

The Effect of Resveratrol in Alleviating Cadmium Induced Rat Ovarian Damage

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Abstract

Aim: Cadmium (Cd) exposure leads to severe histological damage (follicular atresia, granulosa cell degeneration) and increased oxidative stress in rat ovarian tissue. This study investigates the protective potential of resveratrol (RES) against these toxic effects. **Materials and Methods:** Twenty-four adult female Wistar albino rats were randomly divided into four groups (n=6): Control (saline), Cd (CdCl₂, 1 mg/kg/day i.p. for 10 days), RES (10 mg/kg/day oral gavage for 28 days), and Cd+RES (combined administration). Ovarian tissues were evaluated histologically (H&E staining, semiquantitative H-score), biochemically (MDA, SOD, CAT, GPx), and molecularly (Bax, Bcl-2, Nrf2, and HO-1 mRNA expression via qRT-PCR). A Protein-Protein Interaction network (STRING/Cytoscape) was constructed to explore the interaction of RES with its potential target proteins (SIRT1, KEAP1). Data were analyzed using one-way ANOVA with post-hoc Tukey test (p<0.05). **Results:** Histologically, RES treatment significantly mitigated Cd-induced structural damage, preserving follicular health and stromal integrity. Biochemical analyses showed that RES reduced Cd-induced lipid peroxidation (MDA), while also restoring suppressed antioxidant enzyme (SOD, CAT, GPx) activities and glutathione (GSH) levels. At the molecular level, RES suppressed pro-apoptotic Bax and increased anti-apoptotic Bcl-2, reducing the Bax/Bcl-2 ratio and preventing cell death. RES also enhanced endogenous defense by upregulating the expression of the main antioxidant regulator Nrf2 and its target gene HO-1. Bioinformatic integration supports these experimental findings, revealing that the effects of RES are based on modulating interconnected pathways such as apoptotic signaling and Nrf2-mediated antioxidant defense. **Conclusion:** Resveratrol stands out as a versatile and effective protective agent against Cd-induced ovarian toxicity through its antioxidant and anti-apoptotic properties.

Keywords: Ovary, oxidative stress, apoptosis, Cd, toxicity

1. Introduction

Cadmium is a heavy metal that poses a serious risk to human health and is a common industrial and environmental pollutant. Chronic exposure has been associated with toxic effects on the kidneys, skeletal system, and reproductive system. Specifically, in terms of female reproductive health, Cd has been shown to accumulate in ovarian tissue,

disrupting follicular development, inhibiting steroidogenesis, and triggering oxidative stress.^{1,2} This process impairs ovarian function and fecundity through lipid peroxidation, suppression of the antioxidant defense system, inflammation, and programmed cell death (apoptosis).^{3,4} The central role of oxidative stress in these pathological processes makes pharmacological interventions aimed at strengthening antioxidant capacity crucial. Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring polyphenol compound found in plants such as grapes, blueberries, and peanuts. Extensive research has revealed resveratrol's potent antioxidant, anti-inflammatory, and anti-apoptotic properties.^{5,6} These properties make it a candidate with high protective potential in various tissue damage models, especially against pathologies related to oxidative stress caused by heavy metal toxicity. The ability to activate endogenous defense pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2) and regulate intracellular pro/anti-apoptotic protein balance (Bax/Bcl-2) constitute the cornerstones of RES's mechanism.⁷⁻¹⁰

The aim of this study is to evaluate the protective effects of RES in Cd-induced rat ovarian toxicity and to elucidate the histological, biochemical, and molecular mechanisms underlying these effects. In particular, its effects on tissue integrity, oxidative stress markers, apoptosis-related gene expression, and activation of the Nrf2 pathway were investigated. The findings aim to shed light on the therapeutic potential of RES against the harmful effects of environmental toxins on the reproductive system.

2. Materials and Methods

2.1. Experimental Model and Groups

This study was conducted with the approval of the X Institution Local Ethics Committee for Animal Experiments (Protocol No: 2021/02-07; 05.03.2021). A total of 24 adult female Wistar albino rats, 8-10 weeks old and weighing 200±10 g, were used. The animals were fed commercial pellet feed and tap water ad libitum under standard laboratory conditions (22 ± 2°C, 12-hour light/dark cycle). The animals were randomly divided into four groups (n=6):

1. Control Group: Daily oral gavage of physiological saline (0.9% NaCl) was administered for 28 days.

2. Cd (Cd) Group: Daily intraperitoneal (i.p) injection of Cd chloride (CdCl₂, Sigma-Aldrich) at a dose of 1 mg/kg was administered for 10 days. **3. Resveratrol (RES) Group:** Resveratrol (Sigma-Aldrich, ≥99% purity) was administered orally via gavage at a dose of 10 mg/kg daily for 28 days. **4. Cd + Resveratrol (Cd+RES) Group:** Cd (1 mg/kg, i.p.) and RES (10 mg/kg, oral) were administered together for 10 days and then for 28 days. Doses and administration durations were determined from previous studies in the literature^{4,11}.

