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Original Article

Angelica Dahurica extracts improve the radiosensitivity of non-small-cell lung cancer cells via deactivating the JAK1/STAT3 axis

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Abstract: Objective: To investigate the effects of *Angelica dahurica* extract (ADE) on radiosensitivity of non-small-cell lung cancer (NSCLC) cells and the JAK/STAT pathway. Methods: The viability and radiosensitivity of NSCLC cell lines (A549, Calu-1, and H460 cells) were determined using CCK-8 and colony formation assays. Apoptosis was measured using flow cytometry. The expression and phosphorylation levels of Janus kinase 1 (JAK1) and signal transducer and activator of transcription 3 (STAT3) were measured using Western blot. In vivo, a Calu-1 cell-derived xenograft tumor model in nude mice was constructed to determine the effect of ADE on radiosensitivity. Results: ADE treatment significantly enhanced the radiosensitivity of NSCLC cell lines, as supported by increased apoptotic rate in irradiation (IR)-induced NSCLC cells. After ADE treatment, the phosphorylation level of STAT3 in IR-induced NSCLC cells was markedly decreased. Reactivation of STAT3 by co-administration of colivelin, a STAT3 activator, abolished the radio-sensitizing effect of ADE on A549, Calu-1, and H460 cells. *In vivo*, the combination of ADE and radiotherapy was well tolerated and significantly inhibited tumor growth. Compared with the control group and radiation group, the radiation + ADE treatment group showed lower STAT3 phosphorylation level in the transplanted tumor tissues. Conclusion: ADE exerts radio-sensitizing effects on NSCLC cells by blocking the JAK/STAT pathway.

Keywords: ADE, NSCLC, radiosensitivity, STAT3, colivelin

Introduction

Lung cancer (LC) is the second most commonly diagnosed cancer worldwide [1]. At present, the most effective treatments yield 5-year overall survival rates (OSRs) of only 6% for small cell lung cancer (SCLC) and 16% for non-SCLC (NSCLC) [2]. Such unfavorable results are largely attributed to the inherent or acquired resistance of LC to chemotherapy and radiotherapy. Therefore, a comprehensive understanding of the molecular mechanisms underlying treatment resistance is of great importance for improving patient survival and identifying effective treatment agents.

Angelica dahurica extract (ADE), a Chinese herbal medicine, is frequently used in combination with other herbs to treat various diseases, such as urinary disorders and inflammation [3]. Imperatorin, an active ADE compound, has been shown to exert antioxidant effects and alleviate hypertension through inhibition of the mitogen-activated protein kinase (MAPK) pathway and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation [4, 5]. Moreover, isoimperatorin and imperatorin have been identified as the principal active components of ADE [6, 7]. Evidence indicates that imperatorin has anti-cancer effects, including the induction of apoptosis and restoration of the chemosensitivity in cancer cells [8]. Similarly, imperatorin has been reported to re-sensitize doxorubicin-resistant leukemia cells (K562/DOX) to DOX and enhance the antitumor effect of DOX on K562/DOX xenograft tumors in NOD/SCID mice [9]. Furthermore, imperatorin exhibits protective effects on cultured neural cells. Although the medicinal properties of ADE have been documented in the Chinese Pharmacopeia, its underlying mechanisms in NSCLC remain unclear.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway mediates cytokine signaling and plays critical roles

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in regulating immune responses and cellular physiological processes [10]. Abnormal JAK-STAT activation has been implicated in various human malignancies. Constitutive activation of JAK leads to persistent activation of STAT3, a well-recognized oncogene [11]. Previous study has reported that transfection with constitutively activated STAT3 induces tumors in nude mice [12]. Moreover, STAT3 activation has been detected in various human cancers, including NSCLC [13-15]. The 5-year overall survival (OS) rate of NSCLC patients with high STAT3 expression was significantly lower than those with low STAT3 expression [16], highlighting STAT3 as a promising therapeutic target in NSCLC.

Although the anti-cancer effects of ADE have been reported, its effect on the radiosensitivity of NSCLC remains unclear. Therefore, this study aimed to explore whether ADE enhances the radiosensitivity of NSCLC cells and to elucidate the underlying molecular mechanisms.

Materials and methods

Cell culture and irradiation

Calu-1, 95D, A549, NCI-H460, NCI-H1650, and NCI-H1299 cell lines were obtained from the Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. RPMI-1640 and McCoy's 5A media were purchased from Sigma Aldrich Co. (St Louis, MO, USA). Colivelin (CLN) (a selective STAT3 activator) was obtained from Selleck Chemicals (Houston, TX, USA).

Calu-1 cells were cultured in McCoy's 5A medium, while 95D, A549 cells, NCI-H460, NCI-H1650, and NCI-H1299 cells were cultured in RPMI-1640 medium. All media were supplemented with 10% fetal bovine serum (FBS). The cells were incubated at 37°C in a humidified atmosphere with 5% CO_2. Irradiation was conducted using 6-MV X-ray energy (dose rate: 200 cGy/min, source-skin distance: 100 cm). At 2.5 days after irradiation, the cells were rinsed three times with phosphate buffered saline (PBS) and then cultured in growth medium containing ADE (100 μM) and/or CLN (50 μM) for 1 day.

