CA, USA). Blots were quantified using ImageJ software (NIH), and protein band intensities in Western blot assays were normalized to β -actin as the loading control.

2.10 Statistical analysis

Quantitative data were expressed as the mean $\pm$ standard deviation (SD). To assess overall differences among multiple groups, one-way analysis of variance (ANOVA) was utilized, followed by Tukey’s *post-hoc* test for pairwise comparisons. Statistical analyses were conducted using GraphPad Prism (9.0, GraphPad, Boston, MA, USA). A *p*-value less than 0.05 was considered statistically significant. All experiments were performed in triplicate. Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Levene’s test to ensure the validity of ANOVA assumptions.

3. Results

3.1 Ech inhibits the growth of CC cells

To assess the impact of Ech on CC cell growth, we performed CCK-8 and colony formation assays on Hela and Siha cells treated with varying concentrations of Ech (25 μ M, 50 μ M and 100 μ M). The chemical structure of Ech is shown in Fig. 1A. The results of the CCK-8 assay demonstrated a statistically significant decrease in cell viability in the Ech-treated groups (Fig. 1B). Similarly, there was a marked decline in the number of colonies following Ech treatment, with the substantial inhibition observed at 100 μ M (Fig. 1C). These results indicate that Ech effectively suppresses CC cell growth.

3.2 Ech reduces the migration and invasion of CC cells

We subsequently investigated the impact of Ech on the migratory and invasive properties of CC cells by performing wound healing and Transwell invasion assays. The wound healing assay demonstrated that Ech significantly inhibited cell migration, as evidenced by a larger scratch area in the groups treated with Ech (Fig. 2A,B). Furthermore, the Transwell in-

vasion assay revealed that the number of invading cells was lower in the Ech-treated groups, with fewer cells penetrating the Matrigel-coated membrane (Fig. 2C,D). Collectively, these findings indicate that Ech effectively inhibits the motility of CC cells.

3.3 Ech suppressed the angiogenic capacity of endothelial cells

To evaluate the effect of Ech on angiogenesis, we performed a tube formation assay using HUVECs with conditioned media from Ech-treated Hela and Siha cells. In the control group, HUVECs formed extensive and well-organized tube-like structures. Conversely, conditioned media from Ech-treated cells resulted in a disrupted and less intricate network (Fig. 3). These results suggest that Ech exerts an anti-angiogenic effect via modulation of the tumor microenvironment.

3.4 Ech downregulates the Wnt/ β -catenin axis in CC cells

We conducted a Western blot analysis of key components in the Wnt/ β -catenin signaling pathway to further investigate the molecular mechanisms through which Ech suppresses CC progression. The results showed a decrease in β -catenin expression following Ech treatment (Fig. 4A). Moreover, Ech significantly downregulated the expression of the downstream targets c-myc and VEGFA (Fig. 4B). Consequently, we conclude that Ech effectively inhibits the Wnt/ β -catenin pathway.

4. Discussion

Cervical cancer (CC) is a significant global health concern for women [13]. These processes are essential for tumor growth and metastasis, as the capacity to proliferate uncontrollably, invade surrounding tissues, and form new blood vessels is vital for tumor survival and expansion. Our study investigated how Ech, a bioactive compound, exerts a potent inhibitory effect on these critical aspects of CC cell behavior. Our findings demonstrate that Ech significantly reduces the growth and invasive potential of cells while also impairing angiogenesis. This disruption of key tumor-promoting processes highlights the importance of targeting cell growth, invasion and angiogenesis as effective therapeutic strategies for the treatment of CC.

Compounds such as curcumin, resveratrol and Epigallocatechin gallate have exhibited promising results in preclinical and clinical settings for the treatment of various cancers, including CC [14, 15]. In line with these findings, our research on Ech further underscores the potential of natural products in cancer treatment. Ech was found to significantly inhibit the growth, motility and angiogenesis of CC cells, reinforcing its therapeutic potential as an anti-tumor agent.

