Research Article

Resveratrol Administration Reverses the Endometriosis-Mediated Outcomes via *Tgfβ* Signaling in Rats

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Abstract | Endometriosis (END) is a chronic inflammatory disorder marked by the existence of endometrial-like tissue in the abnormal sites, resulting in immunological and inflammatory dysregulation. This study was to examine the impact of resveratrol and the AhR antagonist, CH223191, on the modulation of inflammatory and immunological responses in an experimental rat model of endometriosis. Adult female rats and adult male rats were employed in the current study. The female rats were randomly divided into the following: Naïve rats, donor rats for endometrial tissue transplantation, recipient endometriotic rats, and fertile male rats utilized for fertility tests. All endometriotic rats were equally divided into four groups, as follows: END group: Rats in this group served as positive controls and received no treatments; END+RES group: Endometriotic rats received a daily oral dose of resveratrol for four weeks; END+AhR^{-} group: Endometriotic rats received intraperitoneal injections of CH223191 every three days for four weeks; END+DMSO group: Endometriotic rats were given dimethyl sulfoxide (DMSO), which was utilized in the preparation of resveratrol and AhR^{-} treatments intraperitoneally every three days for four weeks, while Naïve rats served as the negative control group. At the endpoint of the experiments, three female rats from each group were mated with two pre-examined fertile male rats for fertility tests. Additionally, nine female rats from each group were euthanized to collect blood for biochemical assessments, peritoneal exudates (PE) for further analysis, spleens for *Tgfβ* gene expression, and uterine horns for histopathological examination. Statistical analysis of collected data revealed a significant ($P<0.05$) reduction in the litter size in all endometriotic rats, except END+RES, in comparison with the control group. Endometriosis in END and END+DMSO rats led to significant ($P<0.05$) upregulation of *Tgfβ* gene expression in splenocytes; these conditions significantly ($P<0.05$) increased TGF-β levels in the circulatory system and PE of these groups. Cancer antigen (CA-125) levels in circulation and PE significantly ($P<0.05$) increased in all endometriotic rats in comparison with the control, except those that were treated with RES did not show statistical change from controls. Upregulated biomarkers TGF-β and CA-125 resulted in deleterious changes in the uterine histological features. In conclusion, this study found that RES could have protective influences in endometriosis pathophysiology via its canonical pathway to suppress inflammatory responses.

Keywords | *Tgf-β*, Resveratrol, AhR, CH223191, Endometriosis, CA-125

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INTRODUCTION

Endometriosis (END) is a persistent, estrogen-dependent inflammatory disorder distinguished by the growth of endometrial-like tissue exterior to the uterine cavity, which comprises active endometrial glands and stroma, leading to chronic pelvic discomfort, dysmenorrhea, and infertility (Allaire *et al.*, 2023; Collie *et al.*, 2025). END

affects around 10% of women of reproductive age (Jones *et al*., 2024). It has been thoroughly examined in experimental animal models, specifically in rats and mice. Rats are often employed in research due to their larger size compared to mice, which simplifies surgical procedures (Zeng *et al*., 2024). Moreover, nonhuman primates, such as baboons, are employed because of their analogous reproductive physiology; although ethical and financial constraints limit their utilization (Kai *et al*., 2023; Apiyo *et al*., 2024). Lesions can be induced by injecting minced endometrial tissue into the peritoneal cavity, closely resembling how lesions form and progress in humans (Taniguchi *et al*., 2020; Alghetaa *et al*., 2023b). Consequently, animal models provide substantial understanding of the etiology and treatment of endometriosis. Molecular pathophysiology of endometriosis could be initiated through various molecules, for example: Transforming growth factor (TGF-β) is a versatile cytokine from the transforming growth factor superfamily, with three different mammalian isoforms: TGF-β1, TGF-β2, and TGF-β3. All normal cells contain TGF-β and its receptors, which can be synthesized by both normal and malignant cells (Zelisko *et al*., 2024). Elevated levels of TGF-β, particularly TGF-β1, have regularly been observed in the peritoneal fluid and endometrial tissue of individuals with endometriosis, promoting the development of the disease. It modulates immunological responses by inhibiting natural killer (NK) cell activity, hence compromising the immune system's ability to eliminate ectopic endometrial cells, facilitating angiogenesis, survival, and implantation of these cells outside the uterine cavity (Soni *et al*., 2019; Adamyan *et al*., 2025; Unser and Monsivais, 2025).

