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Protective effect of resveratrol against ovarian dysfunction in endometriotic rats

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Abstract

Background: Endometriosis (END) is an estrogen-dependent inflammatory disorder associated with pelvic pain, infertility, and ovarian dysfunction. Till today, there is no cure for END, only attempts to alleviate its symptoms. Resveratrol (RES), a natural polyphenolic compound, has revealed anti-inflammatory and anti-estrogenic effects, indicating its potential as a novel beneficial agent. This study aimed to assess the protective impacts of RES on ovarian function and the progression of END in a rat model, concentrating on estrogen signaling, immune-inflammatory responses, coagulation abnormalities, and histological alterations. **Methodology:** END was induced in adult female rats via endometrial tissue transplants harvested from donor rats. Endometriotic rats were divided into untreated (END), vehicle-treated (END+DMSO), and RES-treated (END+RES). Serum and peritoneal exudate of estradiol (E2) levels, percentage of granulocyte cells and Mid cells (monocytes, eosinophils, basophils), coagulation markers (platelet counts, fibrinogen, thrombin time, and prothrombin time), and ovarian histopathology were assessed. **Results:** Analyzed data showed that END and END+DMSO rats had elevated E2 levels, increased granulocyte and Mid cell percentages, a hypercoagulable state, and significant ovarian tissue alterations. However, RES administration to the endometriotic group reversed the deleterious alterations and improved the ovarian architecture. **Conclusions:** Altogether, this study can conclude that RES alleviated significant pathogenic features of END via hormonal, immunological, and coagulative regulation, while protecting ovarian function.

Keywords: Endometriosis, resveratrol, estrogen signaling, inflammatory response, ovarian function

Introduction

Endometriosis (END) is a chronic estrogen-dependent inflammatory illness distinguished by ectopic growth of endometrial tissue outside the uterine cavity, usually affecting the ovaries, peritoneum, and other pelvic organs. It affects about 10% of reproductive-age women and is often accompanied with pelvic pain, dysmenorrhea, and infertility (Agarwal *et al*., 2019; Adilbayeva & Kunz, 2024). Despite being histologically benign, END displays several malignancy-like features, such as local invasion, angiogenesis, and resistance to apoptosis, mostly driven by hormonal and inflammatory dysregulation (Calmon *et al*., 2024; Parmar *et al*., 2025). The pathophysiology of END is intricate, driven by interplay of hormonal, immune, and molecular factors (Lamceva *et al*., 2023; Mariadas *et al*., 2025). Estrogen, particularly 17-β estradiol (E2), is central to lesion progression, enhancing proliferation, inflammation, and angiogenesis (Greygoose *et al.*, 2025). In recent years, natural compounds with anti-inflammatory and antioxidant properties such as curcumin, butyrate, quercetin, genistein, apigenin, green tea, and resveratrol (RES; 3, 5, 4'-trihydroxy-trans-stilbene), have emerged as promising candidates (Ahmed & Mohammed, 2022; AL-Khaqani & Mohammad, 2024; Zaurito *et al*., 2024).

RES is a naturally occurring polyphenol found in peanuts, berries, and grapes, and it has garnered a major interest due to its numerous biological benefits. RES exerts anti-inflammatory, antioxidant, and anti-angiogenic effects and downregulating aromatase expression, thereby lowering local estrogen production (Khayoon & Al-Rekabi, 2020; Alharris *et al*., 2022; Alawady & Alrubeii, 2024). Beyond gynecological disorders, RES has shown protective effects in cancer, cardiovascular, and neurodegenerative conditions (Alharris *et a*l., 2018; Angellotti *et al*., 2023; Al-Hassawi & Al-Sammak, 2024). This study investigated the protective potential of RES in induced rat model of END, focusing on its impact on circulating and peritoneal E2 levels, inflammatory cell profiles (granulocytes and Mid cells), coagulation factors (fibrinogen, thrombin time, and prothrombin time), and ovarian histopathology.