Cell counting kit-8 (CCK)-8 assay

Cells were inoculated in 96-well plates at a density of 2×10^3 cells/well. At days 2, CCK-8 reagent (10 μL; Shanghai Biyuntian Biotechnology Co., Ltd., China) was added into each well, followed with fresh medium (90 μL). The cells were then cultured for 60 min. The optical density (OD) at 450 and 630 nm was measured using a microplate reader.

CellTiter-Glo test

Cell proliferation was tested using CellTiter-Glo kit (Promega) according to the instructions of manufacturer. Briefly, cells were seed in 96-well plates at a density of 2×10^3 cells/well. On day 2, an equal volume of CellTiter-Glo reagent was added to each well. Chemiluminescence was detected using an Envision microplate reader.

Flow cytometry (FCM)

Apoptosis was determined using an Annexin V-FITC/PI Kit (Biyuntian Biotechnology Co., Ltd.) according to the manufacturer's instructions. Next, 100 μL of cell suspension was incubated with Annexin V (5 μL), and propidium iodide (PI; 1 μL) in 1 × Annexin V binding buffer for 15 min at room temperature in the dark. Annexin V binding buffer (400 μl) was added to quench the reaction. The apoptosis rate was measured using a flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

Western blot analysis

Proteins were extracted from the cells using RIPA buffer (Beyotime Biotechnology) at 4°C. Protein samples were separated by SDS-PAGE and transferred onto PVDF membranes. Membranes were incubated with primary antibodies against pJAK1 (1:1000, ab138005), JAK1 (1:1000, ab47435), pSTAT3 (1:200, ab30647), STAT3 (1:1000, ab5073), and GAPDH (1:5000, ab8245) (all from Abcam), followed by incubation with HRP-conjugated secondary antibodies (goat anti-mouse or goat anti-rabbit; 1:1,000; Beyotime Biotechnology). Protein bands were visualized using enhanced chemiluminescence reagents (Millipore Sigma, Burlington, MA, USA).

Xenograft mouse model

BALB/c nude mice (28 days old) were purchased from VitalRiver and maintained at the Laboratory Animal Center of Anhui Medical University. All animal procedures were approved by the Research Ethics Committee of Anqing Municipal Hospital.

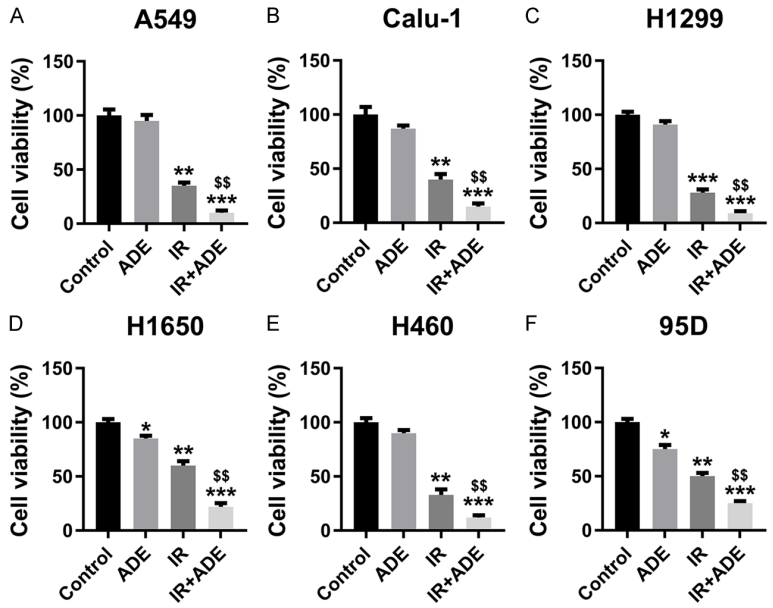


Figure 1. *Angelica dahurica* extract (ADE) enhanced the radiosensitivity of radiation-treated NSCLC cells. A-F. Effects of ADE on the viability of radiation-treated A549, Calu-1, H1299, H1650, H460, and 95D cells, as measured by CCK-8 assay. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control group; $$P < 0.01 vs. IR group.

