Resveratrol Enhances Gemcitabine-Induced Apoptosis in A549 Non-Small Cell Lung Cancer Cells

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Abstract:

Background: Lung cancer is the commonest cause of cancer related mortality. Non-small cell lung cancer (NSCLC) is the most prevalent kind of lung malignancies. Gemcitabine is a first line drug used in NSCLC. However, the therapeutic efficacy of gemcitabine is constrained by the drug resistance and toxicity. Resveratrol is a natural polyphenol with chemosensitizing properties, enhancing the antitumor effects of chemotherapy.

Objectives: To investigate whether resveratrol potentiates the apoptotic effect of gemcitabine in A549 cells and the modulatory effects of gemcitabine- resveratrol combination on PI3K/Akt and STAT3 pathways.

Methods: Exponentially growing A549 cells were treated with gemcitabine, resveratrol, or their combination. Annexin V-fluorescein isothiocyanate (Annexin V-FITC)/propidium iodide (PI) staining was used to measure apoptosis. The protein expression levels of phospho-Akt and phospho-STAT3 were quantified using Western blotting.

Results: The results indicated that gemcitabine-resveratrol combination greatly increased the apoptosis in A549 cells compared with single drug treatments. Moreover, the co-treatment significantly reduced the expression levels of phospho-Akt and phospho-STAT3 compared to each drug alone.

Conclusion: Resveratrol enhanced gemcitabine-induced apoptosis in A549 cells. Moreover, the combination treatment resulted in augmented suppression of both phospho-Akt and phospho-STAT3 expression. These findings suggest resveratrol as potential adjunct to gemcitabine to in the treatment of NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); Gemcitabine; Resveratrol; Apoptosis.

الريسفيراترول يعزز موت الخلايا المبرمج المحفَّز بالجيمسيتابين في خلايا سرطان الرئة ذو الخلايا غير الصغيرة A549

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الخلاصة:

الخلفية: يعد سرطان الرئة السبب الأكثر شيوعاً للوفيات المرتبطة بالسرطان. ويمثل سرطان الرئة ذو الخلايا غير الصغيرة (NSCLC) النمط الأكثر انتشاراً بين أورام الرئة الخبيثة. يُعتبر الجيمسيتابين دواءً من أدوية الخط الأول المستخدمة في علاج سرطان الرئة ذي الخلايا غير الصغيرة. مع ذلك، فإن المقاومة الدوائية والسمية تحد من الفعالية العلاجية للجيمسيتابين. يُعد الريسفيراترول مركباً طبيعياً من عائلة متعددات الفينول، ويمتاز بخصائص محسسة للعلاج الكيميائي، مما يعزز التأثيرات المضادة للأورام للعلاج الكيميائي

الأهداف: تقييم ما إذا كان الريسفيراترول يعزز التأثير المحفِّز لموت الخلايا المبرمج للجيمسيتابين في خلايا A549 ودراسة التأثيرات التعديلية للعلاج المركب بالجيمسيتابين والريسفيراترول على مسارات PI3K/Akt وSTAT3.

الطرق: عولجت خلايا A549 بالجيمسيتابين، أو الريسفيراترول، أو بمزيج من الدوائين. تم تقييم موت الخلايا المبرمج باستخدام تلوين انيكسين في-فلوريسين ايزوثيوسيانات/يوديد البوتاسيوم (Annexin V-FITC/PI). تم تحليل مستوى التعبير لفوسفو-Akt وفوسفو-STAT3 باستخدام لطخة ويسترن.

النتائج: أشارت النتائج إلى أن العلاج المركب بالجيمسيتابين والريسفيراترول أدى إلى زيادة كبيرة في موت الخلايا المبرمج في خلايا A549 مقارنة بالعلاجات الدوائية المفردة. علاوة على ذلك، أدى العلاج المركب إلى انخفاض ملحوظ في مستويات فوسفو-Akt وفوسفو-STAT3 مقارنة بالعلاج بأي من الدوائين بمفرده.

الاستنتاج: عزز الريسفيراترول موت الخلايا المبرمج الذي يسببه الجيمسيتابين في خلايا A549بالإضافة إلى ذلك، أدى العلاج المشترك بالجيمسيتابين والريسفيراترول إلى تعزيز تثبيط فوسفو-Akt وفوسفو-STAT3 . تشير هذه النتائج إلى إمكانية استخدام الريسفيراترول كعامل مساعد للجيمسيتابين في علاج سرطان الرئة ذي الخلايا غير الصغيرة.