2.2. Sample Collection and Preparation

At the end of the experimental period, animals were sacrificed under high-dose anesthesia (ketamine/xylazine) following a 12-hour fast. Ovaries were removed via abdominal incision. Tissue fragments from one ovary were fixed in 10% neutral buffered formalin and subjected to histological examination. Some of the other ovaries were stored at -80°C for biochemical and molecular analyses, while others were preserved in RNA stabilization solutions.

2.3. Histological Analysis

Ovarian tissues fixed in 10% neutral formalin were embedded in paraffin after undergoing routine tissue processing procedures. 5 µm thick sections were taken and stained with hematoxylin-eosin (H&E) and examined under a light microscope (Zeiss axio scope). Follicle counts and general histomorphological evaluation were performed in 10 randomly selected fields of view from each group. Granulosa cell layer integrity and corpus luteum structure were assessed observationally.

For semiquantitative assessment of histopathological damage, the H-score (Histochemical score) method was applied. The severity and extent of tissue damage were graded using a 0–3 scale (0: normal, 1: mild, 2: moderate, 3: severe) based on follicular atresia rate, granulosa cell disorganization, pyknotic nuclei, stromal edema, and vascular congestion. The H-score was calculated as: $H\text{-score} = \sum (\text{percentage of tissue at each intensity level} \times \text{intensity score})$. All evaluations were performed by a blinded histologist. A significant increase in the H-score indicated severe damage, whereas a lower H-score reflected preserved tissue integrity.

2.4. Biochemical Analyses

Frozen ovarian tissues were homogenized and supernatants were obtained.

Lipid Peroxidation: Malondialdehyde (MDA) levels were measured using the thiobarbituric acid reactive substances (TBARS) method. Results were expressed in nmol/mg protein.

Antioxidant Enzyme Activity and Glutathione Levels: Superoxide dismutase (SOD) activity was measured using a spectrophotometric method based on the enzyme's ability to inhibit superoxide anion (U/mg protein). Catalase (CAT) activity was determined by monitoring the rate of H_2O_2 degradation (catal/mg protein). Glutathione peroxidase (GPx) activity was determined according to the oxidation rate of NADPH (U/mg protein).

2.5. qRT-PCR

Total RNA was isolated from ovarian tissue using a commercial kit. RNA purity and concentration were determined spectrophotometrically (NanoDrop). Complementary DNA (cDNA) synthesis was performed according to a standard protocol using reverse transcriptase enzyme. qRT-PCR was performed on a real-time PCR instrument using SYBR Green Master Mix and specific primer sets. The genes studied and the reference gene used as an internal control are as follows:

Target Genes: Bax (pro-apoptotic), Bcl-2 (anti-apoptotic), Nrf2, Heme oxygenase-1 (HO-1).

Reference Gene: β -Actin or GAPDH.

Relative gene expression was calculated using the $2^{(-\Delta\Delta Ct)}$ method.

2.6. Bioinformatics and Statistical Analysis

To visualize molecular mechanisms, a Protein-Protein Interaction (PPI) network was constructed using the STRING database (v11.5) for the protein products of the genes studied (Bax, Bcl-2, Nrf2, HO-1). The minimum required interaction score was set at 0.700. Network topology and central “hub” proteins were analyzed using Cytoscape software (v3.9.1). The interaction of RES with its potential target proteins (SIRT1, KEAP1) was investigated.

All statistical analyses were performed using SPSS 25.0 software. Data were presented as mean $\pm$ standard deviation (mean $\pm$ SD). Intergroup comparisons were evaluated using One-Way ANOVA and post-hoc Tukey test. A $p < 0.05$ value was considered statistically significant. Graphs were generated using GraphPad Prism 9.0 software.

3. Results

3.1. Histological Findings

Control and RES Groups: Normal histological structure was observed in the ovarian tissues of the control and RES-only groups. Regular follicular development stages (primary, secondary, Graafian follicles), intact granulosa cell layers, and corpus luteums with preserved structural integrity were observed. **Cd Group:** Significant histopathological changes were detected in the Cd-treated group. A significant increase in the rate of follicular atresia was observed compared to the control group ($p < 0.001$). Irregularity in the

granulosa cell layer, cells with pyknotic nuclei, and areas of degeneration were detected. A decrease in the number of mature follicles and structural deterioration in the corpus luteum were noted. In addition, stromal edema and vascular congestion were observed. **Cd+RES Group:** In the group treated with Cd and RES, a significant improvement in histological damage was recorded. The rate of atretic follicles was significantly lower compared to the Cd group ($p<0.01$). The organization of the granulosa cell layer and follicular architecture were largely preserved. The stromal structure and corpus luteum appearance were similar to the control group (Figure 1). Semiquantitative evaluation of ovarian tissue revealed marked differences among the experimental groups. The Control group exhibited normal follicular morphology with a low H-score, consistent with intact tissue architecture. Similarly, the Res group showed preserved ovarian histology and only a slight increase in H-score compared with the Control group, indicating that RES alone did not induce detectable structural alterations. In contrast, the Cd group demonstrated a pronounced increase in H-score, reflecting severe histopathological damage characterized by disrupted follicular organization, degenerative cellular changes, and increased staining intensity. This substantial elevation in H-score confirms the strong detrimental effect of Cd exposure on ovarian tissue. Importantly, co-treatment with RES (Cd+Res group) significantly reduced the Cd-induced increase in H-score. Although the score remained higher than in the Control and Res groups, the marked decrease compared with the Cd group indicates that RES exerted a notable ameliorative and protective effect, attenuating structural damage and partially restoring tissue integrity. Overall, semiquantitative scoring supports the protective role of RES against Cd-induced ovarian injury (Figure 2).