Materials and Methods

Resveratrol preparation

RES (purity≥98%) powder was purchased from Hebei Guanlang Biotechnology, China. It was dissolved in an appropriate vehicle (DMSO) and subsequently diluted with distilled water to make the working solutions at the appropriate concentrations, as described in previous studies (Aghetaa *et al*., 2023; Bustani *et al*., 2024).

Ethical approval

The experimental techniques were approved by the Institutional Animal Care and Use Committee at the College of Veterinary Medicine, University of Baghdad, and accompanied with international guidelines for the care and use of laboratory animals (Ethical Approval No. AUP# P.G. 407 issued on 21/2/2024).

Experimental design

Fifty-five adult female rats (Rattus norvegicus), aged 8-10 weeks and weighing around 180-220 g, were employed. All animals were housed in specialized pathogen-free conditions with a controlled environment (22 ± 2ºC; 12-hour light/dark cycle) at the animal house of the College of Veterinary Medicine, University of Baghdad. All animals had unrestricted access to standard chow and water throughout the study. Before any experimental procedures, the animals were given a two-week period to acclimate to the housing environments. Rats were randomly divided into three main groups and recipient rats were divided into three subgroups illustrated in Figure 1.

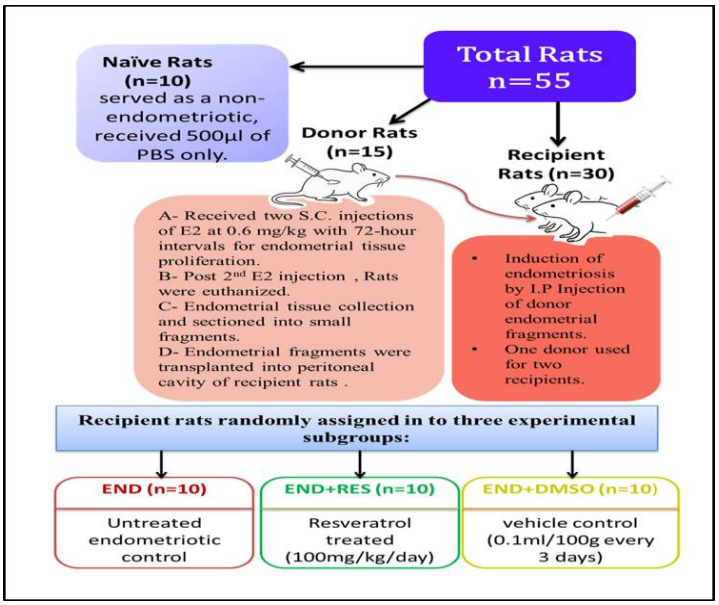

Figure 1: The experimental design and END induction in rats

Samples collection and laboratory analysis

At the end of the experimental period (30 days), five animals from each group were anesthetized using a ketamine-xylazine mixture and then euthanized. Blood samples were collected via cardiac puncture for measurement of the percentage of Mid cells, granulocyte cells, and counting the platelets using the VetScan analyzer system (Abaxis, Inc, USA). Coagulation factors (fibrinogen, prothrombin time, and thrombin time) were measured by the Seamaty Biochemical analyzer (Chengdu Seamaty Technology Co, China), and serum concentration of E2 was evaluated using Sandwich-ELISA kits (SunLong, China). Additionally, the peritoneal fluid was harvested via lavage for the assessment of E2 concentration using Sandwich-ELISA kits (SunLong, China). The ovarian tissue was collected from three animals from each group and fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E) for histopathological evaluation.

Statistical analysis

The collected data were analyzed using GraphPad Prism software (Version 10, 2024; San Diego, CA, USA; https://www.graphpad.com). One-way analysis of variance (ANOVA) was used to estimate statistical differences between various groups under different experimental conditions. Tukey's multiple comparisons test was employed to compare group means. P-value less than 0.05 was considered statistically significant. The statistical significance was denoted in the figures as follows: *P<0.05, **P<0.01, ***P<0.001, and ***P<0.0001.