الكلمات المفتاحية: سرطان الرئة ذو الخلايا غير الصغيرة؛ الجيمسيتابين؛ الريسفيراترول؛ موت الخلية المبرمج.

Introduction:

lung cancer is the commonest cause of cancer related deaths across the world, with approximately 1.79 million deaths, or 18% of total cancer fatalities in 2020. Furthermore, it is the second most prevalent kind of cancer. Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancer cases (1). The prognosis for NSCLC patients is still bad, with a 5-year survival rate of only about 15% (2). Chemotherapy remains the standard treatment for NSCLC, despite the emergence of targeted therapy and immunotherapy (3). Gemcitabine is a first line drug in the management of lung cancer that is used either as a monotherapy or in conjunction with other anticancer drugs (4). The antitumor effects of gemcitabine are exerted by interfering with DNA synthesis (5). Nonetheless, the therapeutic effectiveness of gemcitabine is restricted by drug resistance and dose limiting toxicity (6). Therefore, developing novel therapeutic approaches is crucial to overcome resistance, reduce side effects, and ultimately providing better outcomes for patients. Recently, plant derived natural compounds have gained lot of attention

as possible adjuncts to cancer chemotherapy owing to their minimal toxicity profile, cost-effectiveness, and ability to modulate multiple signaling pathways involved in carcinogenesis. Natural compounds not only exhibit inherent anti-tumor activity but also can synergize with conventional chemotherapeutic agents to improve therapeutic effectiveness while reducing systemic toxicity (7). In this regard, resveratrol, a polyphenol mainly found in grapes and berries, has demonstrated potential in the management of numerous malignancies, involving lung, breast, colorectal, renal, bladder, and liver cancers (8-13). Resveratrol has been evidenced to manipulate numerous signaling pathways linked to inflammation, cell cycle progression, and apoptosis through different molecular mechanisms (14). Furthermore, resveratrol has been confirmed to sensitize tumor cells to chemotherapy and radiation therapy, augmenting death of cancer cells (15). The phosphoinositide 3-kinase (PI3K)/ Protein kinase B (Akt) and signal transducer and activator of transcription 3 (STAT3) pathways are vital signaling pathways which are crucial for controlling cell growth, cell cycle progression, and apoptosis (16, 17). Various cancer types, including lung cancer, were documented to abnormally activate these pathways (18, 19). Furthermore, it has been demonstrated that these pathways are implicated in gemcitabine resistance (20, 21). The study aims to investigate whether resveratrol potentiates gemcitabine-mediated apoptosis in A549 cells and the modulatory effects of the co-treatment with gemcitabine and resveratrol on PI3K/Akt and STAT3 pathways.

Materials and methods:

Cell line and culture conditions

A549 cell line was procured from ATCC (USA). The cells were grown in RPMI-1640 medium complemented with 10% fetal bovine serum (FBS) and 1% antibiotic/antimycotic and kept at 37 °C in a humidified incubator with 5% CO_2.

Apoptosis Assay

Annexin V-fluorescein isothiocyanate (Annexin V-FITC)/propidium iodide (PI) Apoptosis detection Kit (Elabscience, USA) was utilized to identify the apoptotic effects of gemcitabine-resveratrol combination compared to individual drug treatments. A549 cells were cultured in six-well cell culture plates with 5×10^4 cells per well and incubated overnight. Next day, the cells were exposed to gemcitabine, resveratrol or a combination of both at their respective IC_{50} concentrations for 72 h, which were previously determined in our laboratory using an MTT assay under the same culture conditions (22). The cells then trypsinized, rinsed with pre-cooled PBS, and suspended with 100 µL of 1× binding buffer of Annexin V. Then, 2.5 µL each of Annexin V-FITC and PI were added and the resulting mixture was mildly vortexed and left in the darkness at ambient temperature for 15 minutes. The cells were examined with a flow cytometer (BD FACSVerse™) and the percentage of apoptosis was calculated utilizing FlowJo 10.10 software (TreeStar, Ashland, OR, USA). To quantify apoptosis, a gating strategy was employed. First, the primary cell population was identified and cellular debris was excluded based on forward scatter (FSC) and side scatter (SSC) characteristics. Next, doublet discrimination was performed to ensure only single cells were included in the analysis. Compensation was applied utilizing single-stained controls to accurately account for spectral overlap between the fluorochromes. Finally, quadrant gating was established based on Annexin V-FITC (x-axis) and PI (y-axis) fluorescence. Based on this gating, cells were classified into four populations: viable (Annexin V-/PI-), early apoptotic (Annexin V+/PI-), late