Ech is a phenylethanoid glycoside derived from the herb *Echinacea purpurea*, known for its various pharmacological properties [16]. In our study, we observed that Ech suppressed the growth and migration of CC cells, aligning with its previously documented anti-cancer effects. Furthermore, Ech demonstrated the ability to inhibit angiogenesis, underscoring its potential to obstruct tumor-associated blood vessel formation. These findings are consistent with earlier research

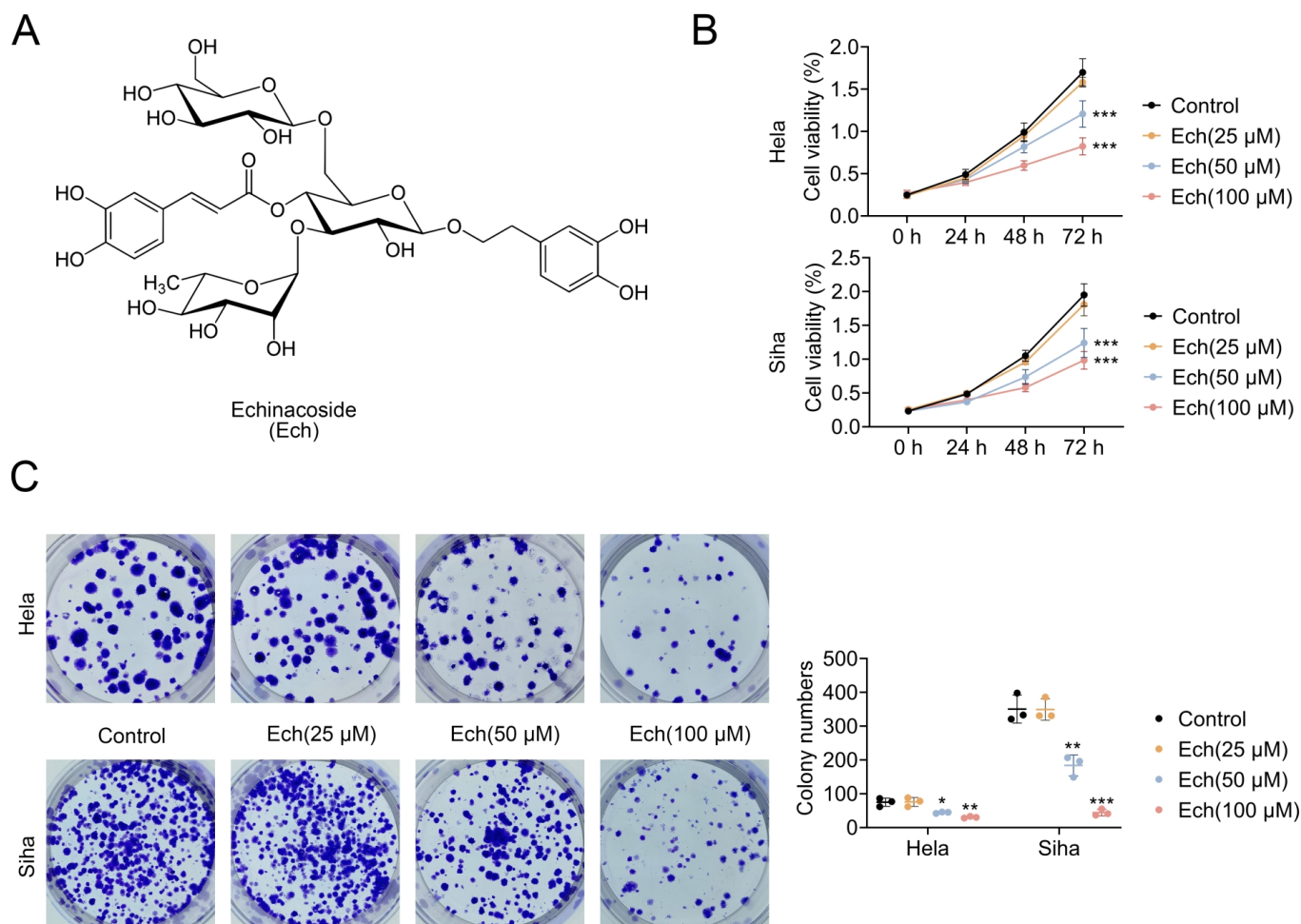


FIGURE 1. Echinacoside (Ech) inhibits cervical cancer cell growth and colony formation. (A) Chemical structure of Echinacoside (Ech). (B) Cell viability assay showing the effects of Ech (25 μ M, 50 μ M and 100 μ M) on HeLa and SiHa cells over a 72-h period. Ech treatment significantly reduced cell viability in both cell lines compared to control. (C) Colony formation assays in HeLa and SiHa cells treated with varying concentrations of Ech (25 μ M, 50 μ M and 100 μ M) for 14 days. Colony numbers were significantly reduced in the Ech-treated groups compared to control. The graph on the right shows the quantification of colony numbers, demonstrating dose-dependent inhibition of cell growth by Ech. Data are presented as mean $\pm$ SD from three independent experiments (n = 3). Statistical significance was assessed using one-way ANOVA with Tukey's *post-hoc* test. * p < 0.05, ** p < 0.01, *** p < 0.001, vs. control.