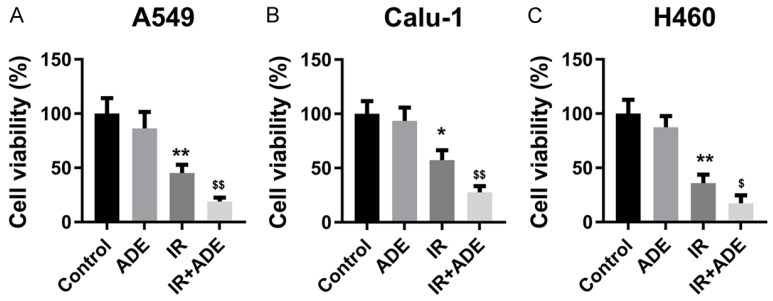


Figure 2. The combination of *Angelica dahurica* extract (ADE) and irradiation significantly inhibited the proliferation of radiation-treated NSCLC cells. A-C. Effects of ADE on the viability of IR-treated A549, Calu-1, and H460 cells, as measured using CellTiter-Glo test. *P < 0.05, **P < 0.01 vs. control group; $P < 0.05, $$P < 0.01 vs. IR group.

Calu-1 cells (5 × 10^6 cells in 100 μL of PBS) were subcutaneously administered into the nude mice. A total of 32 nude mice were randomly divided into four groups (n = 8 per group): Control, ADE, irradiation (IR), and IR + ADE groups. ADE was administered at a dose of 10 mg/kg, once every three days for two weeks. Radiotherapy was delivered at a total dose of 10 Gy (2 Gy/day for 5 consecutive days). The schematics of model establishment is demonstrated in **Figure 7A**. Body weight and tumor sizes were measured every other day to confirm successful modeling. Tumor sizes were calculated using the formula: (mm^3) = length × $width^2$/2. Mice were euthanized by cervical dislocation on day 14 after tumor inoculation, and tumor weight was measured to evaluate the anti-tumor effects.

Statistical analysis

Statistical analysis was performed using SPSS 17.0, and figure generation was performed using GraphPad 5.0 (La Jolla, CA). Data were presented as the mean ± SD of three individual experiments. Comparison between two groups was conducted using Student's *t*-tests, while comparison among multiple groups were conducted using one-way analysis of variance (ANOVA) with Tukey post-hoc test. $P < 0.05$ was considered statistically significant.

Results

ADE treatment promoted radiosensitivity of IR-treated NSCLC cells

The effects of ADE on the viability of NSCLC cells were first evaluated using the CCK-8 assay. ADE treatment alone did not significantly affect the viability of most NSCLC cells, except for NCI-H1650 and 95D cells (**Figure 1A-F**). After irradiation, a sharp decrease was observed in the viability of all six NSCLC cell lines. After the administration of ADE in IR-treated NSCLC cells, the cell viability was further reduced compared with that in the IR-treated groups (**Figure 1A-F**).

Based on these results, A549, Calu-1, and H460 cells were selected for further analysis. Results from CellTiter-Glo test showed that the proliferative capacity of these cells was not changed after ADE treatment but was significantly impaired following IR treatment (**Figure 2A-C**). Importantly, the combination of IR and