Cancer antigen-125 (CA-125) is a high molecular weight glycoprotein classified within the mucin family. It is mostly expressed on the surface of epithelial cells across several tissues, including the female reproductive, respiratory, and gastrointestinal systems. It is produced by normal cells in adult tissues originating from coelomic and Müllerian epithelia (Pourmadadi *et al*., 2023). It is a recognized tumor-associated antigen that serves as a biomarker in clinical contexts, particularly for the diagnosis and monitoring of ovarian cancer or other benign illnesses (Habib *et al*., 2015; Zhang *et al*., 2021).

Elevated CA-125 levels are observed in individuals with endometriosis, reflecting the inflammatory state and extent of pelvic lesion involvement (Ashish *et al*., 2021; Abbas and Shaheed, 2022; Zubrzycka *et al*., 2023). *Aryl hydrocarbon receptor (AhR)* is a ligand-dependent transcription factor present in various tissues that regulates gene expression in response to a broad spectrum of exogenous or endogenous ligands. It plays a crucial role in regulating immune responses, cellular differentiation, and maintaining physiological homeostasis (Neamah *et al*., 2020; Kou and Dai, 2021; Bustani *et al*., 2025). The nature of the ligand is critical, as it determines whether AhR activation promotes detoxification and homeostasis or induces toxicological effects (Jin *et al*., 2021; Sládeková *et al*., 2023; Alghetaa, 2025). Toxic ligands, such as organochlorine insecticides commonly used in vector control, can provoke dysregulated AhR signaling associated with endocrine disruption, immune dysfunction, neurotoxicity, oxidative stress, and even carcinogenesis (Lima *et al*., 2022; Abbasi *et al*., 2023; Abbasi and Daliri, 2024; Al-Okaily, 2024; Abbasi, 2025a, b; Minacori *et al*., 2025). In contrast, certain natural ligands such as resveratrol, quercetin, tryptophan-derived metabolites, curcumin, and indole-3-carbinol induce protective responses and are vital for xenobiotic detoxification (Abdulla and Al-Okaily, 2022; Ahmed and Mohammed, 2022a, b; Sládeková *et al*., 2023; Al-Okaily, 2024; Bahman *et al*., 2024; Bustani and Alghetaa, 2025).

In the context of endometriosis, AhR interfaces with several signaling pathways, including hormonal and inflammatory cascades, thereby influencing disease pathophysiology (Huang *et al*., 2022; Grishanova *et al*., 2023; Gawron *et al*., 2024). Modulating AhR activity through agonist or antagonist molecules may influence key mechanisms underlying disease progression, including inflammation, immune dysregulation, abnormal cell proliferation, and oxidative damage (Ahmed and Mohammed, 2022b; Bahman *et al*., 2024; Mosa *et al*., 2024; Alabsawy and Alghetaa, 2025; Bustani *et al*., 2025). To date, there is no definitive cure for endometriosis; current therapeutic strategies focus primarily on alleviating symptoms and/or its related infertility (Hamilton *et al*., 2024; Parmar *et al*., 2025). Resveratrol (3, 5, 4'-trihydroxystilbene) (RES) is a naturally occurring polyphenolic compound belonging to the stilbene family. It is present in diverse dietary sources, including grapes, red wine, peanuts, berries, and particularly in medicinal herbs. RES has garnered considerable interest due to its wide range of biological functions and potential therapeutic applications (Khayoon and Al-Rekabi, 2020; Abdulla and Al-Okaily, 2022; Prakash *et al*., 2024; Alabsawy and Alghetaa, 2025; Azargoonjahromi *et al*., 2025).

In the context of END, resveratrol offers a multifaceted therapeutic approach in dose-dependent fashion by attenuating inflammation, oxidative stress, cellular proliferation, and angiogenesis, while simultaneously enhancing apoptosis and modulating estrogenic activity (Mukherjee *et al*., 2010; Alghetaa *et al*., 2021, 2023a, b; Dymanowska-Dyjak *et al*., 2024; Gołąbek-Grenda *et al*., 2024; Sienko *et al*., 2024; Verhoog and Spies, 2024). Accordingly, this study aimed to explore the effects of resveratrol and AhR antagonists on inflammatory markers and reproductive outcomes in a rat model of endometriosis.