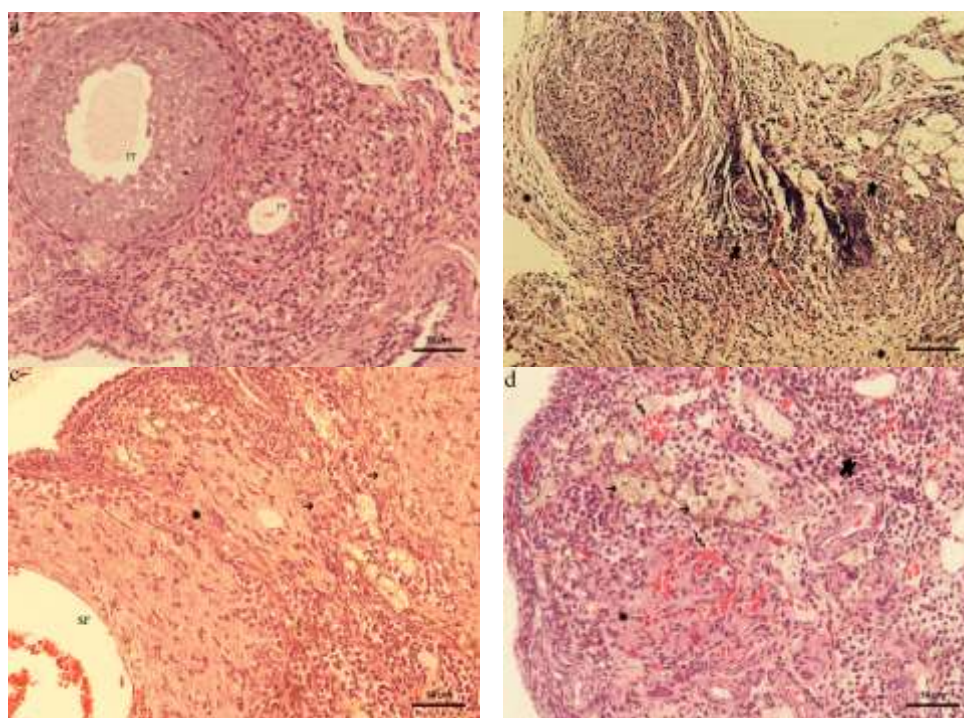


Figure 1. Histopathological evaluation of ovarian tissue following Cd exposure and RES treatment in rats. Representative photomicrographs of hematoxylin and eosin (H&E) stained ovarian sections from each experimental group (scale bar = 50 μ m). A) Control group: Normal ovarian architecture with intact follicles at various developmental stages (primordial, primary, secondary, antral). Granulosa cell layers are well-organized and intact. B) Cd (Cd) group: Severe histopathological alterations including increased follicular atresia (arrows), disorganization and degeneration of granulosa cell layers (arrowheads), and reduced number of healthy antral follicles. Stromal edema and vacuolization are evident. C) Resveratrol (RES) group: Histological appearance comparable to Control, showing preserved follicular morphology and stromal structure, indicating

no adverse effect of RES alone. D) Cd + RES (Cd+RES) group: Noticeable improvement in ovarian architecture compared to Cd group. Follicular integrity is better preserved, granulosa cell layers show reduced degeneration, and stromal structure appears more organized, demonstrating the protective effect of resveratrol co-treatment (PF: Primer follicle, star: infiltration, arrow: atretic follicle, multistar: fibrosis, lightning: hemorrhage).