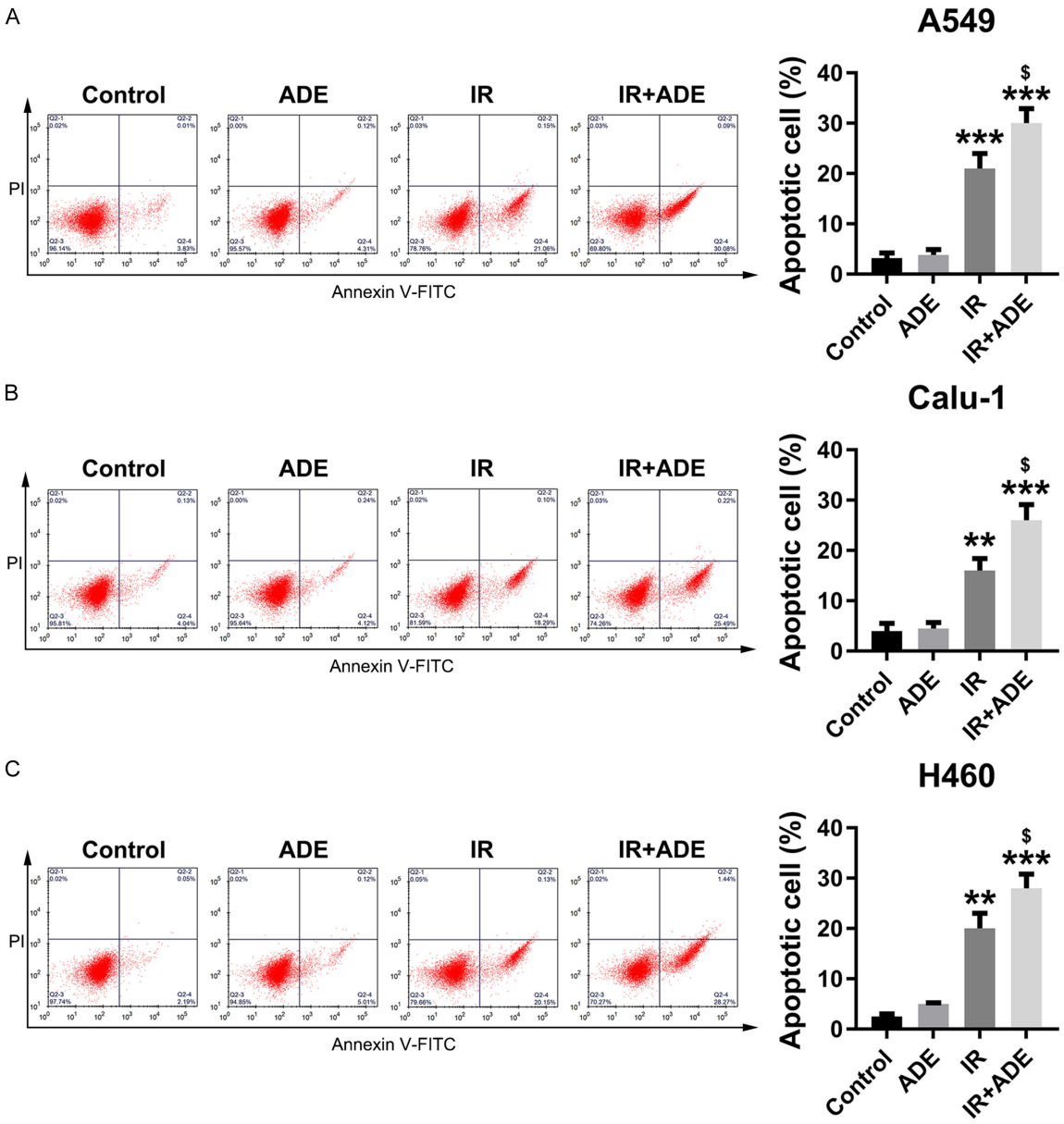


Figure 3. The combination of *Angelica dahurica* extract (ADE) and irradiation robustly induced apoptosis in radiation-treated NSCLC cells. A-C. Effects of ADE on the apoptosis of radiation-treated A549, Calu-1, and H460 cells, as measured using flow cytometry. **P < 0.01, ***P < 0.001 vs. control group; $P < 0.05 vs. IR group.

ADE further reduced the proliferative capacity of these cells. Collectively, these findings indicate that ADE enhances the radiosensitivity of NSCLC cells while exerting minimal effects under non-irradiated conditions.

Radiotherapy combined with ADE promoted apoptosis of NSCLC cells

The effect of ADE on apoptosis in IR-treated NSCLC cells was further investigated. IR treatment significantly increased apoptosis in A549, Calu-1, and H460 cells, whereas ADE treatment alone had no significant effect on apoptotic rates. Moreover, the combination of radiotherapy and ADE treatment further increased apoptosis in these NSCLC cell lines, with the most pronounced effect observed in A549 cells (**Figure 3A-C**).

Effects of ADE on JAK1/STAT3 signaling in irradiated NSCLC cells

The expression and phosphorylation levels of JAK1 and STAT3 in NSCLC cells were detected using western blotting. ADE treatment alone

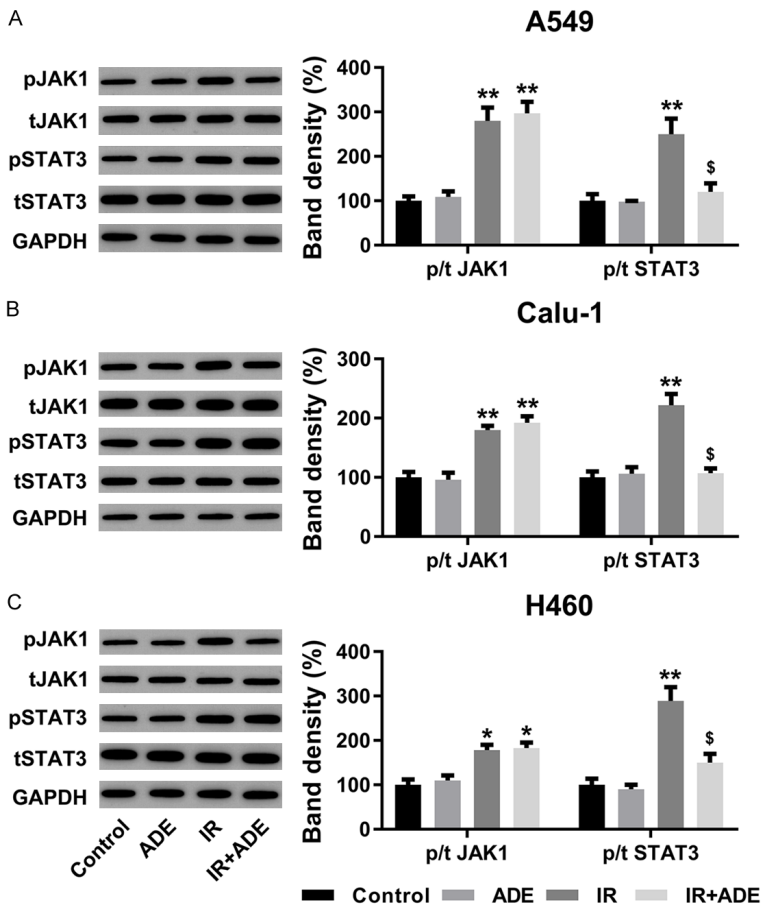


Figure 4. Effects of ADE and IR on JAK1/STAT3 activation in NSCLC cells. A-C. Western blotting was performed to determine the expression and phosphorylation of JAK1 and STAT3 in IR-treated A549, Calu-1, and H460 cells. Relative band densities are shown in the right panel. *P < 0.05, **P < 0.01 vs. control group; $P < 0.05 vs. IR group.

