

Resveratrol reduces the release of pro-inflammatory cytokines and growth factors from ovarian cancer ascites-derived cells

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Abstract

Ovarian cancer remains a leading cause of gynecologic cancer mortality due to late-stage diagnosis and the presence of malignant ascites. Elevated levels of pro-inflammatory cytokines and growth factors in ascites promote tumor progression, angiogenesis, and chemoresistance. Resveratrol, a natural polyphenol with anticancer properties, inhibits pro-inflammatory cytokines and growth factors in various cell types. However, its effects on ascites-derived epithelial ovarian cancer (EOC) cells remain unknown. This study aimed to determine the effect of resveratrol on cytokine and growth factor production in EOC cells isolated from malignant ascites. Primary EOC cells isolated from 11 patients were treated with resveratrol at 6.25 and 12.5 μM for 72 and 144 h. Cell viability and proliferation were determined using trypan blue exclusion and XTT assays, respectively. Interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor- α (TNF- α), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and progranulin (PGRN) levels were quantified by ELISA. Resveratrol did not significantly affect cell viability but significantly reduced cell proliferation in a dose-dependent manner. Resveratrol decreased IL-8 and IL-1 β at both concentrations at 72 h, whereas IL-6 showed a non-significant reduction. At 144 h, IL-8 levels remained significantly reduced only at 12.5 μM . Resveratrol also significantly reduced VEGF and PGRN levels at both concentrations at 72h and 144 h. TNF- α and EGF were not detected. These data demonstrate that resveratrol decreases the secretion of pro-inflammatory and angiogenic factors in ascites-derived EOC cells without inducing cytotoxicity, supporting its potential as an adjuvant in ovarian cancer therapy targeting inflammation and angiogenesis.

Introduction

Ovarian cancer is a major global health problem associated with a high mortality rate. According to Globocan, in 2022, 324,603 women were diagnosed with ovarian cancer, while 206,956 died from this disease. Despite advances in treatment and surgical techniques, the mortality rate associated with ovarian cancer has not significantly reduced [1].

This elevated mortality results from late-stage diagnosis since most patients present with advanced FIGO stage III-IV ovarian cancer. Unfortunately, this late-stage diagnosis is due to the lack of early detection biomarkers and the non-specific symptoms at early stages of the disease [2, 3]. Furthermore, peritoneal dissemination and malignant ascites also occur at advanced stages and significantly limit treatment efficacy at diagnosis [4, 5].

Malignant ascites has significant clinical and biological implications that contribute to poor prognosis [6, 7]. Its presence and volume correlate with advanced FIGO stage and an increased metastatic burden. Also, suboptimal cytoreduction and reduced progression-free and overall survival correlate with ascites [4, 8-10]. Malignant ascites is also a complex tumor microenvironment that is composed of tumor and stromal cells, immune cells, cytokines, metabolites, and extracellular vesicles [11]. This tumor microenvironment influences ovarian cancer progression and metastasis by inducing tumor cell proliferation, epithelial-mesenchymal plasticity, cell migration and invasion, as well as resistance to

platinum-based chemotherapy [12-16]. Additionally, ascites contributes to local immunosuppression and immune evasion [17]. Therefore, malignant ascites is not only an indicator of advanced ovarian cancer and poor prognosis, but it also plays an important role in tumor progression.

Ovarian cancer-associated ascites contains multiple cytokines and growth factors that contribute to a pro-tumorigenic microenvironment within the peritoneal cavity. High concentrations of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)- α , and IL-10, as well as various chemokines, promote tumor cell survival, proliferation, epithelial-mesenchymal transition, and peritoneal dissemination [12, 18, 19]. Also, increased levels of IL-6, IL-8, and IL-1 β in ascitic fluid have been associated with reduced progression-free survival [20-22].

Malignant ascites also contains growth and angiogenic factors, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and members of the epidermal growth factor (EGF) and transforming growth factor (TGF)- β families [19]. These factors promote angiogenesis, enhance vascular permeability, contribute to fluid accumulation, and increase ovarian cancer cell motility and implantation on peritoneal surfaces [23]. In addition, these soluble mediators activate different signaling pathways, including JAK/STAT3, PI3K/AKT, and NF- κ B, in tumor cells exposed to ascites. Activation of these signaling cascades induces chemoresistance and maintains stem-like cell populations [24].