MATERIALS AND METHODS

Experimental animals

This study has been conducted in the laboratory and animal house of the College of Veterinary Medicine University of Baghdad. Eighty-four adult female rats along with 10 adult male rats (*Rattus norvegicus*) both sexes were 8-10 weeks old and weighed about 180-220g at the start point of the experiments. All animals were housed in specific pathogen-free conditions, including a temperature-controlled environment (22±2°C) and a 12-hour light/dark cycle. The animals have been provided with free access to standard food and water. The experimental design adhered to the ethical guidelines established by the Institutional Animal Care and Use Committee at the College of Veterinary Medicine, University of Baghdad, and received animal ethical approval (AUP# P.G.407), which complies with International Standards for the Care and Use of Laboratory Animals. The animals were randomly divided into the following groups: Naïve group (n=12 rats), donors for endometrial tissue transplantation (n=24 rats), recipients (n=48 rats) endometriotic rats and additional fertility-confirmed male rats (n=10) which were employed for fertility tests. Before any experiment performance, all rats were maintained for a two-week acclimatization period.

Induction of experimental endometriosis

Endometriosis (END) was induced using the methodology outlined by (Hirata *et al*., 2005; Fattori *et al*., 2020; Alghetaa *et al*., 2023b), with minor modifications (Figure 1). After a period of acclimation, donor rats received two subcutaneous injections of 0.6 mg/kg estradiol benzoate (E2) with a three-day interval to promote the growth and proliferation of endometrial tissue (Abdel-Hamid *et al*., 2019). On the following day of last E2 treatment, the donor rats were anesthetized by intraperitoneal injection of a ketamine-xylazine mixture (Irwin *et al*., 2023), then euthanized by cervical dislocation after the toe-pinch reflex confirmation test was applied.

Euthanized donor rats undergo a midline laparotomy to expose and excise the uterine horns, which are subsequently placed in a sterile petri dish containing warm phosphate buffered saline (PBS). The horns were longitudinally incised with fine scissors, and the endometrial layer was gently peeled using fine forceps. The collected layer was subsequently immersed in sterile PBS and chopped into small fragments (about 1 mm^2) with a fine scalpel, after which about 50mg of the endometrial tissue fragments were suspended in sterile PBS before being delivered into the peritoneal cavity of recipient rats as demonstrated in Figure 1 (Alghetaa *et al*., 2023b).

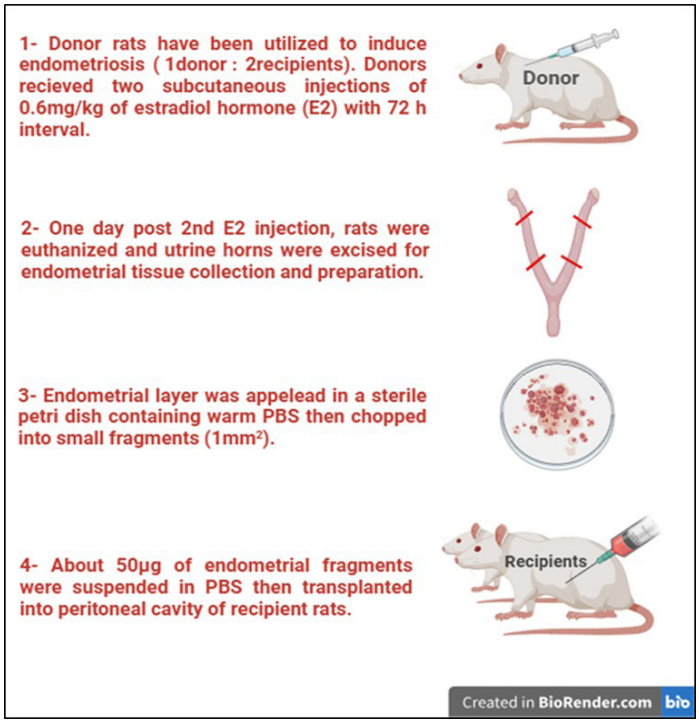

Figure 1: Illustrates the experimental endometriosis induction in rats, created in (http://Biorender.com).