did not significantly change the expression and phosphorylation of JAK1 and STAT3 in non-IR-treated A549, Calu-1, and H460 cells. However, IR treatment significantly increased phosphorylated JAK1/total JAK1 ratio and phosphorylated STAT3/total STAT3 ratio in NSCLC cells, suggesting that the JAK1/STAT3 pathway was activated after IR treatment. Furthermore, combined ADE and IR treatment markedly reduced the phosphorylated STAT3/total STAT3 ratio but did not change the phosphorylated JAK1/total JAK1 ratio (**Figure 4A-C**), indicating that ADE selectively inhibited the phosphorylation of STAT3 without affecting the phosphorylation of JAK1 in IR-treated NSCLC cells.

STAT3 reactivation by CLN in ADE- and IR-treated NSCLC cells

We hypothesized that ADE-induced STAT3 deactivation contributes to the radio-sensitizing effects of ADE on NSCLC cells. Compared with the IR cells, STAT3 phosphorylation was markedly decreased after ADE treatment (**Figure 5A-C**), while JAK1 phosphorylation remained unchanged. However, compared with the IR + ADE group, the co-administration of ADE and CLN significantly increased the phosphorylated levels of STAT3 in IR-treated NSCLC cells (**Figure 5A-C**), indicating that the STAT3 was reactivated after CLN treatment in IR- and ADE-treated NSCLC cells.

Effect of STAT3 reactivation on the proliferation and death of NSCLC cells

We assessed the effect of ADE and CLN co-administration on the proliferation of IR-treated cells using Cell-Titer-Glo test. Compared with ADE treatment alone, the proliferation capacity of NSCLC cells was markedly restored after the co-treatment with ADE and CLN (**Figure 6A-C**).

Moreover, FCM was conducted to detect apoptosis of IR-treated NSCLC cells. ADE treatment further increased the apoptosis of IR cells. However, the co-administration of ADE and CLN reversed this pro-apoptotic effect of ADE (**Figure 6D-F**). These findings suggest that STAT3 deactivation contributes to the ADE-facilitated radiosensitivity in NSCLC cells.

Combined treatment of radiotherapy and ADE in mice with calu-1 cells

Consistent with the *in vitro* results, ADE alone showed no marked effect on the JAK1/STAT3 pathway-related molecules in xenograft tissues. The expression levels of total and phosphorylated JAK1 and STAT3 proteins markedly improved after radiotherapy. However, IR combined with ADE treatment markedly suppressed STAT3 phosphorylation (**Figure 7B**). Compared with the control group, radiotherapy markedly inhibited tumor growth, whereas ADE treat-