Cytokines and growth factors in ascitic fluid play an important role in ovarian cancer progression by promoting cell proliferation, angiogenesis, and peritoneal dissemination. Consequently, identifying compounds that modulate the secretion of these proteins by tumor cells within the ascitic microenvironment is warranted.

Resveratrol (trans-3,5,4'-trihydroxystilbene) is a natural polyphenolic phytoalexin found in grapes, red wine, and peanuts with anticancer, antioxidant, and anti-inflammatory properties, as well as effects on neurological, cardiovascular, and metabolic disorders [25]. Several studies have shown that resveratrol modulates the inflammatory response and reduces the secretion of pro-inflammatory cytokines and other molecules in microglial and astrocyte cultures [26, 27]. Moreover, resveratrol has anti-tumor activity in various human malignancies by inhibiting cellular proliferation and migration as well as inducing cell cycle arrest, autophagy, and apoptosis [28, 29]. In human ovarian cancer cell lines such as OVCAR-3, Caov-3, and SKOV3, resveratrol-induced cell death is mediated by reactive oxygen species generation and autophagy upstream of apoptosis, with the modulation of AKT, ERK, and NF- κ B signaling pathways [30, 31]. Additionally, the anti-angiogenic activity of resveratrol is mediated by downregulating hypoxia-inducible factor 1 α (HIF-1 α) and VEGF [32, 33]. However, whether resveratrol can modulate the production of pro-inflammatory cytokines and growth factors in ovarian cancer ascites-derived cells remains to be investigated. Thus, in the present study, the effect of resveratrol on the secretion of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8, and TNF- α) and growth factors (VEGF, EGF, and progranulin) in primary ovarian cancer cells derived from malignant ascites was determined.

Material and methods

Patients and ascites samples

The study was approved by the Institutional Review Board of the UMAE Hospital de Gineco-Obstetricia No. 4 “Luis Castelazo Ayala”, Instituto Mexicano del Seguro Social, Mexico City, Mexico. All participating women provided written informed consent before samples were collected.

Ascitic fluid samples were collected from 11 patients diagnosed with epithelial ovarian cancer at different stages of the disease. The attending surgeon or oncologist collected the samples during therapeutic procedures or surgery and immediately processed for culture of epithelial ovarian cancer (EOC) cells. Histological tumor grading was established according to the World Health Organization (WHO) classification, and disease stage (I-IV) was assigned according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (Table 1).

Epithelial ovarian cancer primary cultures derived from ascitic fluid

EOC cells were isolated from ascitic fluid samples following the protocol described by Thériault et al. [34]. Briefly, 20-25 mL of fresh ascitic fluid was transferred to a 150 cm² tissue culture flask containing 25 mL of a 1:1 mixture of MCDB 105 (Sigma-Aldrich, USA) and Medium 199 (Cytiva, USA) supplemented with 15% fetal bovine serum (FBS; Cytiva, USA) and an antibiotic/antimycotic solution containing 100 U/mL of penicillin G, 100 µg/mL of streptomycin and 0.25 µg/mL amphotericin B (Cytiva, USA). Cultures were incubated at 37 °C in a humidified atmosphere with 5% CO₂.

The first medium change was performed after 3-4 days, and thereafter the culture medium was replaced every 3-4 days until cells reached 70-80% confluence. Then, ascites-derived EOC cells were detached using a trypsin-EDTA solution (Cytiva, USA) and transferred to a new 75 cm² culture flask with MCDB 105/Medium 199 (1:1) supplemented with 15% FBS and an antibiotic/antimycotic solution and incubated at 37 °C in 5% CO₂. Erythrocytes in the ascitic fluid were removed after the first medium change, and fibroblasts were also removed by partial and repeated trypsinization.

All experiments were performed using cells between passages 3 and 6. The epithelial phenotype of the cultures was confirmed by cytokeratin-7 immunostaining, and all experiments were performed with cell populations containing 98-100% cytokeratin-7-positive cells [34].

