Clinical and Experimental Health Sciences

The Inhibitory Effects of Resveratrol on Tumor Growth and Metastasis in Esophageal Adenocarcinoma

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ABSTRACT

Objective: Resveratrol is a small polyphenol that has been extensively researched across various therapeutic areas. Its inhibitory effect on esophageal cancer cell growth has also been demonstrated in a dose – and time-dependent manner. However, the underlying mechanism of this effect has not been fully elucidated yet. We aimed to investigate the anti-proliferative and anti-metastatic effects of resveratrol on esophageal adenocarcinoma (EAC) cells in vitro.

Methods: The EAC cells were treated with various doses of resveratrol, and cell viability was determined using the WST-1 assay. The apoptosis rate and the level of intracellular reactive oxygen species (ROS) were measured using flow cytometry. Adhesion, wound healing, and colony formation assays were carried out to evaluate the anti-metastatic effects of resveratrol.

Results: Resveratrol decreased the cell viability of OE33 cells in a dose-dependent manner. 150 µM resveratrol reduced cell viability by 49% compared to the control by increasing ROS levels. This inhibition was associated with the induction of apoptosis. The analysis revealed that resveratrol also suppressed the adhesion, migration, and colony forming capacity of the cells.

Conclusions: Resveratrol lower the viability and metastatic potential of EAC cells. These findings suggest resveratrol may be further evaluated clinically for this malignancy in humans.

Keywords: Resveratrol, esophageal adenocarcinoma, anti-tumor, anti-metastatic.

1. INTRODUCTION

Esophageal cancer is the seventh most prevalent cancer worldwide and the sixth leading cause of cancer-related deaths, with an overall poor prognosis. It is classified into two major histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). While ESCC is more common globally, the incidence of EAC has increased more rapidly than any other solid tumor, particularly in western countries (1,2). Chemotherapy and radiotherapy are the primary treatment regimens for EAC patients. However, the emergence of chemoresistance and radioresistance in an increasing number of tumors presents a significant challenge in cancer therapy. Furthermore, these treatments often cause adverse side effects, underscoring the urgent need for the discovery of natural products with effective anti-cancer properties (3).

Recent studies have demonstrated that diets high in vegetables and fruits are linked to a reduced incidence of esophageal cancer. It is hypothesized that flavonoids, a group of bioactive polyphenolic compounds found in fruits, vegetables, and plant-based beverages, may contribute to this reduced risk (4). Resveratrol, a natural polyphenol found in red grapes, wine, nuts, and various common garden plants, is the most widely studied among the many phytochemicals with potential health benefits. Additionally, its chemopreventive and chemotherapeutic properties have been demonstrated in various human carcinomas, such as colorectum, skin, liver, lung, pancreas, breast and prostate (5). Numerous reports highlight resveratrol's role as a cancer chemopreventive agent due to its ability to induce growth inhibition, cell cycle arrest, and apoptosis in various human cancer cell lines (3). Research on squamous cell carcinoma of the head and neck has revealed that resveratrol inhibits proliferation, invasion, as well as inducing cell cycle arrest and apoptosis (6), while studies on pancreatic cancer cells

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suggest that resveratrol shows significant potential as a complementary agent to chemotherapy by suppressing proliferation, angiogenesis, and metastasis (7). Previous studies have also suggested that a diet rich in resveratrol may reduce the risk of EAC (8) and resveratrol treatment has been shown to induce apoptosis in human esophageal carcinoma cells (9). However, the exact molecular mechanisms through which resveratrol exerts its anti-cancer effects remain unclear. Therefore, our study aims to further elucidate the underlying mechanisms of resveratrol treatment in EAC, ultimately contributing to the development of more effective therapeutic strategies for this malignancy.

2. METHODS

2.1. Cell Culture

OE33 human EAC cells (Sigma-Aldrich, Darmstadt, Germany) were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium (PAN Biotech GmbH, Aidenbach, Germany), supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Biochrom, Berlin, Germany) and 100 U/mL penicillin / 100 mg/mL streptomycin (PAN Biotech GmbH, Aidenbach, Germany). The cells were maintained at 37 °C in a humidified atmosphere containing 5% CO_2 and 95% air. Upon reaching 80% confluence, the cells were detached from the culture flask using a solution of 0.25% trypsin and 0.02% EDTA and subsequently transferred to a new culture flask.