highlighting Ech's role in other cancer types, such as breast and ovarian cancer, where it has been shown to reduce cell growth and invasion via different signaling pathways [17]. The concentrations of 25 μ M, 50 μ M and 100 μ M were selected based on prior literature demonstrating their effectiveness in inhibiting cancer cell growth *in vitro* without inducing significant cytotoxicity [17]. While these concentrations may not directly reflect physiological *in vivo* levels, they represent a practical range for evaluating the therapeutic potential of Ech in cell-based assays. Our results contribute valuable insights into the anti-cancer efficacy of Ech, particularly in the context of CC, illustrating its promise as an effective therapeutic agent by targeting both tumor cell functions and the tumor microenvironment.

Our results are consistent with prior studies reporting that Ech suppresses tumor progression in breast and ovarian cancers by modulating key signaling pathways such as Wnt/ β -catenin and PI3K/AKT. However, this study is the first to

demonstrate that Ech inhibits cervical cancer cell growth, migration and angiogenesis specifically through downregulation of β -catenin, c-myc and VEGFA. These findings provide new mechanistic evidence supporting the therapeutic relevance of Ech in gynecologic malignancies [11, 12, 17].

The Wnt/ β -catenin signaling pathway is a critical regulator of cellular processes such as growth, differentiation and migration. It has been implicated in the development and progression of various cancers, including CC. Aberrant activation of this pathway promotes tumor growth by enhancing β -catenin stabilization and increasing the expression of c-myc and VEGFA [4, 18, 19]. In our study, we demonstrated that treatment with Ech significantly decreased β -catenin levels in both cervical cells, leading to reduced expression of c-myc and VEGFA. These findings suggest that Ech effectively inhibits the Wnt/ β -catenin pathway in CC cells, providing a mechanistic basis for its impact on cell growth, migration and angiogenesis [12, 20]. The downregulation of these key signaling molecules by Ech

