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# Resveratrol Modulates Apoptosis- and Cell Cycle-Related Gene Expression in Ishikawa Endometrial Cancer Cells

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**Abstract**

**Background:** The present study investigated the impact of resveratrol on cellular viability, apoptotic activity, proliferative capacity, and estrogen receptor/PTEN-associated signaling pathways in the ER-positive endometrial cancer cell line Ishikawa.

**Methods:** Ishikawa cells were treated with different concentrations of resveratrol, and cell viability was assessed at 24, 48, and 72 hours using the MTT test. Based on dose-response results, sub-cytotoxic doses (15 and 30 µM) were selected for molecular studies. mRNA expression of apoptosis-related genes (BAX, BCL-2, CASP3), the proliferation marker CCND1, estrogen receptor gene ESR1, and tumor suppressor PTEN was quantified using qRT-PCR.

**Results:** Resveratrol treatment caused a progressive, dose- and time-dependent decrease in Ishikawa cell viability. qRT-PCR analysis demonstrated upregulation of pro-apoptotic BAX and CASP3, downregulation of anti-apoptotic BCL-2 and proliferation-associated CCND1, significant suppression of ESR1, and dose-dependent elevation of PTEN expression. An increased BAX/BCL-2 ratio indicates that cellular homeostasis has shifted towards a pro-apoptotic state.

**Conclusion:** These results indicate that resveratrol promotes pro-apoptotic transcriptional responses and reduces cell viability, potentially associated with changes in genes related to estrogen receptor signaling and PTEN pathways. The observed effects at sub-cytotoxic concentrations suggest resveratrol as a promising candidate for experimental adjunct therapy in ER-positive endometrial cancer models.

**Keywords:** Endometrial cancer, Resveratrol, Apoptosis, Cell Proliferation, Estrogen Receptor

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## Resveratrol, Ishikawa Endometriyal Kanser Hücrelerinde Apoptoz ve Hücre Döngüsü ile İlişkili Gen Ekspresyonunu Modüle Eder

**Öz**

**Giriş:** Bu çalışma, ER-pozitif endometriyal kanser hücre hattı Ishikawa'da resveratrolün hücre canlılığı, apoptoz, proliferasyon ve östrojen reseptörü/PTEN ile ilişkili yolaklar üzerindeki etkilerini incelemeyi amaçlamıştır.

**Yöntemler:** Ishikawa hücrelerine farklı konsantrasyonlarda resveratrol uygulanmış ve hücre canlılığı 24, 48 ve 72 saatlerde MTT testi ile değerlendirilmiştir. Doz–yanıt sonuçlarına dayanarak moleküler analizler için sub-sitotoksik dozlar (15 ve 30 μM) seçilmiştir. Apoptoz ile ilişkili genlerin (BAX, BCL-2, CASP3), proliferasyon belirteci CCND1'in, östrojen reseptör geni ESR1'in ve tümör baskılayıcı PTEN'in mRNA ekspresyon düzeyleri qRT-PCR yöntemi kullanılarak kantitatif olarak belirlenmiştir.

**Bulgular:** Resveratrol uygulaması Ishikawa hücre canlılığında doza ve zamana bağlı, progresif bir azalmaya yol açmıştır. qRT-PCR analizleri, pro-apoptotik BAX ve CASP3 genlerinde artış; anti-apoptotik BCL-2 ve proliferasyonla ilişkili CCND1 genlerinde azalma; ESR1 ekspresyonunda belirgin baskılanma ve PTEN ekspresyonunda doza bağlı artış olduğunu göstermiştir. Artmış BAX/BCL-2 oranı, hücresel dengenin pro-apoptotik yönde değiştiğini göstermektedir.

**Sonuç:** Bu bulgular, resveratrolün pro-apoptotik transkripsiyonel yanıtları desteklediğini ve hücre canlılığını azalttığını; bu etkilerin östrojen reseptörü sinyallemesi ve PTEN ile ilişkili genlerde meydana gelen değişikliklerle ilişkili olabileceğini göstermektedir. Sub-sitotoksik konsantrasyonlarda gözlenen etkiler, resveratrolün ER-pozitif endometriyal kanser modellerinde deneysel adjuvan tedavi için umut verici bir aday olabileceğini düşündürmektedir.