Results

E2 levels in the circulation and peritoneal exudate

The concentrations of E2 (pg/ml) in the circulation and peritoneal exudate of the experimental groups are shown in Figures 2-A and 2-B, respectively. A significant (P<0.05) elevation of E2 levels were observed in both the circulation and peritoneal exudate of the END and END+DMSO groups compared to the naïve and END+RES groups. Interestingly, the E2 levels in the circulation of the END+RES were significantly lower than the naïve group. No significant variations in the E2 levels were found among the END and END+DMSO groups in either compartment, nor between the naïve and END+RES groups in the peritoneal exudate.

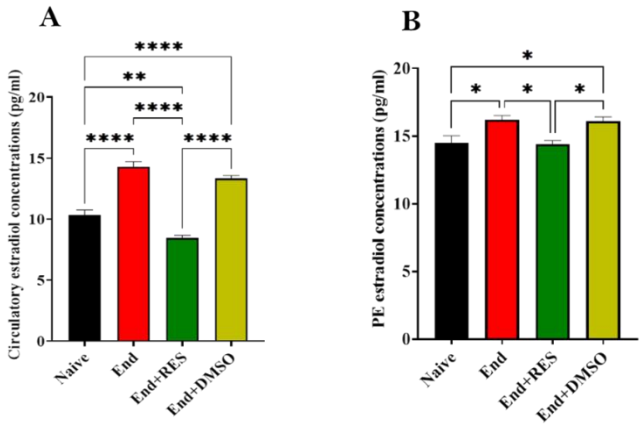

Figure 2: Effect of RES treatment on E2 levels in END-induced rats. A) Circulatory E2 concentration (pg/ml) and B) E2 concentrations in peritoneal exudate (PE) (pg/ml) following RES administration for 30 days to endometrial tissue transplanted rats (n=5)

Percentage of granulocytes and Mid cells

The percentages of granulocytes and Mid cells (monocytes, eosinophils, basophils) are presented in Figures 3A and 3B. Both granulocytes and Mid cell percentages were significantly (P<0.05) elevated in the END and END+DMSO groups compared to the naïve and END+RES groups. However, no significant differences were found among the END and END+DMSO groups or between the naïve and END+RES groups for either cell population.

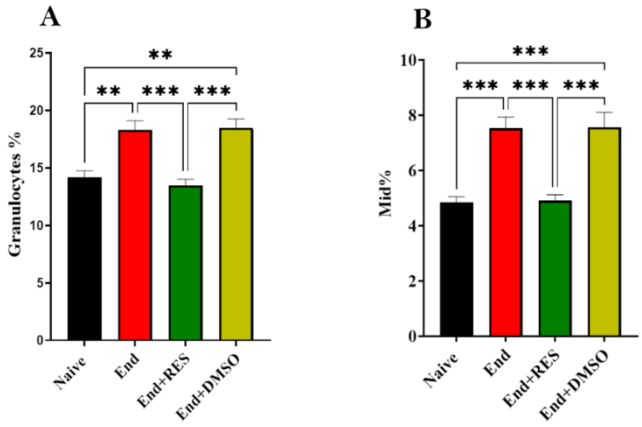

Figure 3: Effect of RES treatment on the percentage of granulocytes and Mid cells in END-induced rats. A) Percentage of granulocytes and B) Percentage of Mid cells following RES administration for 30 days to endometrial tissue transplanted rats (n=5). Naïve group: non-endometriotic rats (negative control). END group: untreated endometriotic rats (positive control). END+RES group: Endometriotic rats were treated with resveratrol. END+DMSO group: Endometriotic rats administered vehicle control. Statistical analysis was conducted using One-way ANOVA followed by Tukey's multiple comparisons test. Significant levels are: **P<0.01 and ***P<0.001

Fibrinogen concentrations (g/l) and platelet counts (×10^3 cells/ml)

Figures 4A and 4B illustrate the concentrations of fibrinogen (g/l) and platelet counts (× 10^3 cells/ml). Both parameters were significantly (P<0.05) elevated in the END and END+DMSO groups relative to the naïve and END+RES groups. However, no significant differences were detected between the END and END+DMSO groups or between the naïve and END+RES groups for either variable.