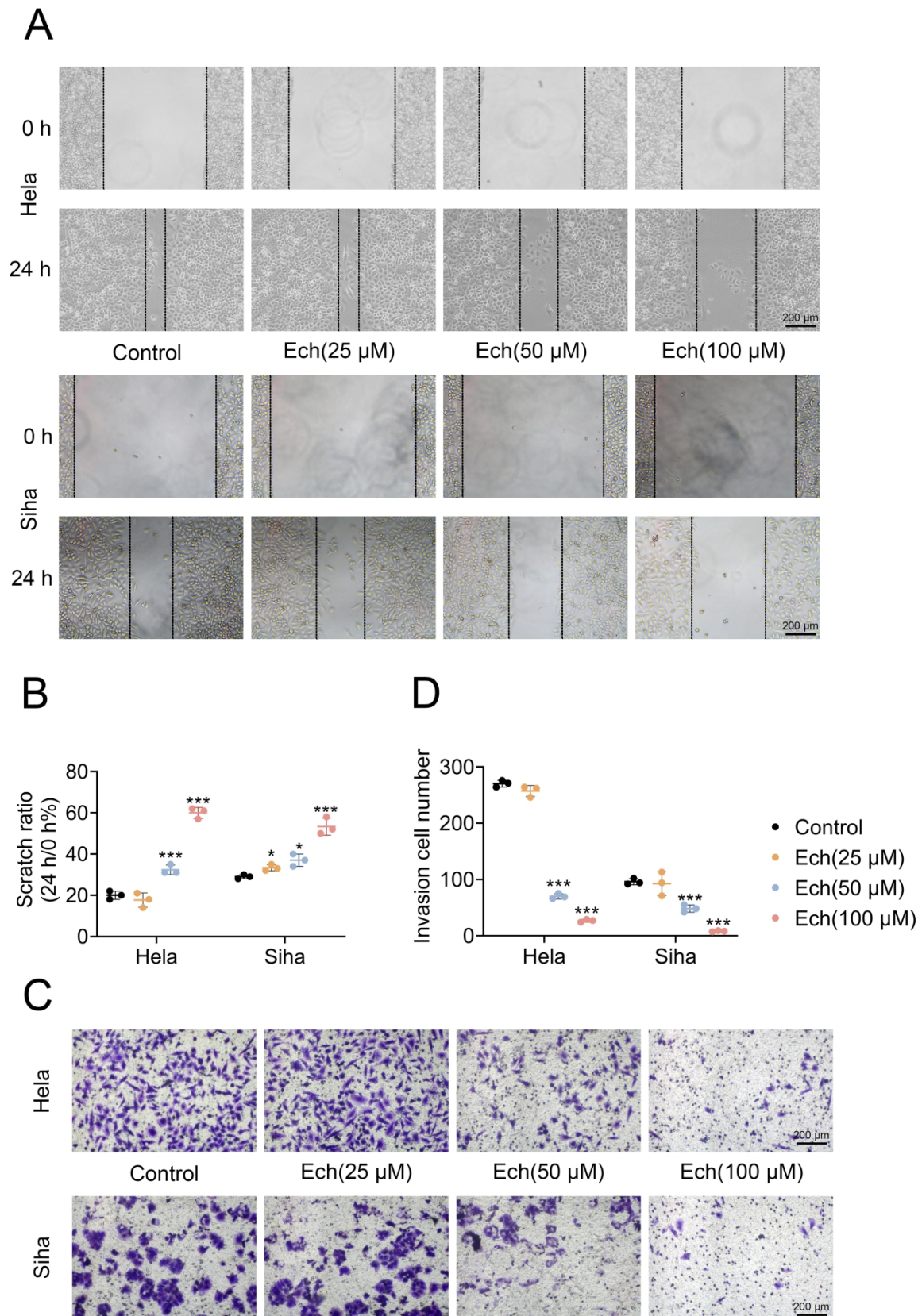


FIGURE 2. Echinacoside (Ech) inhibits the migration and invasion of cervical cancer cells. (A) Representative images of wound healing assays for HeLa and SiHa cells treated with 25 μ M, 50 μ M and 100 μ M Ech at 0 h and 24 h. (B) Quantifying the scratch ratio at 24 h shows a significant reduction in the migration of HeLa and SiHa cells treated with Ech. (C) Representative images of Transwell invasion assays for HeLa and SiHa cells treated with different concentrations of Ech (25 μ M, 50 μ M and 100 μ M). (D) Quantification of the invasion cell number. Data are presented as mean $\pm$ SD from three independent experiments ($n = 3$). Statistical significance was assessed using one-way ANOVA with Tukey's *post-hoc* test. * $p < 0.05$, *** $p < 0.001$, vs. control.

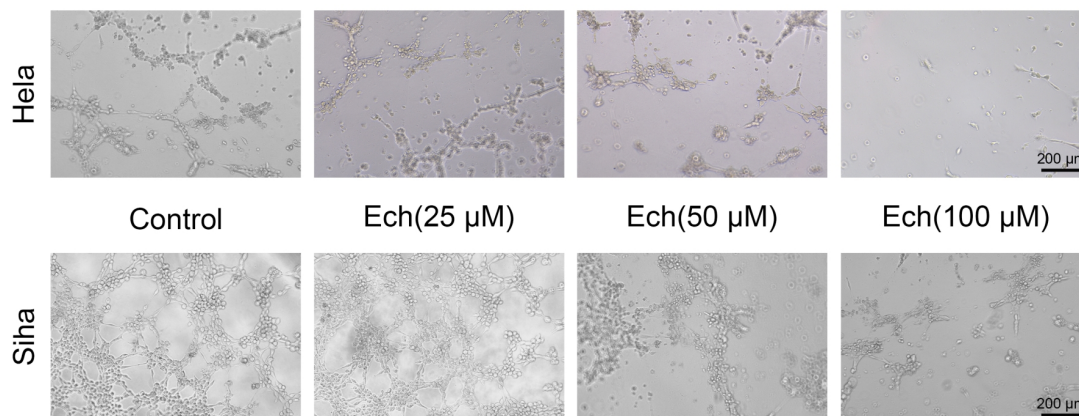


FIGURE 3. Echinacoside (Ech) inhibits the tube formation ability of cervical cancer cells. Representative images showing the effects of Ech (25 μ M, 50 μ M and 100 μ M) on tube formation by HeLa and SiHa cells. Control cells formed robust networks, while Ech treatment reduced the number and complexity of the tube-like structures in a dose-dependent manner. Data are presented as mean $\pm$ SD from three independent experiments ($n = 3$). Statistical significance was assessed using one-way ANOVA with Tukey's *post-hoc* test.