**Anahtar kelimeler:** Endometriyal kanser, Resveratrol, Apoptoz, Hücre proliferasyonu, Östrojen reseptörü.

## INTRODUCTION

Endometrial cancer represents the leading gynecologic malignancy among women in developed countries, with epidemiological data indicating a continuous rise in its incidence over recent decades[1,2]. Although the disease most commonly occurs in the postmenopausal period, it is closely associated with hormonal and metabolic factors such as obesity, chronic anovulation, and prolonged oestrogen exposure[3]. Based on their clinical and molecular characteristics, endometrial cancers are generally divided into two main groups: oestrogen-dependent Type I and oestrogen-independent Type II. Type I endometrial cancers are typically well-differentiated histologically and are characterised by oestrogen receptor (ER) positivity and a better prognosis[1,4].

In the pathogenesis of endometrial cancer, the dysregulated activation of molecular signalling pathways involved in cell proliferation, apoptosis regulation, and cell cycle control plays a significant role. In particular, the PI3K/AKT/mTOR signalling pathways play critical roles in cellular growth, survival, and metabolic regulation, and the excessive activation of these pathways has been strongly associated with the development of endometrial cancer[5,6].

A decrease in the expression or loss of function of the PTEN tumour suppressor gene, which acts as a negative regulator in this pathway, is among the most frequently reported molecular alterations in endometrial cancer[7]. The suppression of apoptosis mechanisms and the uncontrolled progression of the cell cycle contribute to the proliferative advantage gained by endometrial cancer cells.

The BCL-2 protein family constitutes a critical regulatory system governing the equilibrium between cellular survival and programmed cell death, and the equilibrium between pro-apoptotic BAX and anti-apoptotic BCL-2 proteins is considered an important parameter

determining cell fate[8,9]. Furthermore, the overexpression of cell cycle regulators such as cyclin D1 (CCND1) contributes to the acceleration of the G1/S transition and tumour progression[10].

In recent years, natural polyphenolic compounds have attracted considerable attention due to their anticancer potential. Resveratrol is a stilbenoid compound found in various plant sources, primarily grape skins, and possesses antioxidant, anti-inflammatory, and antitumoural properties[11]. The literature has demonstrated that resveratrol inhibits proliferation, induces apoptosis, and modulates cellular signalling pathways in different cancer cell lines[12,13]. Particularly in estrogen receptor-positive cancer models, resveratrol has been reported to exhibit phytoestrogenic and selective estrogen receptor modulator (SERM)-like effects[14,15].

Although studies investigating the molecular effects of resveratrol in endometrial cancer are limited, current data suggest that this compound may exert regulatory effects on cell viability, apoptosis, and the cell cycle. Nevertheless, a comprehensive understanding of how resveratrol modulates apoptotic processes, proliferative activity, and PTEN-associated signaling pathways in ER-positive endometrial cancer cells remains incomplete.

This study aims to investigate the effects of resveratrol administration on cell viability, apoptosis-related gene expression (BAX, BCL-2, CASP3), proliferation marker CCND1, hormone receptor ESR1, and tumour suppressor PTEN expression in the ER-positive endometrial cancer cell line Ishikawa. Accordingly, this study investigates molecular mechanisms that may be associated with the therapeutic effects of resveratrol in endometrial cancer.

## METHODS

### Cell line and experimental in vitro culture conditions

The Ishikawa human endometrial adenocarcinoma cell line was used as the experimental model in this study. Cells were grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin, and maintained at 37°C under humidified conditions with 5% $CO_2$. All experimental procedures were conducted using cells at the logarithmic phase of growth.

### Preparation and treatment with resveratrol

Resveratrol (≥98% purity) was initially prepared as a stock solution in dimethyl sulfoxide (DMSO) and subsequently diluted with complete culture medium to obtain the required working concentrations. Under all experimental conditions, the final DMSO concentration did not exceed 0.1%. Control cells were exposed to culture medium containing an equivalent amount of vehicle (DMSO) without resveratrol.

### Assessment of cell viability

Following seeding into 96-well plates, Ishikawa cells were allowed to attach overnight under standard culture conditions. Subsequently, the effects of resveratrol on cell viability were assessed using the MTT assay. Upon completion of cell attachment, resveratrol (5–100 μM) was administered to Ishikawa cells, and cell viability was subsequently determined at 24, 48, and 72 hours.