apoptotic (Annexin V+/PI+), and necrotic cells (Annexin V-/PI+) (23, 24).

Western blot analysis

Western blotting was performed using Western blot detection kit (Elabscience, USA). A549 cells from various treatment groups were lysed with cold RIPA lysis buffer complemented with a protease inhibitor (PMSF**)** and a phosphatase inhibitor (Na_3VO_4). Subsequent to homogenization and sonication, lysates were cleared by centrifugation. The bicinchoninic acid protein quantification kit (Elabscience, USA) was utilized for quantification of the protein content in whole cell lysates. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was employed to separate equal quantities of total protein, which were then electro-blotted onto a polyvinylidene fluoride (PVDF) membranes. After that, skim milk (5%) was utilized to block the membranes for 90 minutes before incubation with the primary antibodies against phospho-Akt (Ser473), phospho-STAT3 (Tyr705), and GAPDH (Elabscience, USA) at 4ºC overnight on a rocker. Next day, secondary antibody (goat anti-rabbit) was added and incubated with the membranes. Finally, the bands were captured with a ChemiDoc XRS+ imaging system (Bio-Rad, USA) and measured with ImageJ software (National Institutes of Health, USA) (25, 26).

Statistical analysis

Data were analyzed with GraphPad Prism 8.4 Software. Results represent the mean ± standard deviation (SD) of three independent experiments. Differences among groups were assessed with one-way analysis of variance (ANOVA) accompanied by Tukey's post hoc test. The statistical significance was set at $P < 0.05$.

Results:

Apoptotic effects of gemcitabine, resveratrol, and their combination in A549 cells

To investigate the potential of resveratrol to potentiate gemcitabine induced apoptosis, the apoptotic rates of A549 cells exposed to gemcitabine (0.92 µM) and resveratrol (68.72 µM), alone or in combination were determined using Annexin V-FITC/PI staining. The results indicated that gemcitabine alone significantly raised the percentage of early apoptotic cells to 18.03 ± 0.55% in comparison to the control cells (0.52 ± 0.27%) ($p < 0.0001$). In addition, the percentage of early apoptosis cells was also significantly elevated to 15.12 ± 1.06% after treatment with resveratrol alone ($p < 0.0001$). Notably, the level of early apoptosis following co-treatment with gemcitabine and resveratrol was increased by about 1.37 folds compared with the gemcitabine treatment alone ($p = 0.0006$) (Figure 1A and B). A similar pattern has been noted in the late apoptotic cell population. The percentage of late apoptosis cells following treatment with gemcitabine or resveratrol was increased to 14.85 ± 2.29% and 9.06 ± 1.85%, respectively, compared with the control (0.34 ± 0.22%) ($p < 0.0001$ and $p = 0.0009$, respectively). Importantly, following co-treatment with gemcitabine and resveratrol, the percentage of late apoptotic cells was raised by about 2.65 folds relative to gemcitabine treated group ($p < 0.0001$).