Resveratrol treatment

EOC cells were seeded at a density of 2×10^5 cells per well in 12-well tissue culture plates. After overnight incubation, the medium was replaced with fresh medium containing dimethyl sulfoxide (DMSO; Sigma-Aldrich, USA) or resveratrol (Calbiochem, USA) at 6.25 or 12.5 µM. Cells were then incubated for 72 or 144 h. Resveratrol concentrations were selected based on previous reports [35]. The final DMSO concentration in the culture medium did not exceed 0.01%. After resveratrol treatment, conditioned media were collected and stored at -70 °C until further analysis.

Cell viability assay

Cell viability was determined using the trypan blue exclusion assay as previously described [36]. For these experiments, 2×10^4 cells per well were seeded in 96-well plates (Corning, USA) in 100 μ L of culture medium. Cells were treated with resveratrol as described above.

At the end of the treatment (72 or 144 h), cells were trypsinized and resuspended in culture medium. Then, the cell suspension was diluted 1:1 with 0.4% trypan blue solution and loaded onto a hemocytometer. The total number of cells and the number of trypan blue-positive cells were counted. Cell viability was calculated using the following formula: % Viable cells = $[1 - (\text{number of blue cells} / \text{number of total cells})] \times 100$.

XTT cell proliferation assay

Inhibition of cell proliferation by resveratrol was evaluated by measuring mitochondrial dehydrogenase activity using the Cell Proliferation Kit II (XTT; Cell Signaling, USA), following the manufacturer's instructions. Briefly, cells were seeded at a density of 2×10^4 cells per well in 96-well plates and incubated for 24 h. Thereafter, cells were exposed to DMSO or resveratrol at 6.25 or 12.5 μ M in culture medium for 72 or 144 h.

At the end of the incubation time, 50 μ L of XTT solution was added to each well, and the conversion of XTT to formazan was measured at 450 nm with a reference wavelength of 655 nm using a microplate reader after 1 h of incubation.

Enzyme-linked immunosorbent assay (ELISA)

The levels of pro-inflammatory cytokines and growth factors in conditioned culture medium were determined using commercial ELISA kits based on a two-step sandwich ELISA protocol according to the manufacturer's instructions. The cytokines IL-1 β , IL-6, IL-8, TNF- α , and VEGF were measured using ELISA kits from Enzo Life Sciences, whereas EGF and progranulin (PGRN) were determined using ELISA kits from R&D Systems. Samples were analyzed either without dilution or after appropriate dilution. IL-6 and IL-8 samples were diluted 1:10 and VEGF samples were diluted 1:4, whereas the remaining cytokines and growth factors were assayed without dilution. All assays were performed in duplicate. Cytokine and growth factor concentrations were calculated from standard curves generated using recombinant standards provided in each kit.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, USA). The Shapiro-Wilk test was used to determine whether the data were normally distributed. Differences in cytokine and growth factor levels, viability, and cell proliferation between resveratrol-treated groups and the control were analyzed using the Kruskal-Wallis test followed by Dunn's post hoc test. A P-value < 0.05 was considered statistically significant. Statistical analysis of the 72 h data included all patient samples.

In contrast, analysis of the 144 h data included only 10 patients, since one sample was excluded because the cells were detached from the culture plate at this time point.

Results

Patient characteristics

The median age of the patients was 52 years, with a range of 31 to 72 years. Ascitic samples were obtained from five patients with high-grade serous carcinoma, two with undifferentiated carcinoma, two with endometrioid carcinoma, one with clear cell carcinoma, and one with mucinous carcinoma. According to the FIGO classification, one patient presented with stage I disease and ten with stage III disease. Only one patient with recurrent disease had received prior antineoplastic treatment three years before surgery.