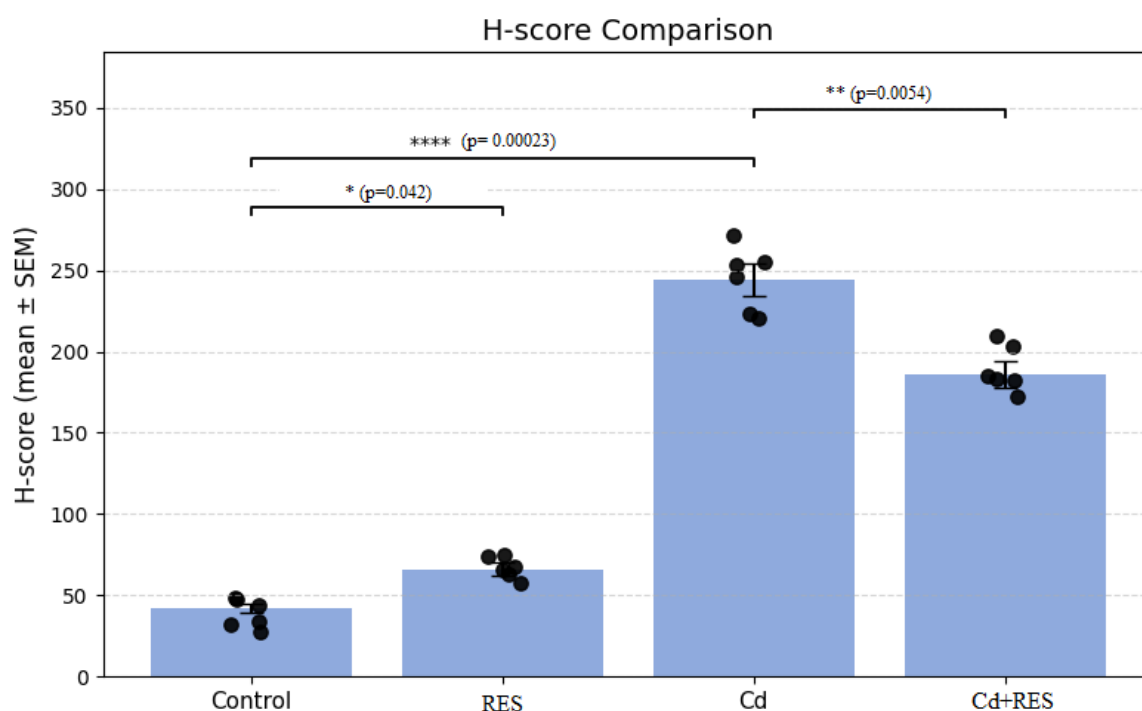


Figure 2. Histological H-score analysis of ovarian tissue across experimental groups. Quantitative H-score measurements demonstrated minimal histological reactivity in the Control and RES (RES) groups, while Cd (Cd) exposed ovaries exhibited a marked increase in H-score, indicating severe histopathological damage. Co-treatment with resveratrol (Cd+RES) significantly reduced the Cd-induced elevation in H-score, reflecting a notable improvement in tissue integrity. Error bars represent SEM. Statistical significance: *** $p < 0.001$ vs. Control; ** $p < 0.01$ vs. Cd; * $p < 0.05$ vs. Control.

3.2. Biochemical Findings

Oxidative stress parameters MDA: In the Cd group, ovarian tissue MDA levels increased approximately 3-fold compared to the control group ($p < 0.001$). In the Cd+RES group, this increase was significantly suppressed, and MDA levels decreased to values close to the control group ($p < 0.001$ compared to Cd).

Antioxidant enzyme activity and GSH levels: SOD, CAT, and GPx: In the Cd group, all antioxidant enzyme activities were significantly suppressed compared to the control group ($p < 0.01$). RES treatment significantly restored the activities of these enzymes ($p < 0.05$ compared to Cd). **GSH:** Cd administration caused a significant depletion of tissue GSH levels ($p < 0.001$). RES treatment provided a partial but statistically significant improvement in GSH levels ($p < 0.05$).