One donor rat was utilized for every two recipient rats to induce endometriosis in all endometriotic groups. All rats having endometrial transplants were treated with different compounds (AhR agonist and antagonist) in accordance with the experimental design, which will be discussed later, commencing the day following transplantation. However, Naïve rats received only an intraperitoneal injection of 500µL PBS.

Animals grouping

- Naïve group: non-endometriotic rats (n=12) served as a negative control group.
- Endometriotic groups: endometriosis-induced rats (n=48) were divided into four subgroups, as follows:
- END group: These endometriotic rats received no treatments and served as positive control.
- END+RES group: Endometriotic rats received a daily oral dose of RES at 100mg/kg for four weeks (Alghetaa *et al*., 2023a).
- END+AhR$^-$ group: Endometriotic rats received intraperitoneal injections of CH223191 at a dosage of 10mg/kg in a volume of 0.1ml/100g (Bustani *et al*., 2024) every three days for four weeks.
- END+DMSO group: Endometriotic rats received dimethyl sulfoxide (DMSO) as the vehicle for the AhR antagonist intraperitoneally at a volume of 0.1 ml/100g b.w., the equivalent volume and concentration that was used for preparation of AhR treatment with three-day intervals for four weeks to normalize any biological effects it may cause (Dawood and Alghetaa, 2023; Bustani *et al*., 2024; Alabsawy and Alghetaa, 2025).

Table 1: Transforming growth factor-beta (*Tgfβ*), and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*) primers.

Gene	Forward '5-3'	Reverse '5-3'	NCBI accession No.
Tgfβ	AGG GCT ACC ATG CCA ACT TC	CCA CGT AGT AGA CGA TGG GC	NM_017008.4
Gapdh	AGA GAC AGC CGC ATC TTC TT	ATG AAG GGG TCG TTG ATG GC	NM_021578.2

Preparation of resveratrol (RES) and AhR antagonist, CH223191 (AhR⁻)

The current study utilized RES powder with a purity of ≥ 98% and AhR antagonist, CH223191 powder with a purity of ≥ 95%, both purchased from Hebei Guanlang Biotechnology, China. The powders were prepared by dissolving them in DMSO and then diluting the solution with distilled water to achieve the appropriate working concentration (Dawood and Alghetaa, 2023; K-Aghetaa et al., 2023; Shniakat *et al*., 2023; Alabsawy and Alghetaa, 2025).

Litter size (pups/dam) index

For fertility assessment, three females from each experimental group were mated with two fertile males for 7 days. Then the number of offspring per female was recorded (Calisir *et al*., 2023; Yugesh *et al*., 2023).

Euthanasia and sample collection

At the end of the experiments, nine rats from each group were euthanized by an overdose of a xylazine-ketamine combination before collection of uterine horn for histopathological examination, blood for biochemical assessments, and peritoneal exudates for further downstream analysis. The spleen was collected as well for gene expression studies.

Gene expression investigation

Spleen tissue was harvested, and approximately 10mg tissue was cut and mechanically smashed and then placed in a tube containing 3ml of RNAlater solution, and then frozen at -20˚C until processed to extract the total RNA and evaluate the gene expression of *Tgfβ* (Ferreira *et al*., 2022). Utilizing quantitative real-time PCR (qRT-PCR) with specific primers (Table 1) and *Gapdh* as the housekeeping gene. The levels of normalized gene expression were calculated using the ΔΔCt method.

Biochemical tests

Blood samples were collected via cardiac puncture and kept in gel tubes for serum separation for assessing circulatory levels of transforming growth factor-beta (TGF-β) and cancer antigen-125 (CA-125).

Peritoneal exudate examination

Peritoneal exudate (PE) was collected for evaluating the TGF-β and CA-125 biomarkers. Briefly, the abdominal skin of euthanized animals was removed to expose the peritoneal sac, then approximately ten ml of PBS was intraperitoneally injected, and the animal was thoroughly rolled for several minutes to suspend all the peritoneal exudates. A small surgical incision was made to allow the peritoneal suspension to be leaked out in a petri-dish prior to its transfer to a conical tube for the centrifugation process. Supernatants were isolated in new Eppendorf tubes to be frozen until the analysis of the aforementioned biomarkers (Alghetaa *et al*., 2023b).