2.2. Treatment with Resveratrol

Resveratrol (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in dimethyl sulfoxide (DMSO; Sigma-Aldrich, St. Louis, MO, USA) to prepare a 500 mM stock solution, which was stored at – 20 °C until use. For cell treatment, the stock solution was diluted in the growth medium. All treatments were conducted following overnight serum starvation. Each experiment was performed in duplicate, and all assays were repeated at least three times.

2.3. Cell Viability Assay

Cell viability was assessed using the WST-1 Cell Proliferation Assay (Roche, Basel, Switzerland). Briefly, OE33 cells were seeded into 96-well plates at a density of 6×10^3 cells/well and allowed to attach overnight. Following serum starvation in FBS-free medium, the cells were treated with resveratrol at varying concentrations (50 µM, 100 µM, 150 µM, and 200 µM). Control cells were treated with medium containing the vehicle. After a 24-hour treatment period, the medium was removed, and 10% WST-1 solution was added. Absorbance was measured at 440 nm after two hours using a 96-well plate reader (Molecular Devices, CA, USA). The viability of the treated cells was calculated as a percentage compared to the control cells.

2.4. Detection of Apoptosis Rate

The apoptosis rate was evaluated using the ApopNexin FITC Apoptosis Detection Kit (Chemicon International, Temecula, CA, USA) according to the manufacturer's protocol. Briefly, cells were seeded into 12-well plates at a density of 6×10^4 cells/well. Following 24 hours of serum starvation in FBS-free medium, cells were treated with 150 µM resveratrol for 24 hours. Subsequently, cells were dissociated, washed, and incubated in 500 µL of binding buffer containing 2 µL of annexin V-FITC and 2 µL of propidium iodide (PI) in the dark for 45 minutes at room temperature. The stained cells were analyzed using FACSCalibur flow cytometry (BD Biosciences, CA, USA), and the results were calculated with CellQuest software (BD Biosciences, CA, USA). Healthy cells were identified as Annexin-V-negative and PI-negative, early apoptotic cells as Annexin-V-positive and PI-negative, late apoptotic cells as Annexin-V-positive and PI-positive, and necrotic cells as Annexin-V-negative and PI-positive. The apoptosis ratio was calculated by summing the percentages of early apoptotic and late apoptotic cells.

2.5. Measurement of Intracellular ROS Levels

Intracellular ROS levels were detected by flow cytometry using 5-(and-6)-carboxy – 2′,7′-dichlorodihydrofluorescein-diacetate (H2DCFDA) (Molecular Probes Co. OR, USA) staining. as a probe. Briefly OE33 cells were seeded into 6-well plates at a density of 1.5×10^5 cells/well and starved overnight in the non-FBS medium. Following serum starvation, the cells were treated with 150 µM resveratrol for 24 hours. After treatment, the cells were collected by trypsinization and were washed with Phosphate-Buffered Saline (PBS). The cells were then stained with 10 µM H2DCFDA for 45 minutes at 37°C in a 5% CO_2 incubator. After incubation, the cells were washed and fluorescence intensity was measured using a flow cytometry (FACSCalibur, BD Biosciences, CA, USA).

2.6. Adhesion Assay

The effect of resveratrol on the adhesive ability of OE33 cells was evaluated using an adhesion assay. Briefly, cells were seeded into 6-well plates at a density of 1.5×10^5 cells/well and starved for 24 hours. After starvation, the cells were treated with 150 µM resveratrol for 24 hours. The cells were then collected by trypsinization, counted, and 5×10^4 cells/well were plated into a 96-well plate pre-coated with 1% fibronectin (Sigma, St. Louis, MO). After 1 hour incubation at 37°C in a 5% CO_2 atmosphere, the cells were washed with PBS, fixed with 3% paraformaldehyde for 10 minutes, and washed again with 2% methanol for 10 minutes. The cells were then stained with 0.5% crystal violet. The stained cells were measured at 540 nm using a 96-well plate reader (Enspire 2300, Perkin Elmer, MA, USA).

2.7. Wound-Healing Assay

Cell migration was assessed using a wound-healing assay. OE33 cells were seeded into a 12-well plate at a density of 2.5×10^4 cells/well and allowed to attach and grow overnight, followed by starvation for 24 hours. A small linear scratch was then gently created using a sterile pipette tip. After the cells were washed with PBS to remove cellular debris, they were treated with 150 µM resveratrol for 24 hours. The migration and wound closure ability, both before and after resveratrol treatment, were compared with microscopy (Carl Zeiss, Jena, Germany).