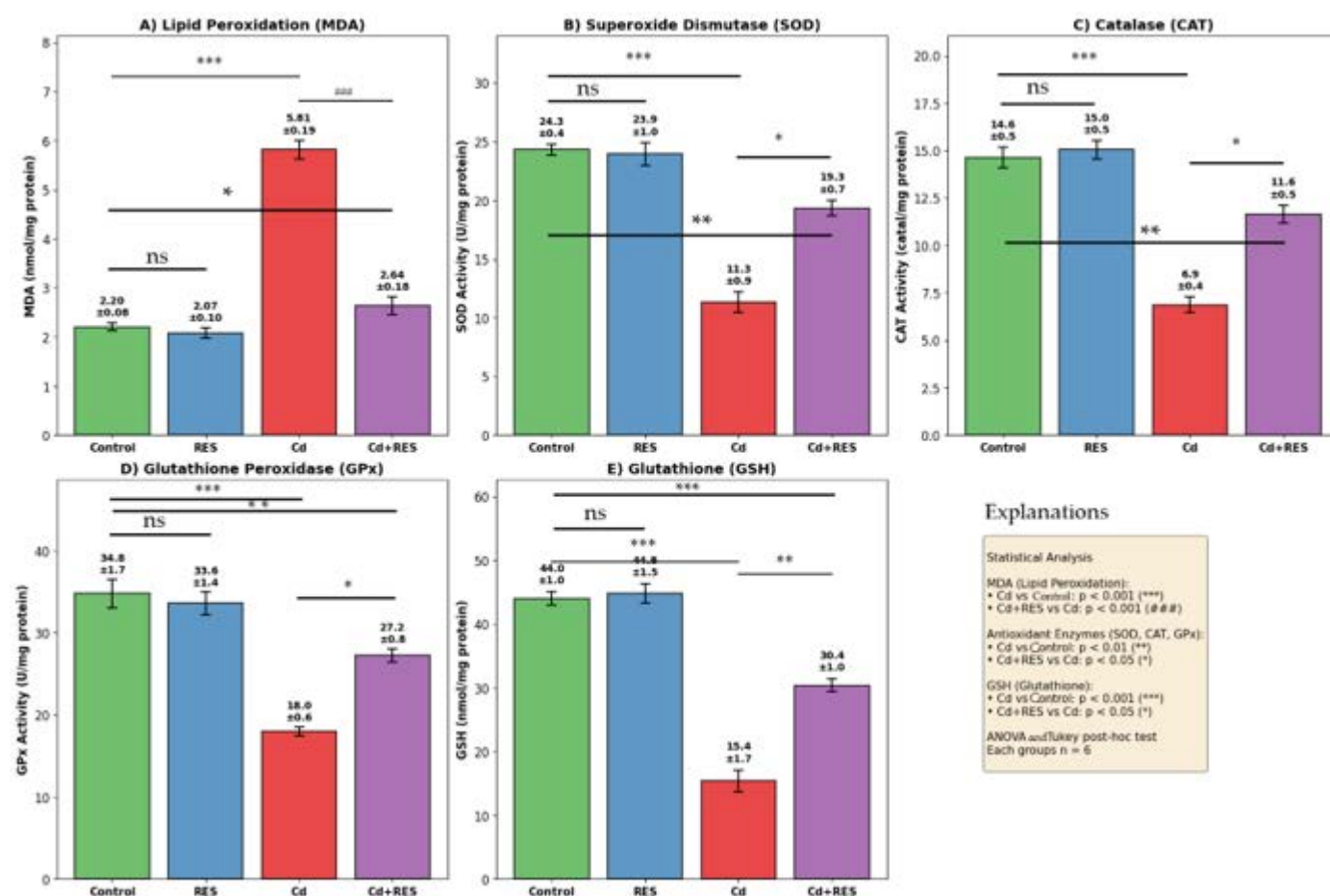


Figure 3. Effect of Cd and RES on oxidative stress parameters in rat ovarian tissue. A) Lipid peroxidation assessed by malondialdehyde (MDA) levels. Cd (Cd) exposure significantly increased MDA levels compared to the Control group ($***p < 0.001$), indicating elevated oxidative damage. Resveratrol (RES) treatment in Cd-exposed rats (Cd+RES group) significantly reduced MDA levels compared to the Cd-alone group ($###p < 0.001$), demonstrating protective effects against lipid peroxidation. B) Superoxide dismutase (SOD) activity. Cd exposure significantly suppressed SOD activity compared to Control ($**p < 0.01$). Co-treatment with RES partially restored SOD activity in the Cd+RES group compared to Cd alone ($*p < 0.05$). C) Catalase (CAT) activity. Similar to SOD, CAT activity was significantly reduced by Cd exposure ($**p < 0.01$). RES treatment showed a protective effect, with significantly higher CAT activity in the Cd+RES group compared to Cd alone ($*p < 0.05$). D) Glutathione peroxidase (GPx) activity. Cd exposure caused significant suppression of GPx activity ($**p < 0.01$). RES co-treatment partially ameliorated this effect, with significantly higher GPx activity in the Cd+RES group compared to Cd alone ($*p < 0.05$). E) Reduced glutathione (GSH) levels. Cd exposure caused marked depletion of GSH levels compared to Control ($***p < 0.001$). RES treatment showed a partial but significant recovery of GSH levels in the Cd+RES group compared to Cd alone ($*p < 0.05$). Data are presented as mean $\pm$ SEM ($n = 6$ per group). Statistical significance was determined by one-way ANOVA followed by Tukey's post-hoc test. Significance levels: $***p < 0.001$, $**p < 0.01$, $*p < 0.05$ compared to Control; $###p < 0.001$, $#p < 0.05$ compared to Cd group.

3.3. Gene Expression Findings

Apoptotic Balance (Bax/Bcl-2 Ratio): In the Cd group, pro-apoptotic Bax gene expression increased ($p < 0.01$), while anti-apoptotic Bcl-2 expression decreased ($p < 0.05$), resulting in a significant approximately 4-fold increase in the Bax/Bcl-2 ratio compared to the control group ($p < 0.001$). In the Cd+RES group, Bax expression was suppressed, Bcl-2 expression increased, and the Bax/Bcl-2 ratio was significantly reduced ($p < 0.01$ compared to Cd).

Nrf2/HO-1 Pathway: Cd exposure did not alter or slightly suppressed the expression of Nrf2 and its target gene HO-1 compared to the control group. In contrast, resveratrol treatment caused a significant increase in both Nrf2 and HO-1 mRNA levels ($p < 0.05$ compared to control and Cd groups).