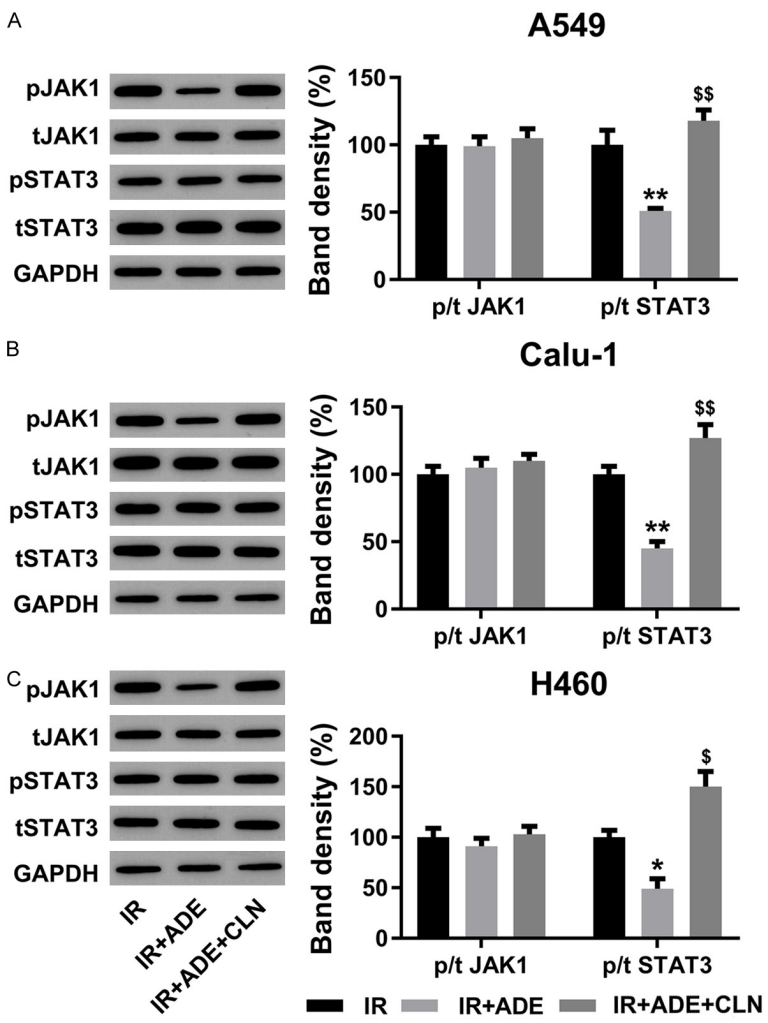


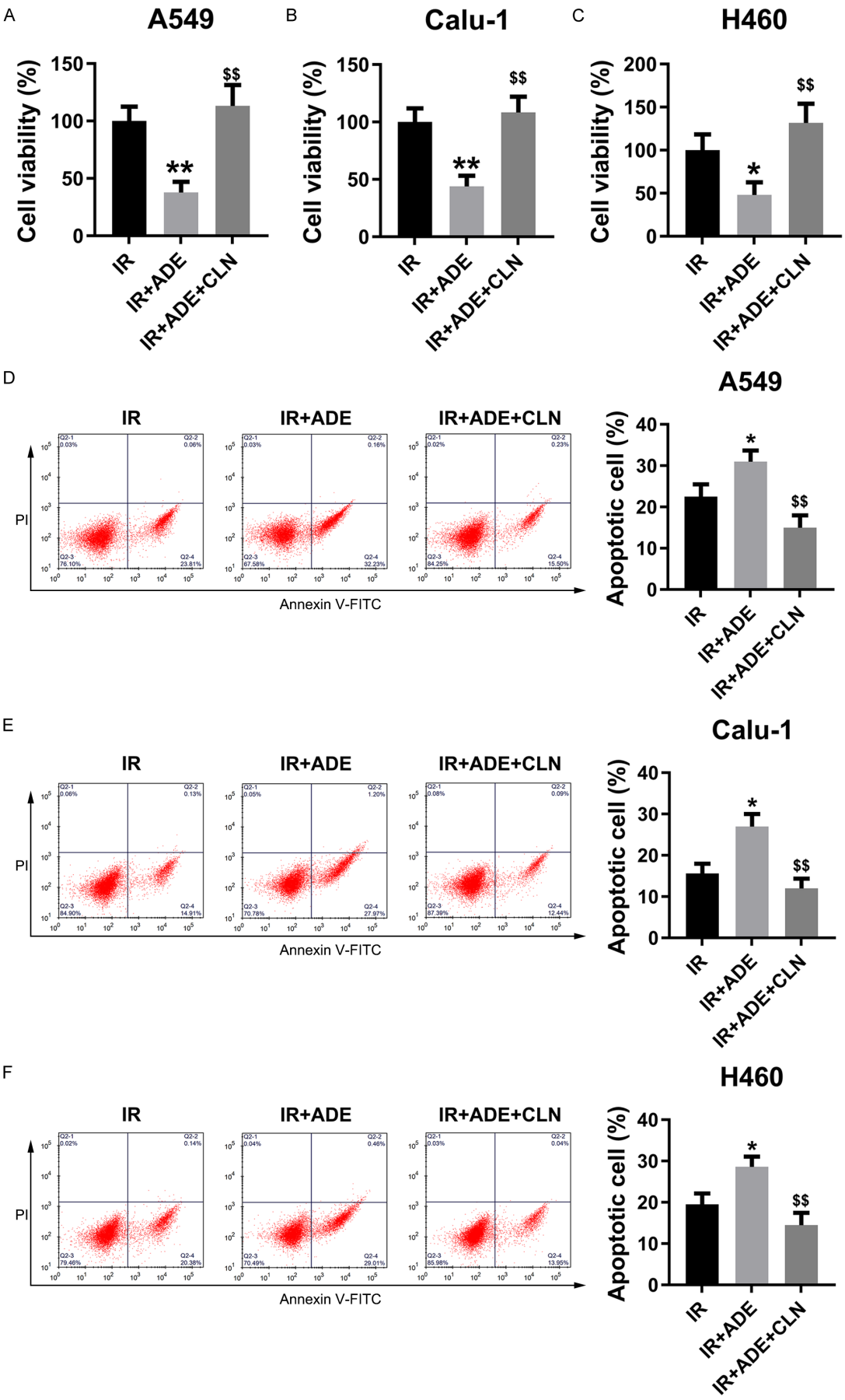
Figure 5. Effects of colivelin on *Angelica dahurica* extract (ADE)-deactivated JAK1/STAT3 pathway in NSCLC cells. Irradiation-induced cells were co-administered with ADE and/or CLN for 24 h. A-C. Western blotting was conducted to determine the expression and phosphorylation of JAK1 and STAT3 in radiation-treated A549, Calu-1, and H460 cells. Relative band densities are shown in the right panel. *P < 0.05, **P < 0.01 vs. IR group; $P < 0.05, $$P < 0.01 vs. IR+ADE group.