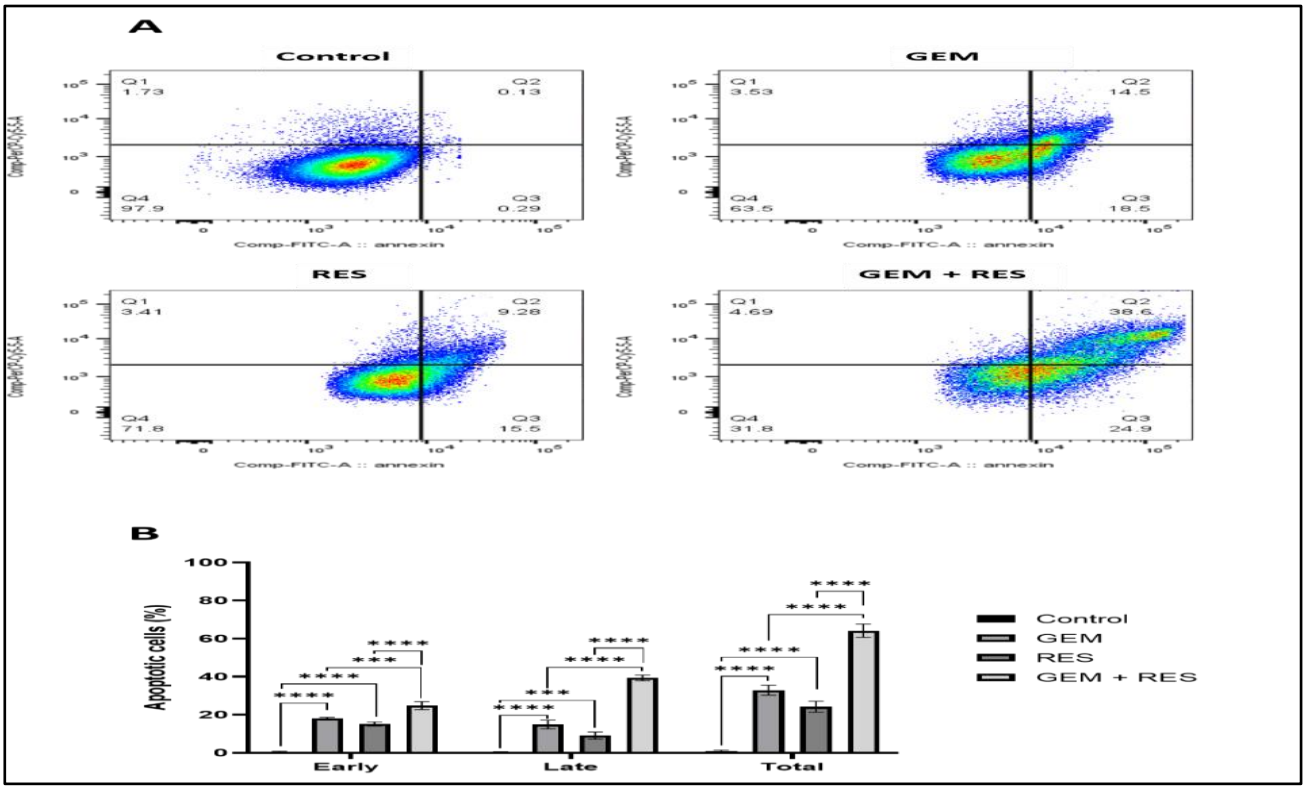

Figure (1): Flow cytometry analysis of apoptotic responses in A549 cells using Annexin V-FITC/PI staining after 72 h of exposure to gemcitabine (0.92 µM) and/or resveratrol (68.72 µM). (A) Representative dot plots showing viable cells (Q4, AV-/PI-), early apoptotic cells (Q3, AV+/PI-), late apoptotic cells (Q2, AV+/PI+) and necrotic cells (Q1, AV-/PI+) identified by quadrant gating based on Annexin V-FITC (x-axis) and PI (y-axis) fluorescence. (B) Bar graph demonstrating quantification of early, late, and total apoptosis under different treatment conditions. Data acquisition was carried out using a flow cytometry. Data were analyzed using FlowJo software (version 10.10). Gating was performed by excluding debris based on forward and side scatter (FSC/SSC), followed by doublet discrimination; compensation was applied using single-stained controls. Results represent the mean ± SD (n=3). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test. ******P* < 0.001, *******P* < 0.0001. GEM = gemcitabine, RES = resveratrol.

Effects of gemcitabine, resveratrol and their combination on phospho-Akt level in A549 cells

Western blot analysis for the expression of phospho-Akt protein in A549 cells (Figure 2A and B) demonstrated non-significant difference in the level of phospho-Akt following treatment with 0.92 µM gemcitabine in comparison with control cells (p = 0.605). Conversely, the treatment with 68.72 µM resveratrol significantly reduced phospho-Akt level compared with control cells (p = 0.0001). Importantly, the combination treatment markedly decreased phospho-Akt level compared with resveratrol treated group (p = 0.0009).