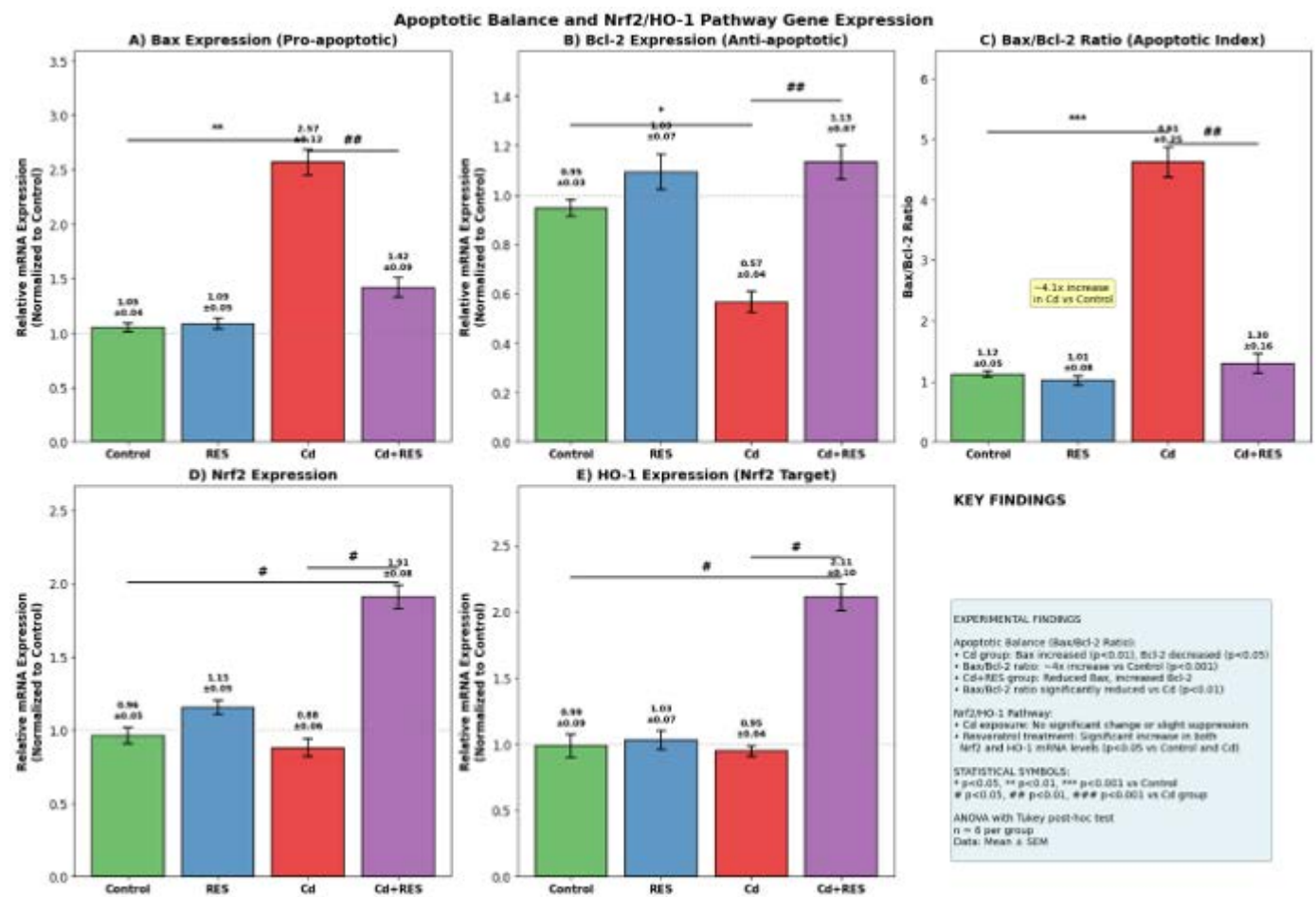


Figure 4. Effects of Cd (Cd) and resveratrol (RES) on apoptotic genes and Nrf2/HO-1 pathway in rat ovary. A) Bax, B) Bcl-2, C) Bax/Bcl-2 ratio, D) Nrf2, and E) HO-1 mRNA expression. Cd increased apoptotic signaling (elevated Bax/Bcl-2 ratio), while RES treatment restored apoptotic balance and activated Nrf2/HO-1 pathway. Data: mean ± SEM, n=6. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs Control; ### $p < 0.001$ vs Cd (ANOVA with Tukey's test).

3.4. Bioinformatics Analysis Findings

Protein-Protein Interaction (PPI) Network: The PPI network constructed through the studied proteins (Bax, Bcl², Nrf², HMOX¹) showed that these proteins are involved in closely related pathways such as apoptosis and oxidative stress response. Network analysis revealed that Nrf² forms a central "hub" node with numerous proteins with which it is linked.

Target Prediction and Molecular Docking: In silico analyses showed that resveratrol can interact with KEAP¹ (a negative regulator of NRF²) and SIRT¹ with high affinity. Potential binding with KEAP¹ is consistent with NRF² release and the associated increase in HO-1 expression. Interaction with SIRT¹ points to an underlying mechanism of RES's apoptotic and anti-inflammatory effects.