ment did not lead to any significant changes. Compared with radiotherapy alone, the combination of radiotherapy and ADE treatment resulted in a significantly greater reduction in tumor growth compared with radiotherapy alone (**Figure 7C**, **7D**), indicating a synergistic antitumor effect *in vivo*.

Discussion

LC remains a life-threatening disease worldwide. Radiotherapy is a key treatment for patients with NSCLC, particularly in those with advanced-stage disease. However, the 5-year OS remains low (5%-10%), and approximately 60% of patients develop distant metastasis and 80% experience local recurrence [17]. These unfavorable outcomes are largely attributable to radio-resistance of tumor cells. Although the combined application of radiotherapy and anti-angiogenic drugs can improve radiosensitivity of tumor cells and patient outcomes, these benefits are often short-lived. Multiple studies have reported that ADE exerts potent anti-cancer effects in various cell lines, including LC cell lines [18-20]. In this study, we demonstrated that ADE exerted minimal cytotoxic effects on non-irradiated NSCLC cells but significantly enhanced the antitumor efficacy of IR through the JAK1/STAT3 pathway.

STAT3 is activated by non-receptor tyrosine kinase (Src) or JAK by Tyr705 residue phosphorylation [21]. Tyr705-phosphorylated STAT3 molecules interact through reciprocal SH2 domain engagement, forming dimers that translocate to the cell nucleus, where they bind DNA and regulate the transcription of genes such as *Bcl2*, *BclXL*, and *Mcl-1* [22]. Multiple studies have shown that STAT3 overexpression enhances NSCLC proliferation, survival, and resistance to radiotherapy [23]. NSCLC patients with high STAT3 expression had a significantly lower 5-year OS rate than those with low STAT3 expression [24], highlighting STAT3 as a potential therapeutic target in NSCLC. Moreover, STAT3 plays a crucial role in the development of cancer radio-resistance by promoting the expression of anti-apoptotic genes [25, 26]. In this study, we found that ADE selectively inhibited STAT3 phosphorylation without directly affecting the phosphorylation of upstream proteins such as JAK1. Furthermore, ADE


A
A549
Cell viability (%)
150
100
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IR
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Calu-1
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IR
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C
H460
Cell viability (%)
200
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IR
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IR+ADE+CLN
PI
Annexin V-FITC
Q2-1 0.03%
Q2-2 0.06%
Q2-3 76.10%
Q2-4 23.81%
Q2-1 0.03%
Q2-2 0.16%
Q2-3 67.58%
Q2-4 32.23%
Q2-1 0.02%
Q2-2 0.23%
Q2-3 84.25%
Q2-4 15.50%
A549
Apoptotic cell (%)
40
30
20
10
0
*
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IR
IR+ADE
IR+ADE+CLN
E
IR
IR+ADE
IR+ADE+CLN
PI
Annexin V-FITC
Q2-1 0.06%
Q2-2 0.13%
Q2-3 84.90%
Q2-4 14.91%
Q2-1 0.05%
Q2-2 1.20%
Q2-3 70.78%
Q2-4 27.97%
Q2-1 0.08%
Q2-2 0.09%
Q2-3 87.39%
Q2-4 12.44%
Calu-1
Apoptotic cell (%)
40
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10
0
*
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IR
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IR
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PI
Annexin V-FITC
Q2-1 0.02%
Q2-2 0.14%
Q2-3 79.46%
Q2-4 20.38%
Q2-1 0.04%
Q2-2 0.46%
Q2-3 70.49%
Q2-4 29.01%
Q2-1 0.03%
Q2-2 0.04%
Q2-3 85.98%
Q2-4 13.95%
H460
Apoptotic cell (%)
40
30
20
10
0
*
$$
IR
IR+ADE
IR+ADE+CLN

Figure 6. Effects of colivelin (CLN) on *Angelica dahurica* extract (ADE)-mediated regulation of proliferation and apoptosis in radiation-treated NSCLC cells. A-C. Effects of CLN on the proliferation of irradiated A549, Calu-1, and H460 cells treated with ADE, as measured using CellTiter-Glo test. D-F. Effects of CLN on the apoptosis in irradiated A549, Calu-1, and H460 cells treated with ADE, as measured using flow cytometry. *P < 0.05, **P < 0.01 vs. IR group; $$P < 0.01 vs. IR+ADE group.