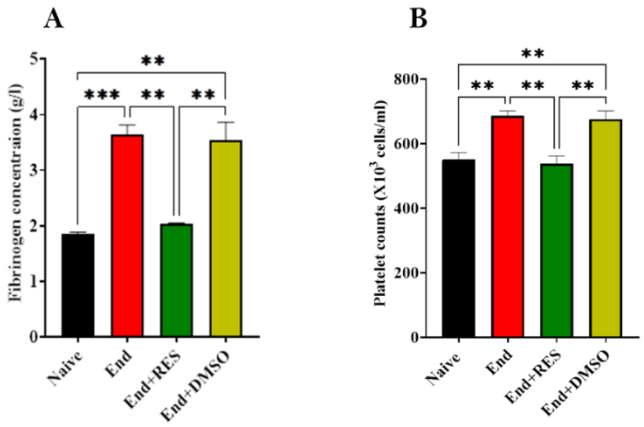

Figure 4: Effect of RES treatment on the Fibrinogen concentrations (g/L) and platelet counts (×10^3 cells/ml) in END-induced rats. A) Fibrinogen concentrations and B) platelet counts following RES administration for 30 days to endometrial tissue transplanted rats (n=5). Naïve group: non-endometriotic rats (negative control). END group: untreated endometriotic rats (positive control). END+RES group: Endometriotic rats were treated with resveratrol. END+DMSO group: Endometriotic rats administered vehicle control. Statistical analysis was conducted using One-way ANOVA followed by Tukey's multiple comparisons test. Significant levels are: **P<0.01 and ***P<0.001

Thrombin and prothrombin times (seconds)

Figures 5A and 5B display the thrombin time and prothrombin time, respectively, across the experimental groups. Both coagulation parameters were significantly (P<0.05) shortened in the END and END+DMSO groups compared to the naïve and END+RES groups. No significant differences were observed between the END and END+DMSO groups, nor between the naïve and END+RES groups, in either thrombin or prothrombin time.

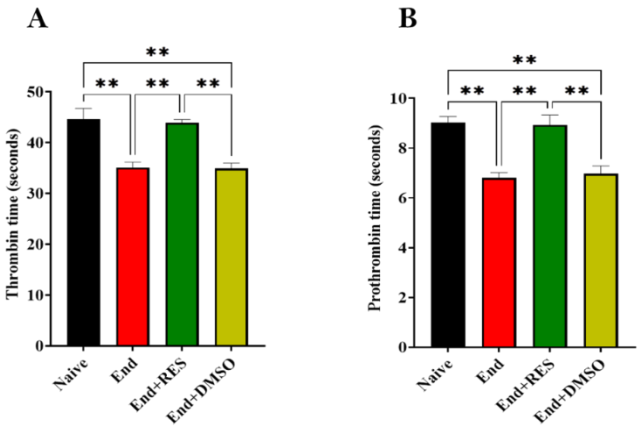

Figure 5: Effect of RES treatment on the Thrombin time (seconds) and Prothrombin time (seconds) in END-induced rats. A) Thrombin time and B) Prothrombin time following RES administration for 30 days to endometrial tissue transplanted rats (n=5). Naïve group: non-endometriotic rats (negative control). END group: untreated endometriotic rats (positive control). END+RES group: Endometriotic rats were treated with resveratrol. END+DMSO group: Endometriotic rats administered vehicle control. Statistical analysis was conducted using One-way ANOVA followed by Tukey's multiple comparisons test. The significant level is: **P<0.01

Histopathological examination of the ovary

Histological examination of ovarian cross-sections stained with hematoxylin and eosin (H&E) revealed marked pathological alterations in the END and END+DMSO groups (Figures 7 and 9, respectively). In contrast, the preserved architecture was observed in the naïve and END+RES groups (Figures 6 and 8, respectively). The pathological changes included follicular atresia, vacuolar degeneration within stromal areas, inflammatory cell infiltration, and hemosiderin deposition. These features suggested an inflammatory response and endometrial tissue remodeling, which were characteristic aspects of END in this experimental model.