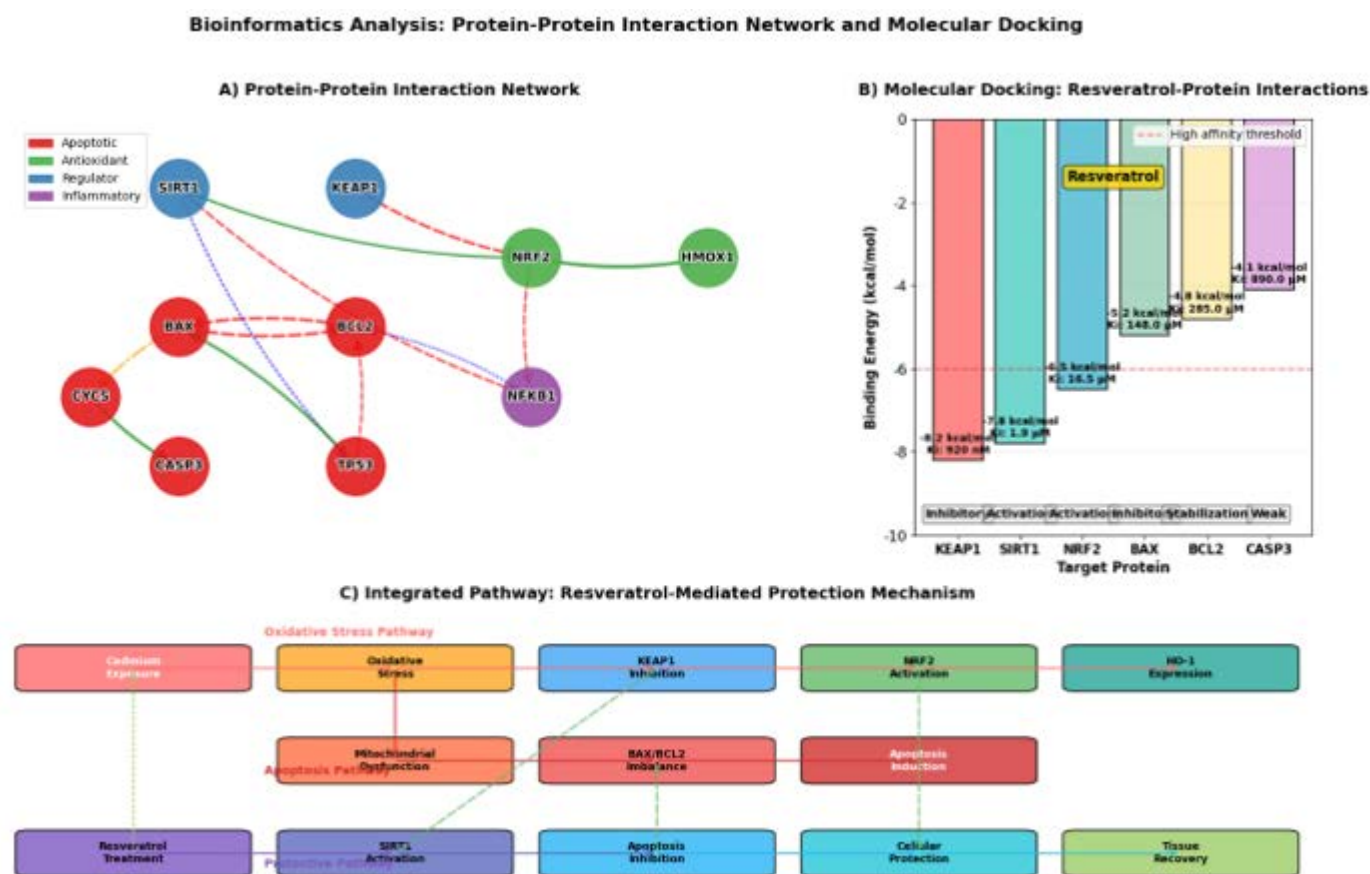


Figure 5. Bioinformatics analysis. A) PPI network: BAX (Bcl-2-associated X protein), BCL2 (B-cell lymphoma 2), NRF2 (nuclear factor erythroid 2-related factor 2), HMOX1 (heme oxygenase-1), KEAP1 (Kelch-like ECH-associated protein 1), SIRT1 (sirtuin 1), CASP3 (caspase-3), TP53 (tumor protein p53), NFKB1 (nuclear factor kappa B subunit 1), CYCS (cytochrome c). B) Docking: binding energies in kcal/mol. C) Pathway model integrating oxidative stress and apoptotic regulation.

4. Discussion

This study provides compelling evidence that resveratrol effectively mitigates Cd-induced ovarian toxicity through a multi-faceted mechanism involving histological preservation, attenuation of oxidative stress, restoration of antioxidant defenses, modulation of apoptotic balance, and activation of the Nrf2/HO-1 pathway, as supported by integrated bioinformatics analysis.

The histological assessment revealed that Cd exposure caused severe architectural disruption in ovarian tissue, characterized by follicular atresia and granulosa cell degeneration, consistent with previous reports of Cd's gonadotoxic effects.¹² The significant elevation in H-score in the Cd group quantitatively corroborates these pathological alterations. RES co-treatment markedly reduced this damage, preserving follicular integrity and stromal organization. This protective effect aligns with RES's known ability to maintain cellular architecture in various toxin-exposed tissues, likely through its stabilizing effects on membrane integrity and cytoskeletal components.¹³

At the biochemical level, Cd induced profound oxidative stress, as evidenced by the approximately three-fold increase in MDA levels a reliable marker of lipid peroxidation. This finding is consistent with Cd's established role in generating reactive oxygen species (ROS) via Fenton-like reactions and depletion of antioxidant reserves.¹⁴ The concurrent suppression of key antioxidant enzymes (SOD, CAT, GPx) and depletion of GSH create a vicious cycle of oxidative damage, compromising the ovary's redox homeostasis essential for folliculogenesis and steroidogenesis.¹⁵ RES's ability to significantly reduce MDA levels

and partially restore antioxidant enzyme activities underscores its potent antioxidant properties. These effects can be attributed to RES's direct free radical scavenging capacity and its ability to upregulate endogenous antioxidant systems, as demonstrated in other models of oxidative organ damage.¹⁶