At the designated time points, MTT reagent was added to each well and incubated to permit the formation of formazan crystals. Absorbance at 570 nm was determined with a microplate reader after dissolving the formazan crystals in DMSO. Cell viability was calculated relative to

the control group, with results presented as percentages, and $IC_{50}$ values were then determined.

### Experimental groups

Based on the $IC_{50}$ values obtained from the MTT assay, sub-cytotoxic concentrations of resveratrol were selected for subsequent gene expression analyses. The experimental design consisted of the following study groups:

**Control (vehicle)**

**Resveratrol 15 µM**

**Resveratrol 30 µM**

Cells were incubated with the selected concentrations of resveratrol for 24 or 48 h prior to further analyses.

### RNA isolation and cDNA synthesis

At the completion of the incubation period, total RNA was extracted from Ishikawa cells using TRIzol™ Reagent (Invitrogen, Thermo Fisher Scientific, USA) in accordance with the manufacturer's protocol. The concentration and purity of the isolated RNA were determined spectrophotometrically with a NanoDrop™ 2000 instrument (Thermo Fisher Scientific, USA). Only RNA samples with acceptable purity (A260/A280 ratio between 1.8 and 2.0) were used for further analyses. Complementary DNA (cDNA) was synthesized from equal amounts of total RNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA), following the manufacturer's protocol.

### Quantitative real-time polymerase chain reaction (qPCR)

Quantitative real-time polymerase chain reaction (qPCR) was performed to evaluate the expression levels of apoptosis-related genes (BAX, BCL-2, and CASP3), the proliferation marker CCND1, the estrogen receptor gene ESR1, and the tumor suppressor gene PTEN. Quantitative PCR amplification was performed using PowerUp™ SYBR Green Master Mix (Applied Biosystems, USA) on a StepOnePlus™ Real-Time PCR platform (Applied Biosystems, USA). Gene expression data were normalized to GAPDH as the endogenous control. Fold changes in transcript levels were determined by the $2^{-}\Delta\Delta Ct$ method in comparison with control samples. Primer sequences specific to each target gene were generated using Primer-BLAST (NCBI) and purchased from a commercial supplier. Each reaction was performed in triplicate, and melt-curve analysis was conducted to confirm amplification specificity.

### Statistical analysis

Each experiment incorporated no fewer than three independent biological replicates, and technical triplicates were applied to individual measurements where relevant. Statistical analyses were performed using GraphPad Prism software (version 10, GraphPad Software, San Diego, CA, USA). Prior to statistical evaluation, the distribution of the data was examined for normality using the Shapiro–Wilk test. Results are presented as mean ± standard deviation (SD). Group-wise comparisons were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test. When applicable, exact p-values were presented, and results were considered statistically significant at $p < 0.05$.

## RESULTS

### Effect of resveratrol on Ishikawa cell viability

Cell viability in the Ishikawa cell line following resveratrol exposure was examined by the MTT assay using concentrations between 5 and 100 µM at 24, 48, and 72 h of incubation (Figure 1, Table 1). A clear reduction in cell viability was observed in response to increasing resveratrol concentrations and longer exposure times.

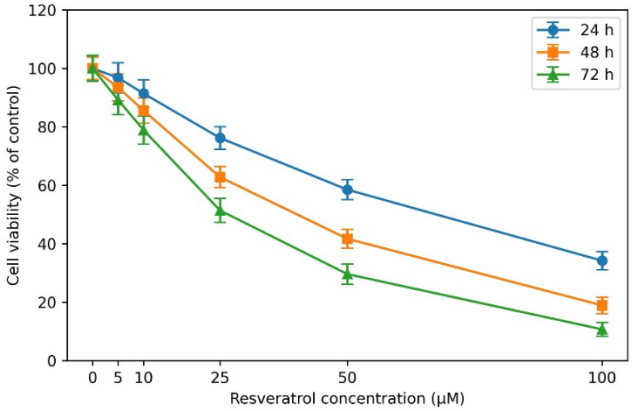


**Figure 1.** Assessment of resveratrol-induced changes in Ishikawa cell viability.

Cells were treated with escalating concentrations of resveratrol (5–100 μM), and metabolic activity was evaluated using the MTT assay at 24, 48, and 72 hours. Viability was normalized to the control group and expressed as a percentage. Data are reported as mean ± SD from a minimum of three independent experiments.