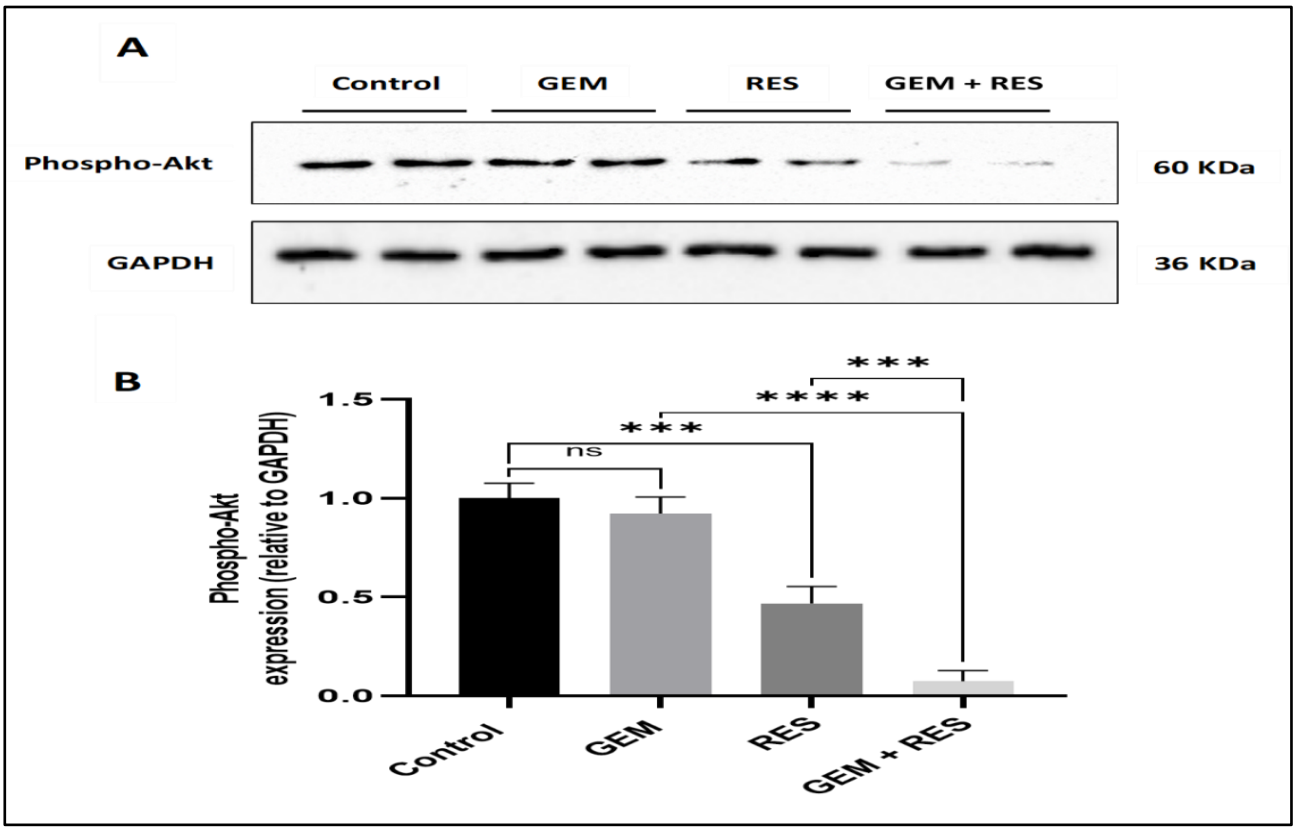

Figure (2): Western blot analysis of the effects of single or combination treatment with gemcitabine and resveratrol on the expression of phospho-Akt in A549 cells. (A) Representative immunoblot showing phospho-Akt and GAPDH (loading control). The cells were treated with gemcitabine (0.92 µM) and/or resveratrol (68.72 µM) for 72 h. Total proteins were extracted, and equal amounts were separated by SDS-PAGE and transferred to PVDF membranes, followed by incubation with the specific antibodies. (B) Protein bands were analyzed utilizing ImageJ software. The data are represented as mean ± SD (n=3). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test. ns: non-significant, ******P* < 0.001, *******P* **< 0.0001. GEM = gemcitabine, RES = resveratrol.**

Effects of gemcitabine, resveratrol and their combination on phospho-STAT3 level in A549 cells

As Figure (3) illustrates, the level of phospho-STAT3 was significantly reduced in A549 cells treated with either gemcitabine (0.92 µM) or resveratrol (68.72 µM) in comparison with the control cells (p = 0.0033 and p = 0.0003, respectively). Notably, the combination treatment greatly decreased the protein levels of phospho-STAT3 compared to either gemcitabine or resveratrol treatment (p < 0.0001 and p = 0.0010, respectively).