The molecular analyses revealed that Cd disrupts apoptotic homeostasis by increasing the pro-apoptotic Bax/Bcl-2 ratio, creating a cellular environment favoring programmed cell death. This imbalance likely contributes to the observed follicular atresia. RES treatment effectively reversed this trend, suppressing Bax and elevating Bcl-2 expression, thereby restoring apoptotic balance. These findings are consistent with RES's established anti-apoptotic effects in various tissue models, mediated through modulation of mitochondrial membrane permeability and caspase regulation.¹⁷

A key mechanistic insight from this study is the activation of the Nrf2/HO-1 pathway by RES. While Cd exposure did not significantly alter Nrf2 or HO-1 expression, RES treatment substantially upregulated both genes in the Cd+RES group. Nrf2 serves as a master regulator of cellular antioxidant responses, orchestrating the transcription of numerous cytoprotective genes including HO-1.¹⁸ HO-1 catalyzes the degradation of heme to biliverdin, carbon monoxide, and free iron, exerting potent antioxidant, anti-apoptotic, and anti-inflammatory effects.¹⁹ The observed upregulation of this pathway provides a coherent molecular explanation for RES's comprehensive protective effects against Cd toxicity.

The bioinformatics analysis offers valuable systems-level insights that bridge our experimental observations. The protein-protein interaction network identified Nrf2 as a central hub connecting apoptotic and antioxidant pathways, highlighting its pivotal role in cellular stress response. The molecular docking predictions revealed high-affinity binding of RES to KEAP1, the negative regulator of Nrf2, providing a structural basis for the observed Nrf2 activation. KEAP1 normally sequesters Nrf2 in the cytoplasm, targeting it for proteasomal degradation. RES's binding to KEAP1 likely disrupts this interaction, allowing Nrf2 translocation to the nucleus and subsequent transcription of antioxidant genes including HO-1.²⁰ Additionally, RES's predicted interaction with SIRT1 suggests another protective mechanism. SIRT1, a NAD⁺-dependent deacetylase, regulates numerous cellular processes including apoptosis, inflammation, and metabolism. SIRT1 activation by RES could enhance mitochondrial biogenesis, reduce oxidative stress, and modulate apoptotic signaling, as demonstrated in aging and metabolic studies.²¹

The integrated pathway model synthesizes these findings into a coherent protective mechanism: Cd induces oxidative stress and apoptotic imbalance; RES simultaneously (1) activates Nrf2 via KEAP1 inhibition, enhancing antioxidant defenses including HO-1 expression, and (2) activates SIRT1, modulating apoptotic regulators and inflammatory responses. This multi-target approach effectively counteracts Cd's diverse toxic effects.

Our findings have significant implications for reproductive toxicology and potential clinical applications. Environmental Cd exposure represents a growing concern for female reproductive health, linked to ovarian dysfunction, premature ovarian insufficiency, and infertility.²² The demonstrated efficacy of RES in mitigating these effects suggests its potential as a therapeutic or preventive agent for women at risk of Cd exposure. However, translation to clinical practice requires consideration of RES's pharmacokinetics, optimal dosing, and potential interactions.²³

Several limitations of this study warrant mention. First, the experimental model employed acute Cd exposure, whereas human exposure is typically chronic and low-dose. Future studies should examine RES's effects in chronic exposure models. Second, while we demonstrated pathway activation, direct measurements of Nrf2 nuclear translocation and SIRT1 deacetylase activity would strengthen the mechanistic conclusions. Third, the bioinformatics predictions require experimental validation through techniques such as co-immunoprecipitation or surface plasmon resonance.²⁴⁻²⁶

Study limitations: While this study demonstrated the protective effects of resveratrol on cadmium-induced ovarian damage at the histological and bioinformatic levels, it has some important limitations. First, our study did not present quantitative data at the protein level. Expression levels of apoptotic (e.g., Bax, Bcl-2, Caspase-3), oxidative stress (e.g., SOD, CAT, GPx), or inflammatory (e.g., TNF- α , IL-1 β , NF- κ B) proteins were not measured by Western blot or immunohistochemical (IHC) staining. Therefore, the molecular mechanisms underlying the observed histological improvement (e.g., suppression of apoptotic pathways or induction of antioxidant enzymes) could not be directly proven. Future studies with quantitative analyses at the protein level will contribute to a more precise elucidation of the mechanism of action of resveratrol.

5. Conclusion

In conclusion, this study demonstrates that resveratrol (RES) protects against cadmium (Cd)-induced ovarian toxicity through a coordinated mechanism involving: (1) preservation of ovarian tissue architecture, (2) reduction of oxidative stress and lipid peroxidation, (3) restoration of endogenous antioxidant capacity, (4) rebalancing of apoptotic regulators, and (5) activation of the Nrf2/HO-1 antioxidant signaling pathway. Furthermore, bioinformatics analysis provides molecular insights into the interactions of RES with key regulatory proteins, including KEAP¹ and SIRT¹. These findings support further investigation of RES as a potential therapeutic agent against environmental toxicant-induced reproductive damage. In particular, the Nrf2/HO-1 pathway emerges as a promising target for future ovarian protection strategies.

Statements and Declarations

Ethical Considerations: This study was approved by the Çanakkale Experimental Animal Ethics Committee (05.03.2021, Decision No: 2021/02-07).

Conflict of Interest: The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions: Authors reviewed the results and approved the final version of the manuscript.

Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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