Enzyme linked immunosorbent analysis (ELISA)

TGF-β (BT-lab kit, China) and CA-125 (BT-lab kit, China) were assessed in the serum and PE of experimental animals at the endpoint of all experiments according to each kit's manufacturer protocol (Abbasi and Moemenbellah-Fard, 2025).

Histopathological findings examination

The left uterine horn was dissected and preserved in 10% neutral-buffered formalin for histopathological assessments (Suvarna *et al*., 2019).

Statistical analysis

Data were analyzed using GraphPad Prism software (Version 10, 2024; San Diego, CA, USA; https://www.graphpad.com). One-way analysis of variance (ANOVA), Tukey's multiple comparisons test was employed to compare group means. Furthermore, to assess the equality of variances across the multiple groups in One-way ANOVA, Brown-Forsythe test was used as well. Whilst, to assess the equality of variances among different samples, Bartlett's test has been employed too. QQ-plots were used to assess the normality of samples distribution. P-value less than 0.05 were considered statistically significant. Statistical significance in the figures is indicated as follows: *P<0.05, **P<0.01, ***P<0.001 and #P<0.0001. For further information about the statistical methodology, Supplementary Tables S1-S6 are available.

RESULTS

Litter size (pups/dam)

The results of litter size (pups/dam) showed a significant decrease (P<0.05) in the END and END+DMSO groups in comparison with the Naïve, END+RES, and END+AhR⁻ groups. No significant differences were observed among the Naïve, END+RES and END+AhR⁻ groups, nor among the END, END+AhR⁻, and END+DMSO groups, as illustrated in Figure 2.

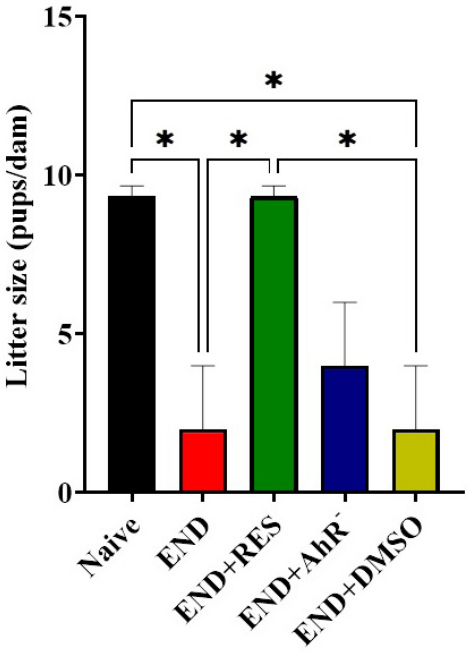

Figure 2: Effects of endometriosis and therapeutic interventions on reproductive outcomes in rats, measured by litter size (pups/dam) index. Naïve group: non-endometriotic rats (negative control). END group: untreated endometriotic rats (positive control). END+RES group: Endometriotic rats were treated with resveratrol (100 mg/kg/day, orally) for four weeks. END+AhR⁻ group: Endometriotic rats were treated with the AhR antagonist CH223191 (10 mg/kg, intraperitoneally, every three days) for four weeks. END+DMSO group: Endometriotic rats received administered vehicle control (DMSO, 0.1 ml/100g body weight, intraperitoneally, every three days) for four weeks. Statistical analysis was performed using One-way ANOVA followed by Tukey's multiple comparisons test (Supplementary Table S1). Significant differences depicted as: *P<0.05.

Expression of transforming growth factor-beta (*Tgfβ*) in splenocytes and translated protein in circulatory and peritoneal fluids

The results of *Tgfβ* gene expression in splenocytes statistically showed a significant (P<0.05) increase in the END group in comparison to all other groups (Figure 3A). Figure 3B, C illustrate that the circulatory and peritoneal exudate concentration (ng/L) of TGF-β protein across the experimental groups was significantly (P<0.05) elevated in the END and END+DMSO groups in comparison with all other groups. Endometriotic rats treated with RES showed a reduction of circulatory and PE TGF-β levels to nearby Naïve group levels (Figure 3B, C). However, blocking of AhR in the END+AhR⁻ group led to significant (P<0.05) upregulation of PE protein in comparison with the Naïve and END+RES groups (Figure 3C) but insignificant changes in circulatory TGF-β in the same compared groups (Figure 3B).