Effect of resveratrol on the viability and proliferation of ascites-derived EOC cells

Treatment with resveratrol did not significantly affect cell viability but significantly reduced cell proliferation in ascites-derived EOC cell cultures. Incubation of EOC cells with 6.25 or 12.5 μ M of resveratrol for 72 or 144 h did not significantly change the percentage of viable cells compared with vehicle-treated controls (Fig. 1a, b). In contrast, treatment with resveratrol at 6.25 or 12.5 μ M resulted in a significant decrease in cell proliferation after 72 h of exposure (Fig. 1c). This inhibitory effect was greater after 144 h of treatment (Fig. 1d).

Effect of resveratrol on cytokine secretion in ascites-derived EOC cells

Due to variability in basal levels of cytokines and growth factors among patients, results are expressed as percentages relative to the control condition (DMSO).

Resveratrol reduced the secretion of several pro-inflammatory cytokines in ascites-derived EOC cells. IL-8 levels in the conditioned medium were significantly reduced in the presence of resveratrol at 6.25 and 12.5 μ M compared with the DMSO vehicle control after 72 h of incubation (Fig. 2a). A similar significant decrease was observed for IL-1 β with both concentrations (Fig. 2c). In contrast, no significant reduction in IL-6 levels was observed at this time point (Fig. 2e). After 144 h of treatment, IL-8 levels remained significantly reduced at the higher concentration (Fig. 2b). At this time point, IL-1 β levels were slightly but not significantly reduced; while IL-6 levels were decreased but did not reach statistical significance with both doses (Fig. 2d, f). TNF- α was not detected in the conditioned medium from these cultures.

Effect of resveratrol on growth factor secretion in ascites-derived ovarian cancer cells

VEGF and PGRN levels in the conditioned medium from ascites-derived EOC cells were significantly reduced after 72 h (Fig. 3a, c) and 144 h (Fig. 3b, d) of treatment with resveratrol at 6.25 and 12.5 μ M compared with the DMSO vehicle control. EGF was not detected in the conditioned medium from these cultures.

Discussion

The present study investigated the effect of resveratrol on the secretion of pro-inflammatory cytokines and growth factors in primary EOC cells derived from malignant ascites. The data presented herein show that IL-8, VEGF, and PGRN secretion was significantly reduced by resveratrol in conditioned medium from ascites-derived EOC cells. The inhibitory effect on IL-8 was observed at both resveratrol concentrations at 72 h, while significance at 144 h was observed only with 12.5 μ M. Similarly, a significant decrease in IL-1 β levels was observed at 72 h with both resveratrol doses; however, this effect did not reach significance at 144 h. This could be due to either an increased variability in cytokine levels or a compensatory inflammatory signaling. In contrast, IL-6 secretion was not significantly decreased, although a trend toward significance ($p = 0.06$) was observed at 144 h of exposure; this may be due to variability in cytokine levels. Therefore, these findings suggest that resveratrol reduces the release of pro-inflammatory and angiogenic mediators, as well as PGRN secretion, in EOC cells isolated from malignant ascites.

Malignant ascites is a complex tumor-associated microenvironment that plays an important role in ovarian cancer progression. It contains various soluble factors, including cytokines, chemokines, and growth factors, which contribute to cell survival, proliferation, immune evasion, and peritoneal dissemination [18, 37, 38]. IL-6, IL-1 β , and IL-8 have been associated with ovarian cancer progression and poor clinical outcome, as well as correlated with reduced progression-free survival [20-22, 39]. Additionally, high IL-8 levels have been associated with aggressive disease behavior, including increased proliferation, anchorage-independent growth, angiogenic potential, adhesion, and invasion [40]. Similarly, IL-6 in malignant ascites increased invasion and the expression of epithelial-mesenchymal transition-related proteins in EOC cells [12]. VEGF is a key regulator of angiogenesis and vascular permeability and plays a central role in the development of malignant ascites in ovarian cancer [41]. Elevated VEGF have been associated with advanced tumor stages, ascites volume, and reduced patient survival [42]. PGRN has also been implicated in tumor growth, inflammation, and resistance to therapy in several malignancies, including ovarian cancer [43]. Therefore, the reduction of these cytokine and growth factor secretions could be an important mechanism through which resveratrol modulates the tumor-promoting properties of the ascitic microenvironment.