2.8. Colony Formation Assay

A colony formation assay was performed to assess the effects of resveratrol on the proliferative potential of OE33 cells. Briefly, the cells were seeded into a 6-well plate at a density of 1.5×10^5 cells/well. After 24 hours of starvation, the cells were treated with 150 µM resveratrol for 24 hours. Following treatment, the cells were collected by trypsinization and counted. The cells were then reseeded into a new 6-well plate at a density of 500 cells per well and allowed to continue growing for 1 week in a humidified incubator at 37°C with 5% CO_2. After 1 week, the medium was discarded, and the cells were stained with dimethylmethylene blue for 45 minutes. Excess stain was removed by washing with PBS, and the blue-black colonies were observed and counted using microscopy.

2.9. Statistical Analysis

All experiments were performed in at least three independent replicates. Statistical analyses were conducted using Jamovi 2.3.26 (Sydney, Australia). Student's t-test was used for comparisons between two groups, whereas one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was applied for comparisons among three or more groups. All data are expressed as mean ± standard deviation (SD). A p-value of < .05 was considered statistically significant.

3. RESULTS

3.1. Resveratrol Reduced Viability of OE33 Cells.

The effect of resveratrol on the viability of OE33 EAC cells was determined using WST-1 assay. The cells were cultured in different concentrations of resveratrol (50–200 µM) for 24 hours. According to the assay, resveratrol decreased cell viability in a dose-dependent manner. A statistically significant decline was observed at concentrations above 100 µM, reaching 49% at 150 µM, while the percentage of viable cells dropped to 21% at 200 µM ($p < .05$). Based on this test result, 150 µM resveratrol concentration was used in subsequent experiments as it was close to the IC50 value (Figure 1).

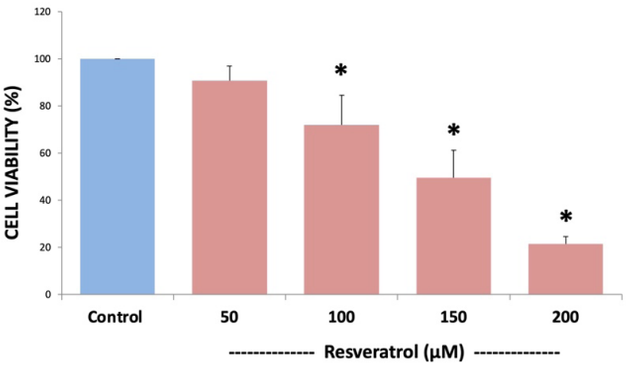


Figure 1. *Resveratrol reduced the viability of OE33 cells in a dose-dependent manner. OE33 cells were exposed to different concentrations of resveratrol for 24 hours. Subsequently, cell viability was determined by the WST-1 assay. * $p < .05$. N = 4 independent experiments.*

3.2. Resveratrol Induced Apoptosis in OE33 Cells.

To investigate whether resveratrol's viability-reducing effect occurs through the induction of apoptosis, the apoptosis rate in the cells was measured after treatment. As shown in Figure 2, exposure to resveratrol increased the apoptosis ratio in the cells from 15±2% to 52±12%, as well as decreased the percentage of normal cells from 84±2% to 34±3% significantly ($p < .05$). This data showed that resveratrol exerts its cytotoxic effect by inducing apoptosis.