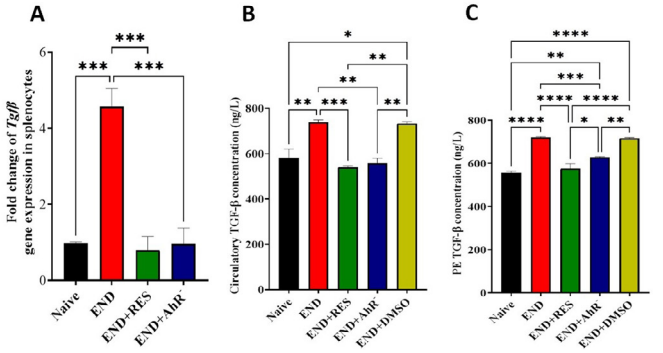

Figure 3: Modulation of *Tgfβ* gene expression and *TGF-β* protein levels, following AhR signaling manipulation by using AhR ligands for four weeks in endometrial tissue transplanted rats (n=5). Naïve group: non-endometriotic rats (negative control). END group: untreated endometriotic rats (positive control). END+RES group: Endometriotic rats were treated with resveratrol (100 mg/kg/day, orally) for four weeks. END+AhR⁻ group: Endometriotic rats were treated with the AhR antagonist CH223191 (10 mg/kg, intraperitoneally, every three days) for four weeks. END+DMSO group: Endometriotic rats received administered vehicle control (DMSO, 0.1 ml/100g body weight, intraperitoneally, every three days) for four weeks. (A) *Tgfβ* gene expression in splenocytes. (B) circulatory TGF-β concentration (ng/L), and **C)** TGF-β concentrations in peritoneal exudate (PE, ng/L). Statistical analysis was performed using One-way ANOVA followed by Tukey's multiple comparisons test (Supplementary Table S2-S4). Significant differences are depicted as: *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001.

Levels of cancer antigen-125 (CA-125) in serum and PE

The statistical analysis of CA-125 concentrations (U/ml) in the circulation and peritoneal exudate of the experimental groups is illustrated in (Figure 4A, B). CA-125 showed significant (P<0.05) increases in the END, END+AhR⁻, and END+DMSO groups in comparison with the Naïve and END+RES groups. However, neither significant distinctions were observed between the Naïve and END+RES groups nor among the END, END+AhR⁻, and END+DMSO groups.

Histopathological investigation of the uterine horn

Histopathological examination of uterine horn cross-sections stained with hematoxylin and eosin (H and E) revealed notable pathological alterations in the END, END+AhR⁻, and END+DMSO groups (Figures 6, 8, and 9, respectively), in contrast to the Naïve and END+RES groups (Figures 5 and 7, respectively). Observed hyperplasia of endometrial and stromal cells, vacuolar degeneration in several stromal regions, infiltration of inflammatory cells around endometrial glands, and neutrophil aggregation

within endometrial glands. These findings are indicative of an inflammatory response and endometrial tissue remodeling, hallmark features of endometriosis in the employed experimental model.