Previous studies have shown that resveratrol can inhibit several signaling pathways, including NF- κ B, STAT3, and PI3K/AKT, which are known to induce pro-inflammatory cytokine production and tumor cell survival [44, 45]. Therefore, we hypothesize that resveratrol might reduce pro-inflammatory cytokines and growth factors by inhibiting these signaling pathways. However, further studies are needed to verify this hypothesis.

This study has several limitations that should be considered. The number of ascitic fluid samples obtained from patients with ovarian cancer for EOC cell isolation was relatively small. Additionally, all experiments were performed in vitro, and the molecular mechanisms of the resveratrol-induced effects were not investigated. However, the use of primary ascites-derived EOC cells is a relevant experimental model that better reflects the biological characteristics of the ovarian cancer microenvironment than established cell lines. Also, cell viability was not significantly affected by resveratrol; thus, the decrease in cytokine levels is unlikely to be due to cytotoxic effects. However, the effect of reduced cell proliferation cannot be completely excluded.

In conclusion, the present study demonstrates that resveratrol reduces the secretion of pro-inflammatory cytokines and growth factors in EOC cells derived from malignant ascites. These findings suggest that resveratrol may modulate the inflammatory and angiogenic tumor microenvironment associated with ovarian cancer progression. Further studies are required to determine the molecular mechanisms underlying these effects and to evaluate the potential therapeutic implications of resveratrol in ovarian cancer.

Declarations

Funding

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Fabian Arechavaleta-Velasco: Designed the statistical analysis, conducted the data analysis, interpreted the results, performed all ELISA assays, drafted the manuscript, and supervised the writing process. Aleida Olivares: Maintained the cell cultures, performed resveratrol treatments, assessed cell viability, and collected conditioned media. Victor Valdespino-Castillo, Moises Zeferino-Toquero, and Horacio Reyna-Amaya: Collected malignant ascites fluid samples. Isaias Estrada-Moscoso: Performed the pathological evaluation, including tumor staging and histological classification of the samples. Laura Diaz-Cueto: Conceived the study, developed the experimental design, conducted cell culture experiments, contributed to data interpretation, and participated in the design of the statistical analysis.

Data Availability

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

Ethics approval

The study was approved by the Institutional Review Board of the UMAE Hospital de Gineco-Obstetricia No. 4 “Luis Castelazo Ayala”, Instituto Mexicano del Seguro Social, Mexico City, Mexico (R-2014-3606-28).

Consent to participate

All participating women provided written informed consent prior to sample collection. Samples were de-identified and assigned coded identifiers to ensure patient confidentiality.

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Table

Table 1. Patients´ characteristics, ascites fluid, histological tumors and stage of disease

<i>Patient</i>	<i>Age</i>	<i>Histological Tumor Type</i>	<i>Stage</i>	<i>Ascites Aspect</i>	<i>Volume (ml)</i>
1	46	Undifferentiated (Second recurrence)	III	Chylous	150
2	31	Endometroid	I	Bloody	50
3	35	Serous high grade	III	Pale yellow-brown	150
4	60	Endometroid	III	Pale yellow-brown	150
5	53	Serous high grade	III	Bloody	50
6	57	Serous high grade	III	Pale yellow-brown	200
7	63	Serous high grade	III	Bloody	100
8	52	Serous high grade	III	Pale yellow	75
9	43	Clear cell	III	Bloody	50
10	72	Mucinous	III	Pale yellow	50
11	49	Undifferentiated	III	Pale yellow	70