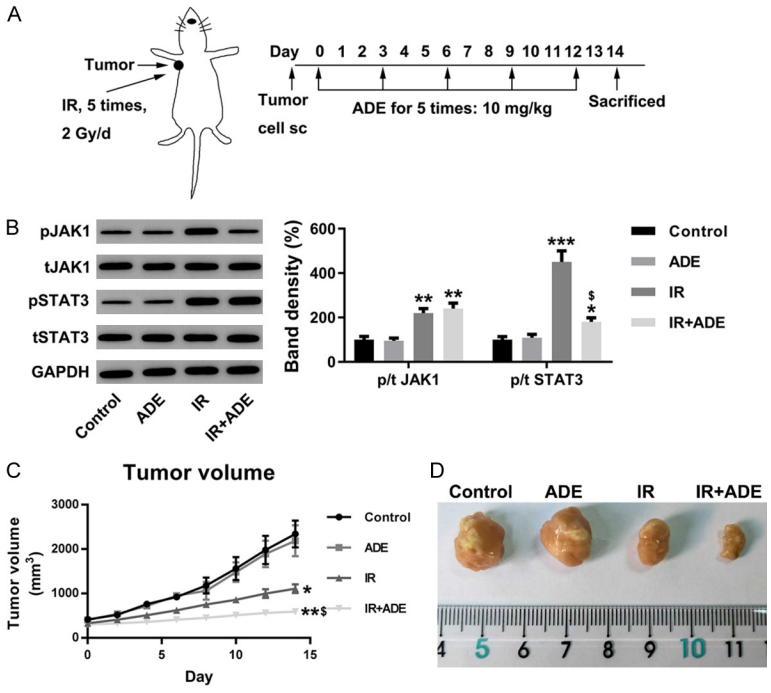

Figure 7. Effects of Angelica dahurica extract (ADE) treatment in mice with Calu-1 cells. A. Tumor model establishment and treatment scheme. Approximately 5 × 10^6 Calu-1 cells were subcutaneously administered to the mice. After 10 days, ADE (10 mg/kg, once daily) was administered and radiotherapy was performed for 14 days. Two groups were treated with 10 Gy radiation (2 Gy X/day, 5 times). The mice were euthanized one day following the final administration, and tumor sizes were calculated to evaluate anti-tumor effects. B. The expression and phosphorylation levels of JAK1 and STAT3 in the tumor tissue were measured using western blotting. C. Tumorigenesis was assessed every other day for two weeks. Tumor size was measured. D. Representative image of tumors in each group (n = 8). *P < 0.05, **P < 0.01, ***P < 0.001 vs. control group; $P < 0.05 vs. IR group.

enhanced IR-triggered apoptosis of NSCLC cells, but had no effect on the non-radiation-treated NSCLC cells, suggesting that ADE may prevent radiation-induced activation of the JAK1/STAT3 pathway in LC cells, thereby restoring radio-sensitivity of resistant NSCLC cell lines, consistent with a previous report that RNAi-mediated STAT3 depletion improved the radiosensitivity of A549 cells and counteracted the radioresistance of A549-IRR cells by down-regulating Bcl2/Bcl-XL [27]. These findings suggest that the STAT3-related pathway plays an important role in the acquisition of radioresistance and may serve as a treatment target.

Angelica dahurica Radix is a traditional herbal medicine with anti-cancer properties. However, the mechanisms underlying its anti-cancer activities are incompletely understood. Zheng et al. reported that *Angelica dahurica* Radix significantly decreased the expression of p53, Bcl, Bax and induced apoptosis through caspase cascade and cell cycle arrest in colon cancer cells. The ethanol-ethyl acetate fraction showed anti-cancer activities in HT-29 cancer cells [28]. Another study by Lee et al. indicated that a chloroform-soluble fraction of the *Angelica dahurica* roots inhibited IR-induced migration NSCLC A549 cells at a non-cytotoxic concentration (50 μM), which is consistent with our findings [29]. Our study indicated that ADE, alone or in combination with radiation therapy, significantly improved the radiosensitivity of Calu-1 xenografts in mice. Compared with ADE treatment alone, the combination treatment resulted in a significant decrease in tumor burden. Consistent with the *in vitro* experiments, ADE also blocked IR-induced JAK1/STAT3 activation, leading to enhanced apoptosis of tumor cells.

Conclusion

ADE enhances the radiosensitivity of NSCLC cells by inhibiting STAT3 phosphorylation, and reactivation of STAT3 attenuates the radiosensitizing effects of ADE on NSCLC cell lines. Nevertheless, several limitations to this work should be acknowledged. First, the precise molecular mechanisms by which ADE affects

STAT3 activation is still unclear, warranting further proteomic analysis. Second, how JAK/STAT activation is linked to the proliferation and apoptosis of NSCLC cell lines remains to be further elucidated. Despite these limitations, our findings provide novel mechanistic insights into the anti-cancer effects of ADE and confirm its potential in radiotherapy for NSCLC.

Disclosure of conflict of interest

None.

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