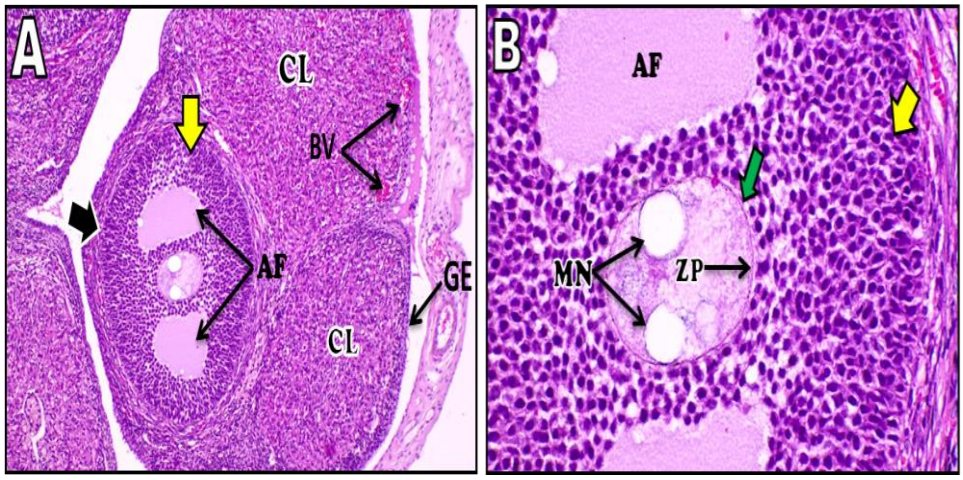

Figure 6: Photomicrograph of histological sections of the ovary from a naive rat (A &B). Images show normal ovarian architecture surrounded by the germinal epithelium (GE). The corpus luteum (CL) exhibits normal luteal cells and also shows well-vascularized stroma that contains normal blood vessels (BV). A Graafian follicle (black arrow) characterized by well-organized granulosa cells (yellow arrow) and a distinct antral fluid (AF). A mature Oocyst (green arrow) with a visible micronucleus (MN) is enclosed by well-defined zona pellucida (ZP). H&E. A: 100x and B: 400x

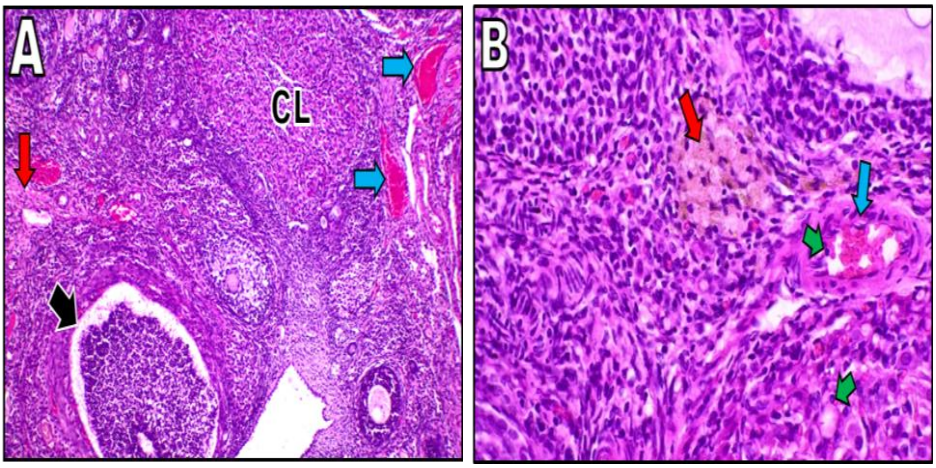

Figure 7: Photomicrograph of histological sections of the ovary from END rats (A &B). Images reveal follicle atresia (black arrow) and are characterized by the absence of follicular lumen and surrounded by a thick fibrous capsule. Notable histopathological alterations include congested blood vessels (blue arrow), hemosiderin deposition (red arrow), and infiltration of inflammatory cells within the stromal tissue (green arrow). H&E. A: 100x and B: 400x