Figures

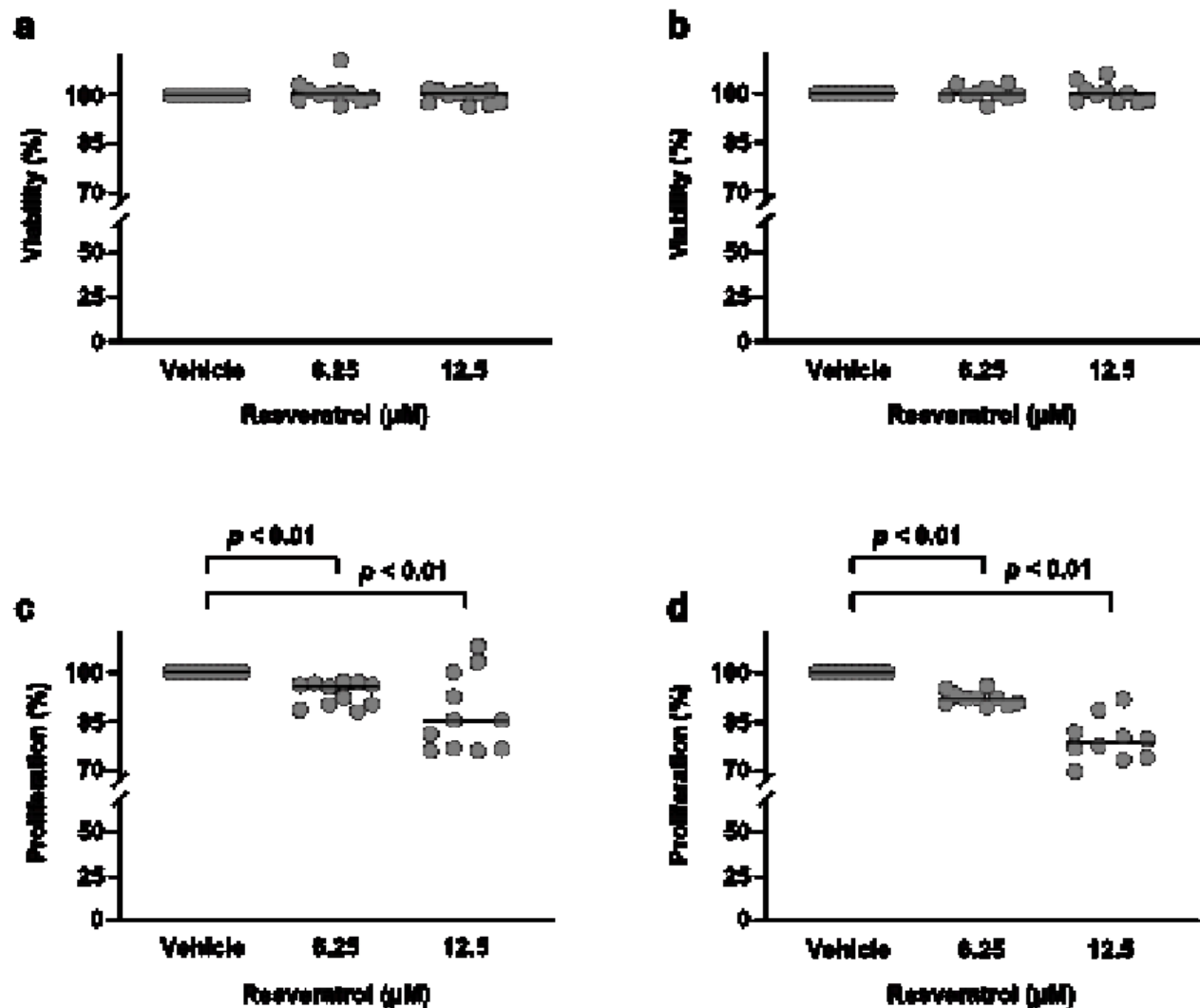


Figure 1

Effects of resveratrol on the viability (a, b) and proliferation (c, d) of ascites-derived epithelial ovarian cancer cells. Cells were exposed to different concentrations of resveratrol for 72 h (a, c) and 144 h (b, d). Cell viability was determined by the trypan blue exclusion assay, while cell proliferation was evaluated by quantifying XTT conversion. Each dot represents an individual patient-derived sample, and horizontal lines within the symbols indicate the median. No significant differences in viability were observed at either concentration or time point. In contrast, resveratrol significantly reduced proliferation at both 6.25 and 12.5 μ M compared with vehicle-treated controls at 72 h and 144 h as determined by Kruskal-Wallis test ($p < 0.01$).