**Table I:** Effects of resveratrol on cell viability in Ishikawa cells (%). Ishikawa cells were treated with increasing concentrations of resveratrol (5–100 μM) for 24, 48, and 72 hours, and metabolic activity was evaluated using the MTT assay. Results are expressed as mean ± SD, and distinct superscript letters denote statistically significant differences relative to control values ($p < 0.05$).

| | ***(% viability)*** | | |
|---|---|---|---|
| ***Resveratrol (μM)*** | **24 h** | **48 h** | **72 h** |
| ***Control*** | 100.0 ± 4.2[a] | 100.0 ± 3.8[a] | 100.0 ± 4.5[a] |
| ***5*** | 96.8 ± 5.1[a] | 93.5 ± 4.6[a] | 89.2 ± 5.0[a] |
| ***10*** | 91.4 ± 4.7[b] | 85.6 ± 4.3[b] | 78.9 ± 4.8[b] |
| ***25*** | 76.2 ± 3.9[c] | 62.8 ± 3.6[c] | 51.4 ± 4.1[c] |
| ***50*** | 58.5 ± 3.4[c] | 41.7 ± 3.2[c] | 29.6 ± 3.5[c] |
| ***100*** | 34.2 ± 3.1[c] | 18.9 ± 2.8[c] | 10.7 ± 2.4[c] |

While treatment with lower concentrations (5-10 μM) produced only modest effects on cell viability, exposure to concentrations of 25 μM or higher resulted in pronounced and statistically significant decreases ($p=0.0008$). The cytotoxic response intensified with prolonged incubation, such that a significant decline in viability was evident at lower concentrations after 72 h of treatment.

Analysis of the dose–response curves indicated approximate $IC_{50}$ values of ~50 μM at 24 h, 30-35 μM at 48 h, and ~25 μM at 72 h. On the basis of these findings, sub-cytotoxic resveratrol concentrations of 15 μM and 30 μM were chosen for subsequent gene expression experiments.

## Effects of resveratrol on apoptosis-, proliferation-, hormone receptor–, and PTEN-related gene expression

To characterize the molecular response to resveratrol exposure, Ishikawa cells were incubated with 15 μM and 30 μM resveratrol, and the mRNA expression levels of apoptosis-associated genes (BAX, BCL-2, and CASP3), the proliferation marker CCND1, the estrogen receptor gene ESR1, and the tumor suppressor gene PTEN were quantified by qPCR (Figure 2, Table 2).

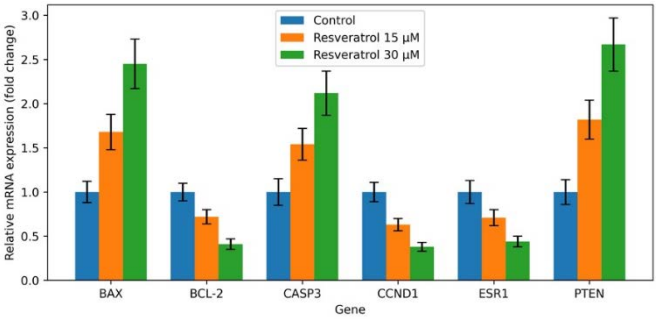


**Figure 2.** Gene expression changes in Ishikawa cells following resveratrol exposure.

Cells were treated with resveratrol (15 and 30 μM), and relative mRNA expression levels of apoptosis-related genes (BAX, BCL-2, and CASP3), the proliferation marker CCND1, the estrogen receptor gene ESR1, and the tumor suppressor gene PTEN were analyzed by qPCR. Gene expression levels were normalized to GAPDH and expressed as fold changes relative to the control group. Data are presented as mean ± SD from at least three independent experiments.