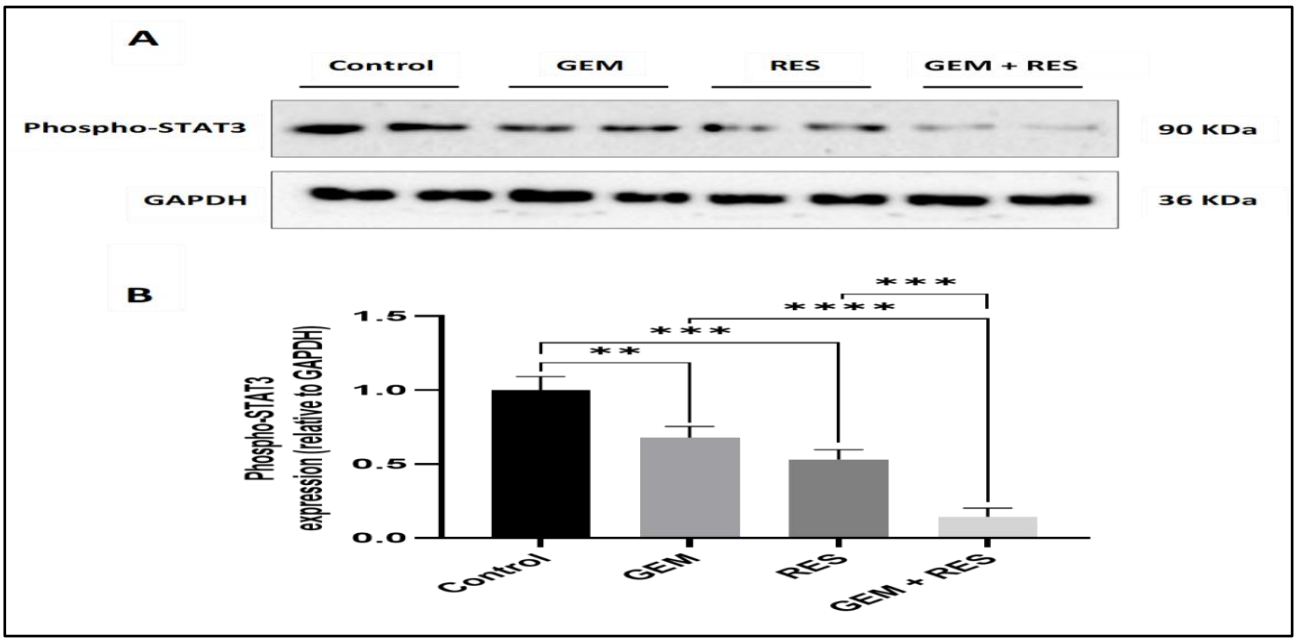

Figure (3): Western blot analysis of the effects of gemcitabine, resveratrol, or their combination on the expression of phospho-STAT3 protein in A549 cells. (A) Representative immunoblot showing phospho-STAT3 and GAPDH (loading control). The cells were exposed to gemcitabine (0.92 µM) and/or resveratrol (68.72 µM) for 72 h. Total proteins were extracted, and equal amounts were separated by SDS-PAGE and transferred to PVDF membranes, followed by incubation with the specific antibodies. (B) The protein bands were analyzed utilizing ImageJ software. Data are presented as mean ± SD (n=3). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test. **$p < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. GEM = gemcitabine, RES = resveratrol.

Discussion:

NSCLC is the most frequent sub-class of lung cancer, with a high incidence rate (27). Chemotherapy is the main treatment strategy for managing NSCLC, with gemcitabine utilized as one of the major chemotherapeutic drugs in the treatment regimen (28). However, resistance to gemcitabine is frequently identified as a primary limitation in lung cancer management (29). Hence, the therapeutic effect of gemcitabine needs further improvement. The present study aimed to assess the potential of resveratrol to enhance the apoptotic effect of gemcitabine in A549 cells.