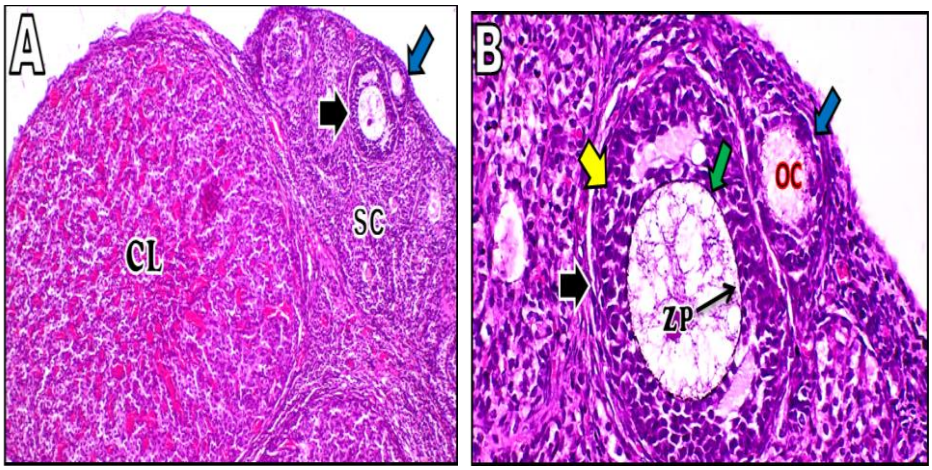

Figure 8: Photomicrograph of histological sections of the ovary from END+RES rats (A &B). Images display normal ovarian architecture, including stromal cells (SC) and a corpus luteum (CL) with normal luteal cell morphology. In panel B, a primary follicle (blue arrow) is identified by an enlarged Oocyst (OC) surrounded by a single layer of cuboidal granulosa cells and an emerging zona pellucida (ZP). A secondary follicle (black arrow) exhibits multiple layers of granulosa cells (yellow arrow) and a mature Oocyst (green arrow) enclosed by well-defined zona pellucida (ZP). H&E. A: 100x and B: 400x