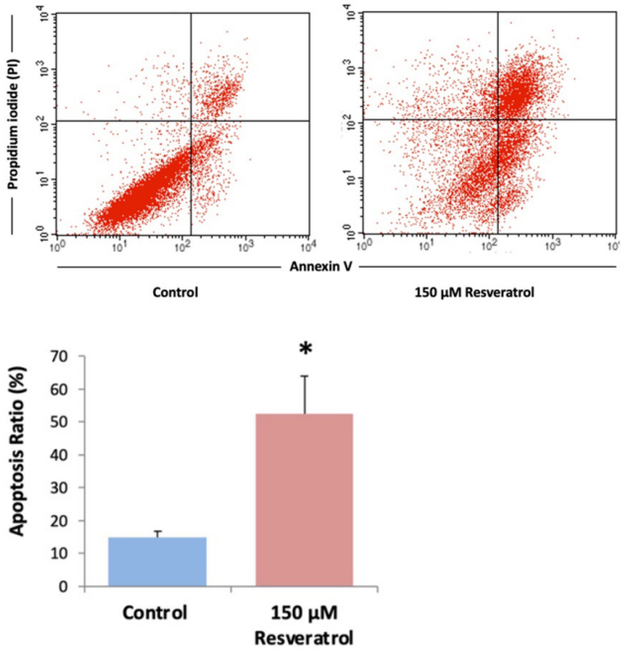


Figure 2. *Resveratrol induced apoptosis in OE33 cells. Following a 24-hour treatment with resveratrol, the cells were stained with Annexin V-FITC and PI and analyzed by flow cytometry. (A) Representative dot plots of OE33 cells after the treatment. Viable (healthy) cells were Annexin V^-/PI^-, early apoptotic cells were Annexin V^+/PI^-, late apoptotic cells were Annexin V^+/PI^+, and necrotic cells were Annexin V^-/PI^+. (B) The apoptosis ratio was calculated by summing the percentages of early and late apoptotic cells. * $p < .05$. N = 3 independent experiments.*

3.3. Resveratrol Increased Intracellular ROS Levels in OE33 Cells.

To understand the mechanism by which resveratrol reduces the viability of OE33 cells, intracellular ROS levels were measured with H2DCFDA using flow cytometry after 24 hours resveratrol treatment. It was observed that 150 µM resveratrol increased ROS levels in the cells by 236% ($p < .001$) (Figure 3). This demonstrates that resveratrol reduces viability of OE33 cells by increasing ROS levels, which leads to the activation of apoptosis.

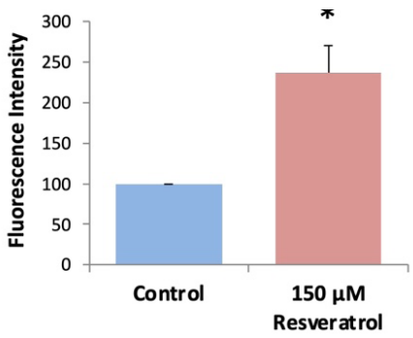
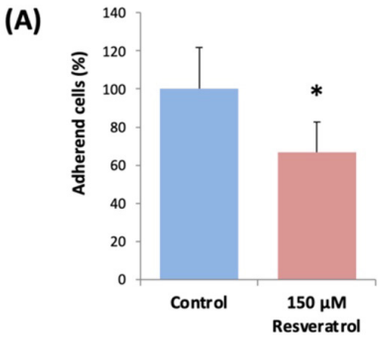
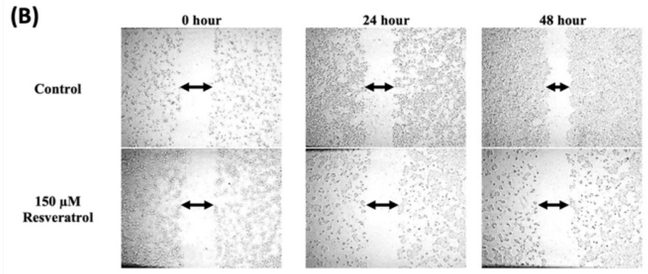


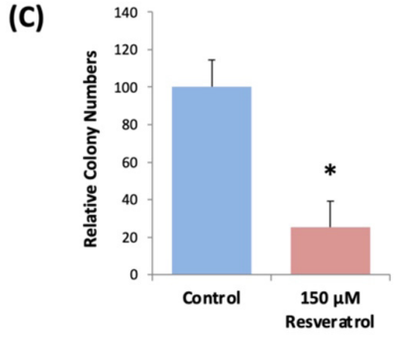
Figure 3. *Resveratrol increased intracellular ROS levels in OE33 cells. Following a 24-hour treatment with resveratrol, intracellular ROS levels were quantified using 5-(and-6)-carboxy-2′,7′-dichlorodihydrofluorescein diacetate (H2DCFDA) staining and analyzed by flow cytometry. The fluorescence intensity reflects the intracellular ROS levels. * $p < .05$. N = 3 independent experiments.*

3.4. Resveratrol Inhibited the Metastatic Potential of OE33 Cells.

The processes of metastasis involve three key actions: migration, adhesion, and colony formation. 150 µM resveratrol treatment reduced the adhesive ability of OE33 cells, which is depicted by the lower percentage of cells (~67%) that can adhere to the surface coated with fibronectin compared to control (Figure 4A). Furthermore, wound healing assay revealed that resveratrol prevented the cells to cover the wound area (Figure 4B). This might be due to significantly decreased migration and higher mortality of the treated cells compared with untreated cells. Additionally, colony formation assay showed that resveratrol reduced colony formation by ~75% in OE33 cells compared to untreated cells (Figure 4C, 4D). These results suggested that resveratrol inhibits the metastatic potential of OE33 cells.