**Table II:** Expression levels of selected genes in resveratrol-treated Ishikawa cells. Ishikawa cells were exposed to resveratrol at sub-cytotoxic concentrations (15 and 30 µM), and the relative mRNA expression levels of apoptosis-associated genes (BAX, BCL-2, and CASP3), the proliferation-related gene CCND1, the estrogen receptor gene ESR1, and the tumor suppressor gene PTEN were quantified by quantitative real-time PCR (qPCR). Gene expression data were normalized against GAPDH and expressed as fold changes relative to the control condition. Values represent mean ± SD, with statistically significant differences between groups denoted by distinct superscript letters ($p < 0.05$).

| *Gene* | *Functional category* | *Control* | *Resveratrol 15 µM* | *Resveratrol 30 µM* |
|---|---|---|---|---|
| ***BAX*** | Apoptosis (pro) | $1.00 \pm 0.12^{a}$ | $1.68 \pm 0.20^{b}$ | $2.45 \pm 0.28^{c}$ |
| ***BCL-2*** | Apoptosis (anti) | $1.00 \pm 0.10^{a}$ | $0.72 \pm 0.08^{b}$ | $0.41 \pm 0.06^{c}$ |
| ***CASP3*** | Apoptosis | $1.00 \pm 0.15^{a}$ | $1.54 \pm 0.18^{b}$ | $2.12 \pm 0.25^{c}$ |
| ***CCND1*** | Proliferation | $1.00 \pm 0.11^{a}$ | $0.63 \pm 0.07^{b}$ | $0.38 \pm 0.05^{c}$ |
| ***ESR1*** | Hormone receptor | $1.00 \pm 0.13^{a}$ | $0.71 \pm 0.09^{b}$ | $0.44 \pm 0.06^{c}$ |
| ***PTEN*** | Tumor suppressor | $1.00 \pm 0.14^{a}$ | $1.82 \pm 0.22^{b}$ | $2.67 \pm 0.30^{c}$ |

Treatment with resveratrol resulted in a significant, dose-dependent upregulation of BAX and CASP3 expression, while BCL-2 expression was markedly reduced ($p=0.0006$). In parallel, CCND1 expression was significantly downregulated at both resveratrol concentrations relative to the control group ($p=0.0004$).

A significant decrease in ESR1 transcript levels was also detected following resveratrol exposure, whereas PTEN expression showed a clear dose-dependent increase compared with control cells ($p < 0.001$).

Consistent with these findings, calculation of the BAX/BCL-2 ratio revealed a pronounced increase in apoptotic propensity. The ratio rose from $1.02 \pm 0.14$ in the control group to $2.33 \pm 0.31$ in cells treated with 15 µM resveratrol and further to $5.98 \pm 0.62$ in the 30 µM treatment group ($p < 0.001$).

## DISCUSSION

In the current investigation, resveratrol was examined for its impact on cell viability and transcriptional regulation of genes associated with apoptosis, cell cycle control, hormone receptor expression, and PTEN-related pathways in ER-positive endometrial cancer Ishikawa cells. The findings demonstrate that resveratrol reduces cell viability and promotes transcriptional shifts indicative of pro-apoptotic activity, while concurrently influencing the expression of genes involved in cell cycle control in a dose- and time-dependent manner. Overall, these results imply that resveratrol may regulate transcriptional networks associated with hormone receptor signaling and tumor suppressor–related pathways.

MTT assay findings indicated that resveratrol led to a pronounced decline in metabolic activity and cell viability in Ishikawa cells, with detectable decreases observed at progressively lower concentrations as the duration of incubation increased. In particular, the decrease in $IC_{50}$ values observed at 48 and 72 hours suggests that prolonged resveratrol exposure enhances cellular stress responses and reduces cell viability over time. This finding is consistent with previous reports showing that resveratrol reduces metabolic activity and cell viability in various cancer cell models[16-18] and supports the development of similar biological responses in endometrial cancer cells.

Apoptosis-related gene expression analyses have revealed that resveratrol may activate intrinsic apoptotic pathways in Ishikawa cells. The increase in pro-apoptotic BAX and CASP3 expression, together with the decrease in anti-apoptotic BCL-2 expression, suggests that resveratrol may contribute to shifting the cellular balance toward apoptotic processes. A

dose-related elevation in the BAX/BCL-2 ratio, an important indicator of apoptotic tendency, suggests that this effect is not limited to the transcriptional level but may also be functionally significant. These findings align with earlier reports demonstrating that resveratrol activates mitochondria-dependent apoptotic pathways across a range of solid tumor models[19-22].