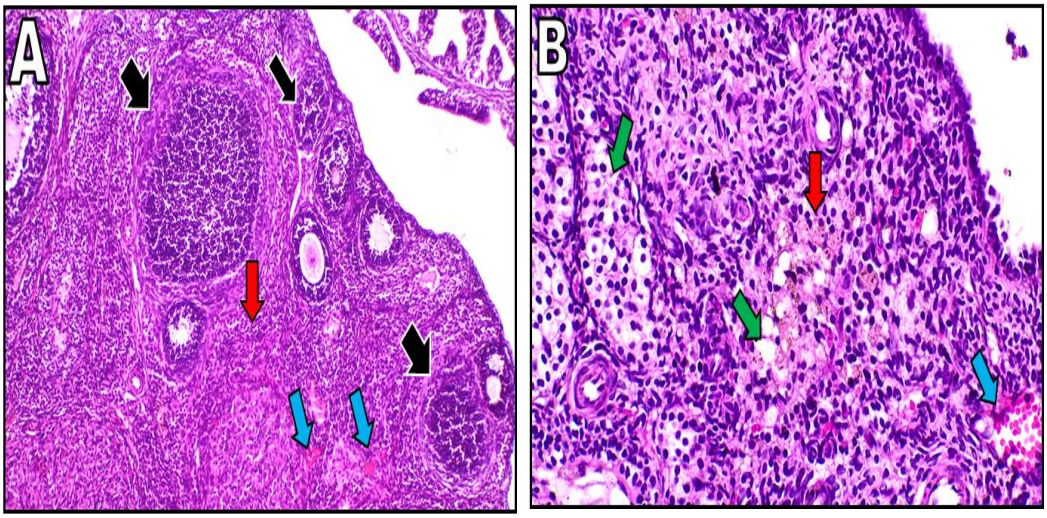

Figure9: Photomicrograph of histological sections of the ovary from END+DMSO rats (A &B). Images reveal multiple instances of follicular atresia (black arrow) and are characterized by the absence of follicular luminal and surrounded by a thick fibrous zone. Vacuolar degeneration of stromal cells (green arrow) and localized hemosiderin deposition (red arrow). H&E. A: 100x and B: 400x

Discussion

The present study estimated the protective effects of RES in the rat model of END, focusing on ovarian function, inflammatory responses, coagulation dynamics, and histopathological changes. The findings lighten the ability of RES to attenuate critical pathological features of END via modulation of estrogen signaling, immune-inflammatory responses, and coagulative homeostasis. E2 is central to END progression, promoting lesion growth, angiogenesis, and resistance to apoptosis, while promoting inflammatory responses within the peritoneal microenvironment (Greygoose *et al*., 2025; Peng *et al*., 2025). In this study, both serum and peritoneal E2 levels were significantly elevated in the untreated END and END+DMSO groups, reflecting the hyper estrogenic state associated with END (Othman *et al*., 2021; Jasim & Yaseen, 2024). E2 can influence macrophage and mast cells, and stimulates production of chemokines and cytokines, such as TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1). Moreover, gut microbiota dysbiosis associated with END can disrupt the estrobolome activity, thereby altering estrogen reabsorption and promoting a hyper-estrogenic milieu. It also increases gut permeability and facilitates lipopolysaccharide translocation, triggering Toll-like receptor-mediated inflammatory responses. These hormonal and immune effects act synergistically exacerbate the pathophysiology and severity of END (Alghetaa *et al*., 2023; Nannini *et al*., 2025; Neykhonji *et al*., 2025). RES treatment reduced both systemic and local estrogen, supporting earlier reports that it acts as a phytoestrogen with anti-estrogenic activity through mechanisms such as aromatase suppression and estrogen receptor modulation (Khazaei *et al*., 2020; Han *et al*., 2021). Interestingly, circulating E2 levels in RES-treated rats were even lower than those of naïve controls, suggesting a systemic inhibitory effect on estrogen biosynthesis. The immune system is closely linked to estrogen signaling in END, where granulocytes and other immune cells sustain inflammation and lesion survival through cytokine release and oxidative stress (Chantalat *et al*., 2020; Dash *et al*., 2024). In this study, granulocyte and Mid cell counts were elevated in untreated rats but normalized with RES therapy, highlighting its immunomodulatory role. These effects may involve inhibition of NF-κB and STAT3 signaling, pathways known to drive chronic inflammation in END (AL-Khaqani & Mohammad, 2024; Chauhan *et al*., 2025). A further hallmark of END is the pro-thrombotic environment created by inflammation-coagulation crosstalk. Elevated fibrinogen, shortened clotting times, and increased platelet counts in untreated rats indicated a hypercoagulable state that could facilitate lesion vascularization and fibrosis (Ding *et al*., 2019; Aziz *et al*., 2023). RES restored these parameters toward baseline, suggesting its benefits extend to hemostatic regulation (Gal *et al*., 2021; Yu *et al*., 2024).

Histological examination of the ovaries from untreated END rats and vehicle-treated rats displayed hallmarks of ovarian dysfunctions, including follicular atresia, hemosiderin deposition, and vascular congestion, reflecting sustained inflammation and oxidative stress. By contrast, RES preserved ovarian structure, consistent with its antioxidant and anti-apoptotic properties (Wang *et al*., 2021; Abdulla & Al-Okaily, 2022; AL-Salamy & Alghetaa, 2025; Bustani & Alghetaa, 2025).