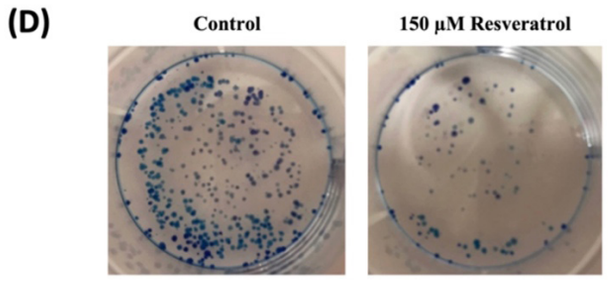


Figure 4. *Resveratrol inhibited the metastatic potential of OE33 cells. Following a 24-hour treatment with resveratrol, (A) cell adhesion ability was assessed, (B) cell migration was evaluated by microscopy, and (C, D) cell colonies were quantified. * $p < .05$. N = 3 independent experiments.*

4. DISCUSSION

The global incidence of EAC has been steadily increasing, particularly in Western countries. Despite its rising prevalence, effective therapeutic options remain limited, highlighting the urgent need for novel treatment strategies (10). Natural polyphenols have gained attention as potential anti-cancer agents due to their minimal side effects (11).

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a well-known polyphenolic compound which was initially extracted in 1940 from the roots of white hellebore (Veratrum grandiflorum) (12). Subsequently it was found in a variety of dietary sources, including grapes, nuts, apples, red fruits, black olives, capers, brown or red rice (13). A wide range of health-promoting effects of resveratrol was exhibited including hepatoprotective, neuroprotective anti-inflammatory, antioxidant and anti-carcinogenesis activities (14). Resveratrol was first identified as an inhibitor of carcinogenesis in a mouse skin cancer model, which subsequently sparked increased research interest. It has been shown that resveratrol reduces the incidence and

progression of various malignancies, including lungs, breast, prostate, cervical, ovarian liver pancreatic, colorectal, gastric, oral, and also esophageal cancers (15,16).

In a study conducted on male Sprague-Dawley rats, Woodall and colleagues examined the impact of resveratrol on the progression from reflux esophagitis to Barrett's metaplasia, dysplasia, and EAC. Their findings demonstrated that resveratrol significantly mitigated the severity of esophagitis while also reducing the incidence of carcinoma and intestinal metaplasia. These results suggest that resveratrol offers substantial protective effects against esophageal cancer development (17). A population-based case–control study observed that a diet rich in resveratrol was associated with a reduced risk of esophageal cancer in the Swedish population (8). However, the underlying mechanisms of this protective effect of resveratrol remain to be fully elucidated. Because of that, in the present study, we investigated the effects of resveratrol on EAC cells and found that resveratrol decreased cell viability in a dose dependent manner. The inhibitory effects of resveratrol on the growth of various cell types, including ESCC and EAC cells, have been previously demonstrated. Consistent with our findings, these studies also reported that the cytotoxic effects of resveratrol are both dose – and time-dependent (9,13,18,19). It is well known that resveratrol exerts dual effects. At high concentrations (≥25 µM), it induces cytotoxicity (19), whereas at lower concentrations, it promotes the expression of cell survival proteins (20). Consistently, we also observed the cytotoxic effects of resveratrol at higher doses (≥100 µM).

Previous studies have shown that the underlying mechanism of resveratrol's cytotoxic effect involves the induction of apoptosis and cell cycle arrest (14,21). Resveratrol has been shown to induce apoptosis in human esophageal carcinoma cells in a dose – and time-dependent manner, primarily through decreased expression of the anti-apoptotic protein Bcl-2 and increased expression of the pro-apoptotic protein Bax (9). Apoptosis aside, previous research has also linked resveratrol-induced growth inhibition with cell cycle arrest (14). Resveratrol is known to activate p53 and p21, leading to cell cycle arrest and senescence. In EAC cells, resveratrol treatment increased p27Kip1 levels, leading to cell cycle arrest and suppression of cell proliferation (22). Furthermore, Tang et al. demonstrated that resveratrol inhibits the growth of ESCC cells by inducing cell cycle arrest at the sub-G1 phase in a dose-dependent manner (18). Dhir et al. (23) observed that resveratrol stimulates apoptosis through ROS production. They suggested that resveratrol influences key cellular pathways, including DNA repair, transcription, and proliferation, via this mechanism. In line with their findings, we also demonstrated that resveratrol enhances apoptosis by increasing ROS levels. We extended these findings by demonstrating that resveratrol's pro-apoptotic effect via ROS also contributes to its antimetastatic activity in EAC cells.