The significant decrease in CCND1 (Cyclin D1) gene expression, evaluated as a proliferation marker in the study, following resveratrol administration indicates a pause in the G1/S transition of the cell cycle. Cyclin D1 plays a central role in regulating cell proliferation and has been implicated in tumor progression and the development of aggressive phenotypes in endometrial cancer, with elevated expression levels widely regarded as an indicator of unfavorable prognosis[23,24]. In this context, resveratrol-induced suppression of CCND1 expression may reflect transcriptional modulation of genes involved in cell cycle regulation.

Given that most endometrial cancers are estrogen dependent, signaling through hormone receptors is considered a major contributor to both tumor initiation and progression[25]. The significant decrease in ESR1 expression observed after resveratrol administration in this study suggests that resveratrol may exhibit anti-oestrogenic or SERM-like effects in ER-positive endometrial cancer cells. The literature reports that resveratrol possesses phytoestrogenic properties and can modulate cellular responses in an agonist or antagonist manner by binding to oestrogen receptors[26-28]. In this regard, the findings support the potential of resveratrol to influence transcriptional regulation of genes involved in cell cycle progression.

PTEN functions as a key tumour suppressor by negatively regulating the PI3K/AKT/mTOR signalling axis, which is commonly activated during the development of endometrial cancer, making it an important molecular target[29,30]. In this study, the significant increase in PTEN gene expression following resveratrol administration suggests that the observed transcriptional changes may be associated with modulation of genes related to this pathway. It has been proposed that the increase in PTEN expression may contribute to the suppression of AKT activity and the attenuation of cellular survival signals[31]. This is consistent with the pleiotropic effects of resveratrol, which targets multiple signalling pathways.

This study has several limitations. First, the findings were obtained using a single ER-positive endometrial cancer cell line. Second, confirmatory analyses at the protein level (e.g., Western blot or flow cytometry) were not performed, which limits direct interpretation of signaling pathway activity. Nevertheless, gene expression analyses performed at sub-cytotoxic doses allowed the evaluation of early transcriptional responses to resveratrol exposure. Future studies incorporating protein-level validation and additional cell models, including ER-negative endometrial cancer cell lines or non-malignant endometrial epithelial cells, will be necessary to better determine the ER-dependent specificity of the observed transcriptional responses.

In conclusion, this study demonstrates that resveratrol reduces cell viability, induces pro-apoptotic transcriptional responses, and modulates the expression of genes involved in cell cycle regulation in Ishikawa cells. These transcriptional changes were also associated with altered expression of hormone receptor–related and PTEN-related genes. The data obtained indicate that resveratrol may serve as a promising adjunct therapeutic strategy or supportive agent in ER-positive endometrial cancer, and that this effect needs to be confirmed by further in vitro, in vivo, and translational studies.

Since the present study primarily evaluated transcriptional changes, the findings should be interpreted as preliminary molecular responses to resveratrol exposure. Future investigations incorporating protein-level validation approaches such as Western blotting, immunocytochemistry, or flow cytometry will be necessary to confirm the functional consequences of the observed gene expression changes.

## CONCLUSION

The present findings indicate that resveratrol reduces cell viability and triggers transcriptional alterations associated with pro-apoptotic activity in the ER-positive Ishikawa endometrial cancer cell line. Resveratrol treatment was associated with increased expression of apoptosis-related genes, suppression of CCND1 expression, decreased ESR1 levels, and increased PTEN expression. These molecular findings suggest that resveratrol may influence transcriptional regulation of genes associated with hormone-dependent proliferation and PI3K/AKT-related signaling pathways in endometrial cancer. These effects, observed at sub-cytotoxic doses, indicate that resveratrol could be considered as a potential complementary or supportive agent in ER-positive endometrial cancer. Nevertheless, the biological and clinical relevance of these observations should be validated through additional in vitro and in vivo investigations.

**Ethics Committee Approval:** The present study was an in vitro experimental study performed on a commercially available human endometrial cancer cell line (Ishikawa). No human participants, patient data, or animal subjects were involved; therefore, ethical committee approval was not required.

**Conflict of Interest:** The author declares no conflict of interest.

**Financial Disclosure:** The author declares that this study received no financial support.

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