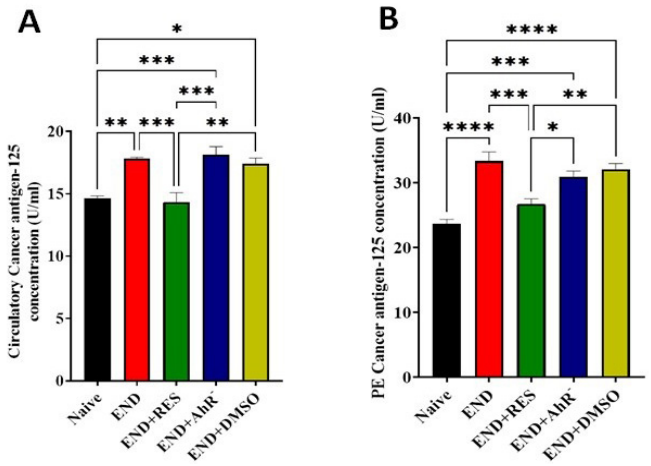

Figure 4: Influences of CA-125 protein levels, following AhR signaling manipulation by using AhR ligands for four weeks in endometrial tissue transplanted rats (n=5). Naïve group: non-endometriotic rats (negative control). END group: untreated endometriotic rats (positive control). END+RES group: Endometriotic rats were treated with resveratrol (100 mg/kg/day, orally) for four weeks. END+AhR⁻ group: Endometriotic rats were treated with the AhR antagonist CH223191 (10 mg/kg, intraperitoneally, every three days) for four weeks. END+DMSO group: Endometriotic rats received administered vehicle control (DMSO, 0.1 ml/100g body weight, intraperitoneally, every three days) for four weeks. (A) circulatory CA-125 concentration (U/ml), and (B) CA-125 concentrations in peritoneal exudate (PE, U/ml). Statistical analysis was performed using One-way ANOVA followed by Tukey's multiple comparisons test (Supplementary Table S5, S6). Significant differences are depicted as: *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001.

DISCUSSION

Immune-inflammatory dysregulation and aberrant angiogenesis are implicated in the pathogenesis of endometriosis (END), contributing to both reproductive dysfunction and histopathological abnormalities across human and animal models (Wahl *et al*., 2020; Bonavina and Taylor, 2022; Alghetaa *et al*., 2023b; Viganò *et al*., 2024). In our experimental END model, we observed significant impairments in reproductive performance, specifically a reduction in litter size, along with elevated levels of TGF-β and CA-125 in both serum and/or peritoneal exudate (PE), and distinct pathological changes in uterine horn histology. These findings support and extend previous studies reporting a negative correlation between elevated CA-125 and TGF-β levels and fertility in endometriosis patients (Lin *et al*., 2018; Gica *et al*., 2020). The observed reproductive dysfunctions in the END, END+AhR⁻, and END+DMSO groups is likely a multifactorial outcome of chronic inflammation, oxidative stress, and hormonal imbalance, which are hallmarks of END that adversely affect ovulatory function, endometrial receptivity, and embryo implantation (Omer *et al*., 2017; Kitajima, 2022; Rosales, 2022; Alghetaa *et al*., 2023b; Leone Roberti Maggiore *et al*., 2024).

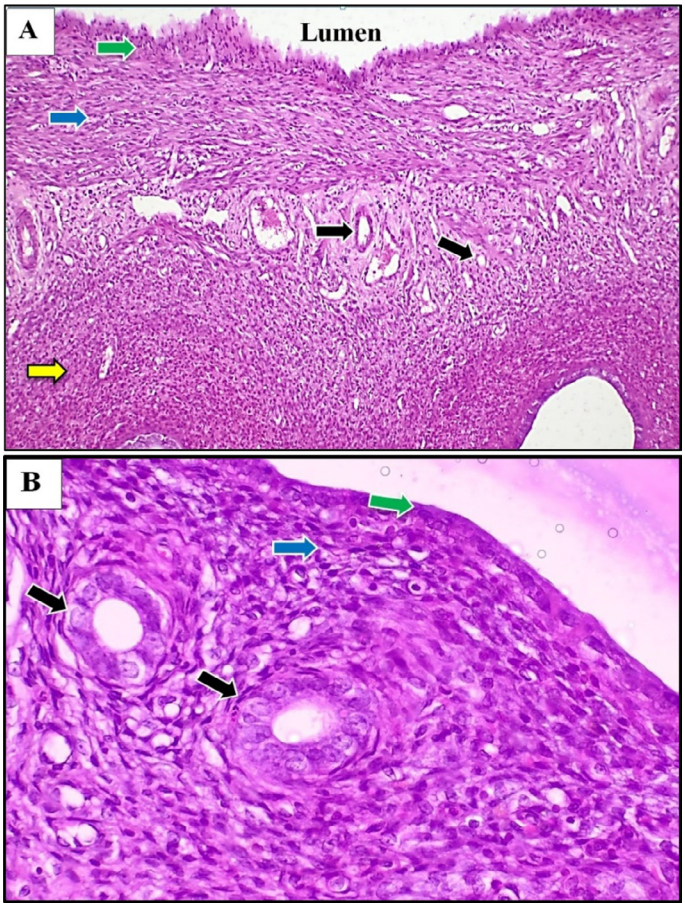

Figure 5: Photomicrograph section in uterine horn of Naïve rats (A and B). Normal myometrium (yellow arrow), normal endometrial glands (black arrows), normal endometrium (blue arrows), and well-organized luminal epithelium (green arrows). All sections are stained with H and E. A: examined under 100x and B: examined under 400x.