Metastasis, the final stage of carcinogenesis, is the leading cause of death in cancer patients, including those with esophageal cancer (24). Previous studies on pancreatic, liver, renal, ovarian, and kidney cancer cell lines have shown that resveratrol significantly reduces the metastasis of cancer cells (24,25,26). In the current study, we observed that all three steps of metastasis, i.e. migration, adhesion, and colony formation were inhibited by resveratrol treatment. Based on our knowledge, this is the first study to highlight the anti-metastatic effects of resveratrol on EAC cells. Metastasis of cancer cells requires disruption of the cell-extracellular matrix (ECM) interaction and degradation of the ECM. A disintegrin and metalloproteinase (ADAM) proteins, which are proteolytic enzymes responsible for destroying the ECM, are overexpressed in many types of cancers, including esophageal cancers, and correlate with cancer progression and metastasis. Lin et al. (24) observed that resveratrol reduced the migration of ESCC cells by decreasing ADAM9 protein levels, which supports our findings.

On the other hand, it is also known that resveratrol has biphasic, dose-dependent effects, altering its role in oxidative stress. These biphasic concentration-dependent effects of resveratrol, acting as an antioxidant at low doses and a prooxidant at high doses, have been observed both in vitro and in vivo. Both low and high concentrations offer beneficial effects: low doses contribute to cancer prevention, while high doses are cytotoxic and aid in cancer treatment (19). It has been suggested that at lower doses, the antioxidant potential of resveratrol is mediated through both free-radical scavenging and the upregulation of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, which protect cells and DNA from ROS-induced damage through various mechanisms (13). At higher doses, increased ROS generation may lead to organelle and DNA damage, resulting in apoptosis, autophagy, necrosis, or senescence in cancer cells (16). Based on our data, we also hypothesize that the inhibitory effect of resveratrol on cell viability at higher concentrations is mediated by apoptosis, which is triggered by increased ROS production in EAC cells.

Despite accumulating evidence supporting resveratrol's anticancer properties in vitro and in preclinical studies, its clinical translation remains limited, which results in conflicting reports on its efficacy. A key limitation is the compound's poor bioavailability and low aqueous solubility. Resveratrol is rapidly metabolized and eliminated, making it difficult to achieve and sustain therapeutically effective plasma concentrations (27). Although generally considered safe, adverse effects such as diarrhea, nausea, and anemia have been reported, particularly at high doses. In rare cases, complications such as nephrotoxicity, impaired lipid metabolism, and thrombocytopenia have also been observed. These findings underscore the importance of dose optimization and improved delivery strategies to enhance the clinical applicability of resveratrol (20).

This study has several limitations. First, the use of in vitro cell line models may not fully replicate the biological diversity and complexity of tumors in vivo. Therefore, the effects of resveratrol observed in our study may differ in a clinical setting. Second, our study primarily focused on short-term

effects of resveratrol, and long-term treatment studies are needed to evaluate potential prolonged effects and outcomes. Additionally, although significant findings were made regarding resveratrol's impact on cell proliferation and apoptosis, the exact molecular mechanisms underlying these effects remain incompletely understood, and further research is needed to elucidate these pathways.

5. CONCLUSION

In conclusion, our findings demonstrate that resveratrol reduces the viability of EAC cells in a dose-dependent manner by inducing apoptosis through increased intracellular ROS production. Additionally, resveratrol suppresses the metastatic potential of these cells, highlighting its ability to modulate key cellular processes involved in esophageal cancer progression. These results suggest that resveratrol holds potential as a complementary agent alongside conventional chemotherapy for the treatment of EAC. However, further in vivo studies and clinical investigations are required to fully elucidate its therapeutic potential and mechanisms of action.

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Research idea: S.B.
Design of the study: S.B.
Acquisition of data for the study: S.B., B.Ç., A.M.Y.G.
Analysis of data for the study: S.B.
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Revising it critically for important intellectual content: S.B.
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