Conclusions

This study provides compelling preclinical evidence that RES exerts protective effects against END-associated ovarian dysfunction by targeting multiple interrelated pathological processes. This occurs through its ability to downregulate estrogen biosynthesis and signaling, modulate immune-inflammatory responses, normalize coagulation parameters, and preserve ovarian histoarchitecture. The attenuation of systemic and peritoneal estradiol levels, suppression of inflammatory immune cell infiltration, and correction of pro-thrombotic conditions indicate that RES may ameliorate the hormonal, immunological, and vascular dysregulation associated with END. These findings support the therapeutic potential of RES as a multi-targeted natural compound.

Acknowledgments

Not applicable

Authors' Contributions

HA design, conceptualization, review the draft and last version of this manuscript. AA wrote the draft, revised and wrote the last version of this manuscript. Both HA and AA have reviewed and approved the submitted version of the manuscript.

Conflicts of Interest

The authors declare that they have no competing interest regarding the publication of this article.

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التأثير الوقائي للريسفيراترول على اختلال وظيفة المبيض في نموذج الجرذان للانتباذ البطاني الرحمي

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المستخلص

الخلفية: الانتباذ البطاني الرحمي هو اضطراب التهابي مزمن يعتمد على هرمون الإستروجين، ويصاحبه ألم في الحوض وعقم وخلل في وظيفة المبيض. حتى اليوم، لا يوجد علاج شافٍ للانتباذ البطاني الرحمي، وإنما محاولات لتخفيف أعراضه. وقد أظهر الريسفيراترول (RES)، وهو مركب متعدد الفينولات طبيعي، خصائص مضادة للالتهابات ومضادة للإستروجين، مما يشير إلى إمكاناته كعامل علاجي جديد. هدفت هذه الدراسة إلى تقييم الآثار الوقائية للريسفيراترول على وظيفة المبيض وتطور الانتباذ البطاني الرحمي المستحدث في نموذج الجرذان، مع التركيز على إشارات الأستروجين، والاستجابات المناعية-الالتهابية، واضطرابات التخثر، والتغيرات النسيجية. **المنهجية:** جرى استحداث الانتباذ البطاني الرحمي لدى إناث جرذان بالغة عن طريق زراعة أنسجة بطانة الرحم المأخوذة من جرذان مانحة إلى جرذان مستقبلة، وقُسِّمت الحيوانات المستقبلة الى ثلاث مجموعات: جرذان غير معالجة (END)، وجرذان معالجة بالناقل (END+DMSO)، وجرذان معالجة بالريسفيراترول (END+RES). قيمت مستويات هرمون الإستراديول (E2) في المصل والسائل البريتوني، والنسبة المئوية لخلايا granulocyte وخلايا Mid (الوحيدات، الحَمِضات، والخلايا القاعدية) ومعايير التخثر (عدد الصفائح الدموية، الفيبرينوجين، زمن الثرومبين، وزمن البروثرومبين)، اضافة الى تقييم مقاطع نسيجية من المبيض. **النتائج:** أظهرت الجرذان في مجموعة END ومجموعة END+DMSO ارتفاعًا معنوياً في مستويات هرمون E2، وزيادة معنوية في نسبة خلايا granulocyte وخلايا Mid، وارتفاعاً معنوياً بمعايير التخثر، مع تغيرات ملحوظة في أنسجة المبيض. في حين، أدى إعطاء الريسفيراترول الى الجرذان المصابة بالانتباذ البطاني الرحمي الى عكس التغيرات الضارة وتحسين أنسجة المبيض. **الاستنتاجات:** اجمالاً، يمكن لهذه الدراسة أن تستنتج أن RES خَلَّص السمات المرضية المهمة لـ END عبر التنظيم الهرموني والمناعي والتخثر، مع حماية وظيفة المبيض.

الكلمات المفتاحية: بطانة الرحم، الريسفيراترول، إشارات الإستروجين، الاستجابة الالتهابية، وظيفة المبيض