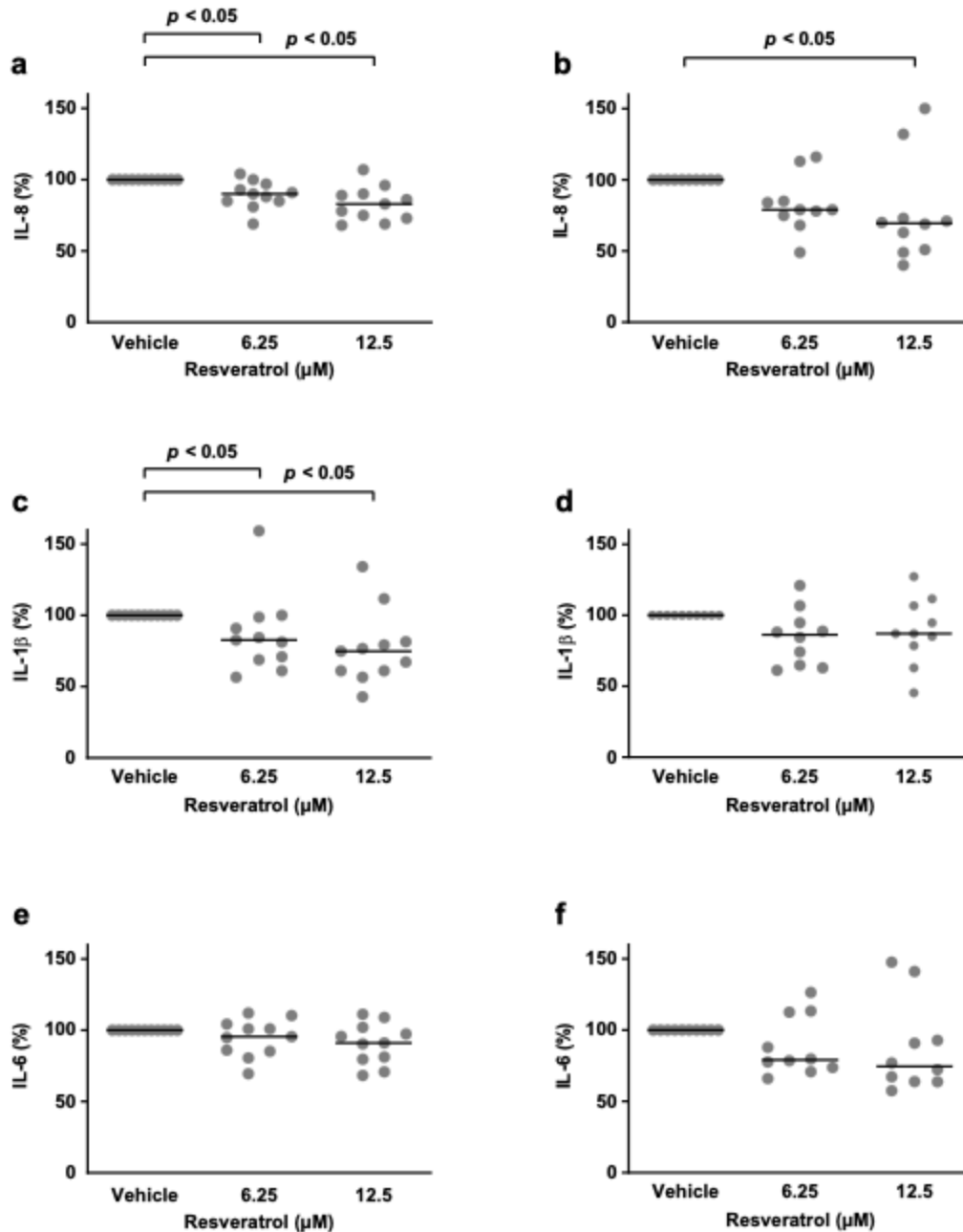


Figure 2

Effect of resveratrol on pro-inflammatory cytokine secretion in ascites-derived epithelial ovarian cancer cells. Cells were exposed to 6.25 and 12.5 μ M of resveratrol for 72 h and 144 h, respectively. Levels of IL-8 (a, b), IL-1 β (c, d), and IL-6 (e, f) were quantified by ELISA. The results are expressed as a percentage relative to vehicle-treated controls. The horizontal lines within the symbols represent the median values. Statistical analysis using the Kruskal-Wallis test followed by Dunn's test revealed that after 72 h of exposure, resveratrol significantly reduced IL-8 (a) and IL-1 β (c) levels at both concentrations ($p < 0.05$), while IL-6 (e) showed no significant changes. In contrast, after 144 h of resveratrol exposure, only IL-8 (b) levels were significantly reduced at 12.5 μ M.