Resveratrol has shown promising antineoplastic effects against various types of cancer. Many studies revealed that resveratrol prompts apoptosis by modulating both intrinsic and extrinsic apoptotic mechanisms (30, 31). In this study, the flow cytometry data demonstrated that both gemcitabine and resveratrol induced apoptosis in A549 cells. A key finding in this study is that co-treatment with gemcitabine and resveratrol greatly raised apoptosis in A549 cells compared with single drug treatments. This finding is consistent with our previous work, which demonstrated a synergistic cytotoxic interaction between these agents in A549 cells using combination index and isobologram analyses (22). It also aligns with extensive research that has recognized resveratrol as a chemosensitizer that improves the efficacy of conventional chemotherapy

(32, 33). Previous studies indicated that resveratrol has the potential to augment gemcitabine's apoptotic effects in pancreatic cancer models. For instance, it has been proven that the apoptotic impact of gemcitabine can be enhanced by resveratrol via targeting c-Met/PARP1 pathway (34). In addition, has been demonstrated that resveratrol could synergistically augment gemcitabine effects by downregulation of NF-κB constitutive activation (35). Moreover, resveratrol has shown to make pancreatic cancer cells more sensitive to gemcitabine via targeting sterol regulatory element binding protein 1 (SREBP1) and suppression of YES activated protein (YAP) (36, 37). Collectively, these findings indicate the capacity of resveratrol to act as a broad spectrum chemosensitizer, augmenting the apoptotic effects of gemcitabine across different cancer types.

Aberrantly active PI3K/Akt signaling is frequently observed in many cancers. Activated (phosphorylated) Akt phosphorylates downstream targets to mediate cancer cell resistance to apoptosis (38). A study by Tuya *et al*. revealed that the treatment with trichosanthin potentiates the apoptotic impact of gemcitabine through modulation of Akt signaling axis (39). Furthermore, it has been reported that alantolactone enhances gemcitabine-induced apoptosis via targeting Akt/GSK3β axis (40). In this study, Western blot results demonstrated that resveratrol significantly suppressed the level of phospho-Akt. Moreover, the co-treatment with gemcitabine and resveratrol greatly reduced the levels of phospho-Akt relative to single drug treatments. Previous research has demonstrated that resveratrol can sensitize NSCLC cells by targeting PI3K/Akt pathway. For instance, Rasheduzzaman *et al*. reported that resveratrol can enhance the sensitivity of lung cancer cells to TRAIL by decreasing Akt phosphorylation level with the associated suppression of NF-κB expression (41). Furthermore, resveratrol has been demonstrated to sensitize A549 cells to cisplatin via enhanced inhibition of phospho-Akt, resulting in modulation of autophagy (42). STAT3 is a key effector of the JAK/STAT3 signaling cascade. Persistently active STAT3 is frequently observed in NSCLC, and has also been hypothesized to significantly reinforce tumor resistance to both traditional and targeted therapies. STAT3 inhibits both intrinsic and extrinsic apoptotic pathways, allowing cancer cells to tolerate radiation and cytotoxic drugs (19). It has been reported that inhibition of STAT3 activation promotes the chemo-sensitivity of tumor cells to gemcitabine (43). Notably, resveratrol has been shown to trigger apoptosis and suppress chemoresistance by downregulation of STAT3 activation (44). In this study, Western blot results further revealed that the combination treatment suppressed the level of phospho-STAT3 more profoundly than either drug alone. Collectively, these findings suggest that the observed enhanced apoptotic effect could be mediated, at least in part, by modulation of PI3K/Akt and STAT3 pathways.

Conclusion

The present study elucidated that resveratrol potentiated gemcitabine induced apoptosis in A549 cells. Furthermore, the co-treatment with gemcitabine and resveratrol resulted in enhanced suppression of phospho-Akt and phospho-STAT3, suggesting that the modulation of PI3K/Akt and STAT3 pathways could be involved in the sensitizing effect of resveratrol. The results suggest the potential of resveratrol as an adjunct to gemcitabine to improve NSCLC treatment outcomes.

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