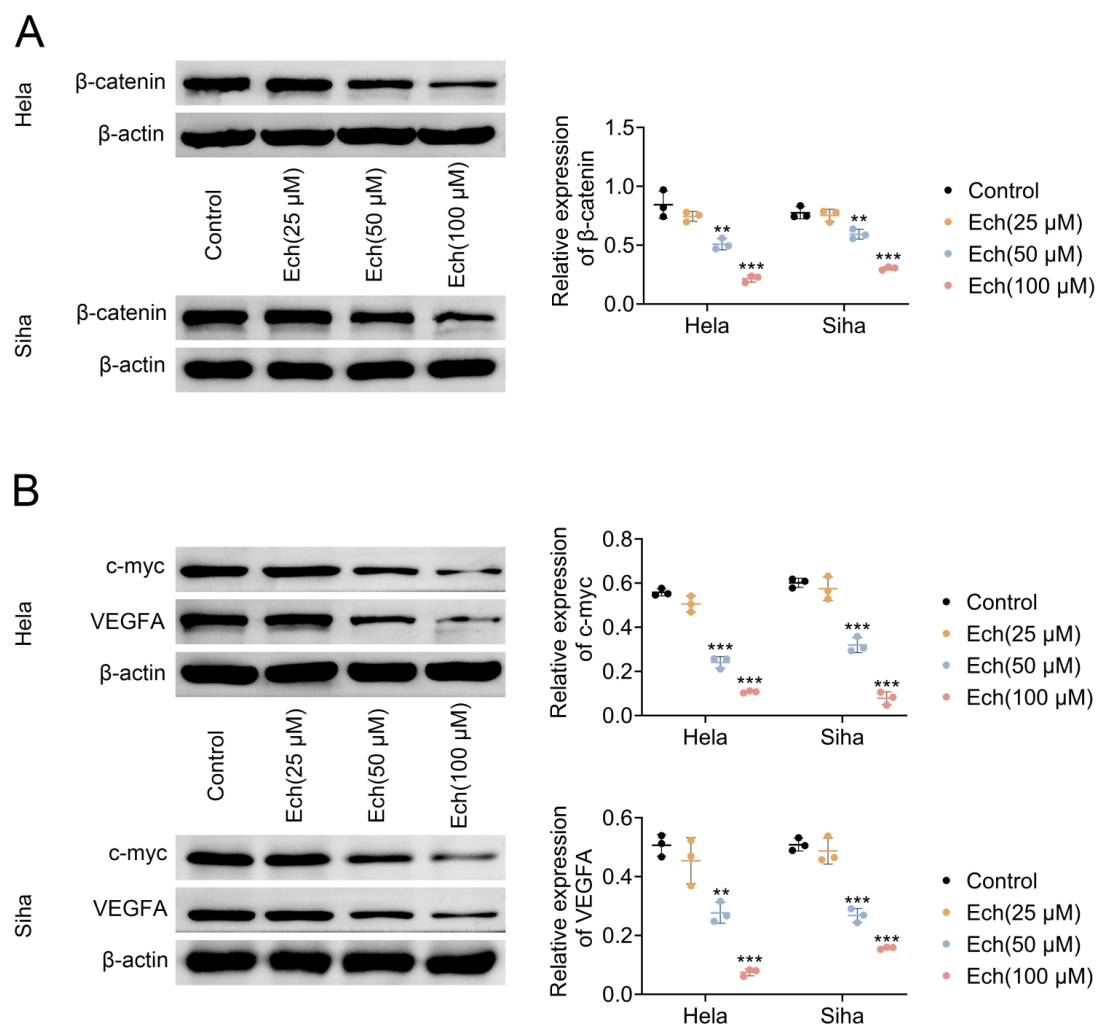


FIGURE 4. Echinacoside (Ech) inhibits the Wnt/ β -catenin signaling pathway in cervical cancer cells. (A) Western blot analysis showing the expression of β -catenin in HeLa and SiHa cells treated with different concentrations of Ech (25 μ M, 50 μ M and 100 μ M). β -actin was used as a loading control. (B) Western blot analysis of c-myc and VEGFA expression in HeLa and SiHa cells following treatment with Ech. β -actin was used as a loading control. ** $p < 0.01$, *** $p < 0.001$, vs. control. Data are presented as mean $\pm$ SD from three independent experiments ($n = 3$). Statistical significance was assessed using one-way ANOVA with Tukey's *post-hoc* test.

highlights the potential of targeting the Wnt/ β -catenin axis as a therapeutic strategy for CC treatment.