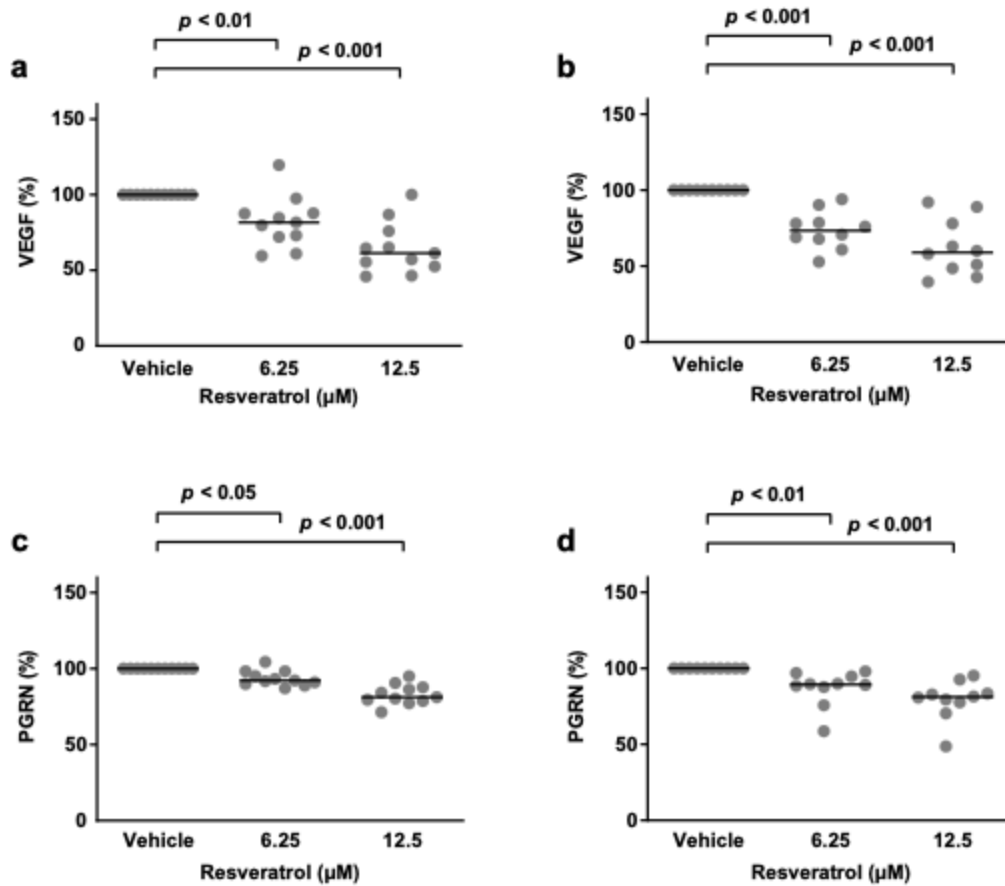


Figure 3

Effect of resveratrol on growth factor secretion in ascites-derived epithelial ovarian cancer cells. Cells were exposed to 6.25 and 12.5 μM of resveratrol for 72 h and 144 h, respectively. Levels of VEGF (a, b) and PGRN (c, d) were quantified by ELISA. The results are expressed as a percentage relative to vehicle-treated controls. The horizontal lines within the symbols represent the median values. Statistical analysis using the Kruskal-Wallis test followed by Dunn's test revealed that resveratrol significantly reduced VEGF (a, b) and PGRN (c, d) levels at both concentrations compared with vehicle-treated controls at 72 h and 144 h of exposure ($p < 0.05$).