Our study provides important insights into the effects of Ech in cancer treatment; however, several limitations warrant consideration. First, the *in-vitro* findings must be validated *in-vivo* to confirm Ech's therapeutic efficacy and safety in preclinical models. Additionally, further studies are required to elucidate the precise molecular mechanisms through which Ech exerts its effects on the Wnt/ β -catenin axis and other signaling pathways. It may also enhance its anti-cancer efficacy by exploring the potential of combining Ech with other chemotherapy agents or targeted therapies. One notable limitation of our mechanistic analysis is that we focused exclusively on a select number of representative targets within the Wnt/ β -catenin signaling pathway. To comprehensively elucidate the intricate signaling cascade modulated by Ech, it is imperative that we incorporate additional downstream effectors and perform a broader range of functional assays in future studies.

While our findings demonstrate that Ech effectively downregulates the expression of β -catenin and its downstream targets c-myc and VEGFA, the precise molecular mechanism by which Ech modulates the Wnt/ β -catenin pathway remains to be fully elucidated. One possibility is that Ech may interfere with β -catenin stability or its nuclear translocation by targeting upstream signaling components or interacting directly with β -catenin. Future studies utilizing molecular docking simulations, CETSA (cellular thermal shift assay), and pull-down experiments will be necessary to determine whether Ech binds directly to β -catenin or its regulators such as Glycogen Synthase Kinase 3 Beta (GSK3 β), Dishevelled (Dvl) or Frizzled receptors. Uncovering these interactions will provide a more comprehensive understanding of the molecular basis for Ech's anti-tumor effects and may reveal novel therapeutic targets within the Wnt/ β -catenin axis.

In future research, it will be imperative to validate our *in vitro* findings using *in vivo* cervical cancer models to confirm the therapeutic efficacy and safety of Ech. Additionally, investigating the synergistic effects of Ech in combination with existing chemotherapeutic agents could reveal enhanced anti-cancer activity. Moreover, future research can focus on evaluating the pharmacokinetics, bioavailability and potential side effects of Ech to assess its viability for clinical application. Pharmacokinetic and bioavailability studies are necessary to evaluate the absorption, distribution, metabolism, as well as excretion characteristics of Ech, which are critical for its development as a potential therapeutic agent.

Compared with small-molecule Wnt/ β -catenin inhibitors such as ICG-001 or XAV-939, which directly block β -catenin-mediated transcription or promote its degradation, Ech exhibits similar inhibitory effects on downstream targets like c-myc and VEGFA, but with the added advantage of being a natural compound with multi-target potential and lower reported toxicity [21, 22]. These features suggest that Ech could serve as a complementary or alternative therapeutic strategy in cancers with aberrant Wnt signaling, including cervical cancer.

Although our findings demonstrate that Ech downregulates β -catenin and its downstream targets, functional rescue experiments (*e.g.*, β -catenin overexpression or Wnt3a stimulation) were not performed and remain necessary to confirm direct

causality. Future studies will be designed to include these approaches to validate the specificity of Ech's action on the Wnt/ β -catenin axis. While our study focused on downstream targets of the Wnt/ β -catenin pathway, we did not explore the effect of Ech on upstream regulators such as GSK3 β or Dishevelled (Dvl). Future studies should employ CETSA, pull-down assays, or molecular docking approaches to determine whether Ech directly interacts with these key signaling components. Another limitation of our study is the lack of *in vivo* validation, which is essential to confirm the therapeutic efficacy and safety profile of Ech in an animal model of cervical cancer. In addition, apoptosis-related mechanisms were not assessed; future studies incorporating Annexin V/Propidium Iodide (PI) staining, caspase activation, and Terminal Deoxynucleotidyl Transferase dUTP Nick-End Labeling (TUNEL) assays will be important to elucidate whether Ech also induces apoptotic cell death.

5. Conclusions

In conclusion, our study demonstrates that Echinacoside (Ech) effectively inhibits the proliferation, migration, invasion and angiogenesis of cervical cancer cells by suppressing the Wnt/ β -catenin signaling pathway. These findings provide mechanistic evidence supporting the therapeutic potential of Ech as a natural compound targeting multiple hallmarks of cancer.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YHY—designed the study and carried them out. TF, NYS, LM, HEX, XJK—supervised the data collection; analyzed the data. TF, NYS, LM, HEX—interpreted the data; prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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