TGF-β is one of the mediators that is involved, and it is particularly important for promoting immunosuppressive and fibrotic processes in the endometriotic environment. Increased TGF-β levels have repeatedly been associated with survival, invasion, and angiogenesis of ectopic lesions (Soni *et al*., 2019; Nanda *et al*., 2020; Garcia Garcia *et al*., 2022). In our investigation, the increase correlated with unfavorable histological characteristics, indicating a mechanistic association between TGF-β overexpression and tissue remodeling in the uterine horn. Furthermore,

TGF-β, in synergy with IL-6, facilitates the differentiation of naïve CD4+ T cells into Th17 cells, hence enhancing IL-17 production, which is a significant factor in inflammatory amplification and lesion persistence (Shi *et al*., 2022; Sisnett *et al*., 2024; Adamyan *et al*., 2025).

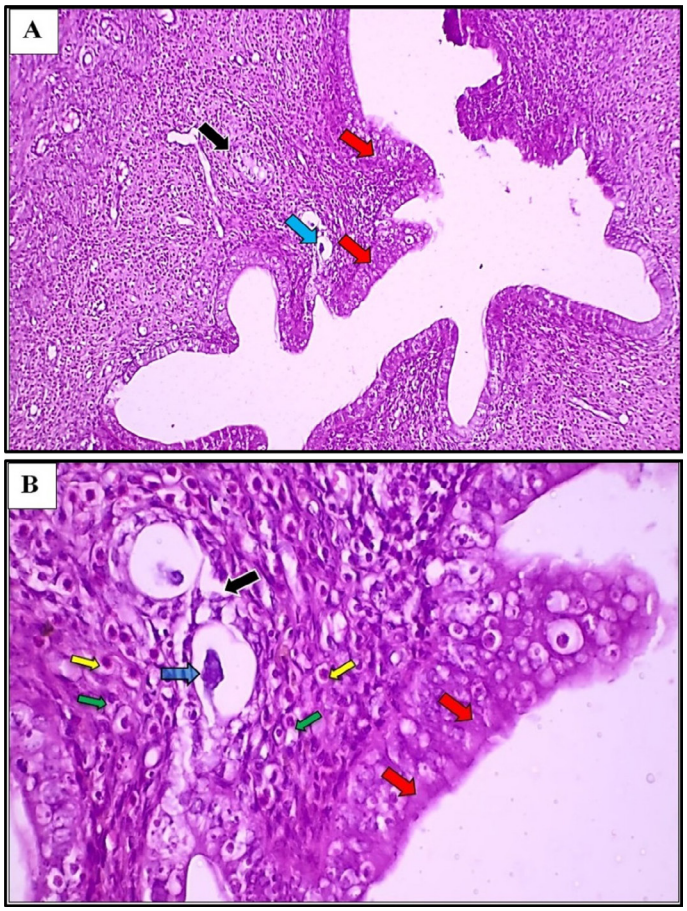

Figure 6: Photomicrograph section in uterine horn of END rats (A and B). Vacuolar degeneration in some epithelial cells lining the tubular glands (black arrows), endometrium hyperplasia (red arrows), with inflammatory cells infiltration particularly monocytes (green arrows) and eosinophil (yellow arrows) and aggregation of neutrophils within the lumen of affected glands (blue arrows). All sections are stained with H and E. A: examined under 100x and B: examined under 400x.

Our findings corroborate previous studies indicating increased IL-17 levels in endometriosis patients, which upregulate the expression of anti-apoptotic genes (e.g., Bcl-2, MCL1), suppress NK cell cytotoxicity, and activate ERK1/2 signaling, hence facilitating ectopic cell survival (Abbas and Shaheed, 2022; Kang *et al*., 2023). TGF-β also activates the SMAD pathway and inhibits the tumor suppressor PTEN, thereby increasing EMT markers and adhesion molecules that facilitate lesion invasiveness and fibrogenesis (Young *et al*., 2017; Soni *et al*., 2019; Zubrzycka *et al*., 2023b). Conversely, inhibition of TGF-β and NF-κB signaling has been shown to reduce fibrosis and lesion burden in deep endometriosis, making

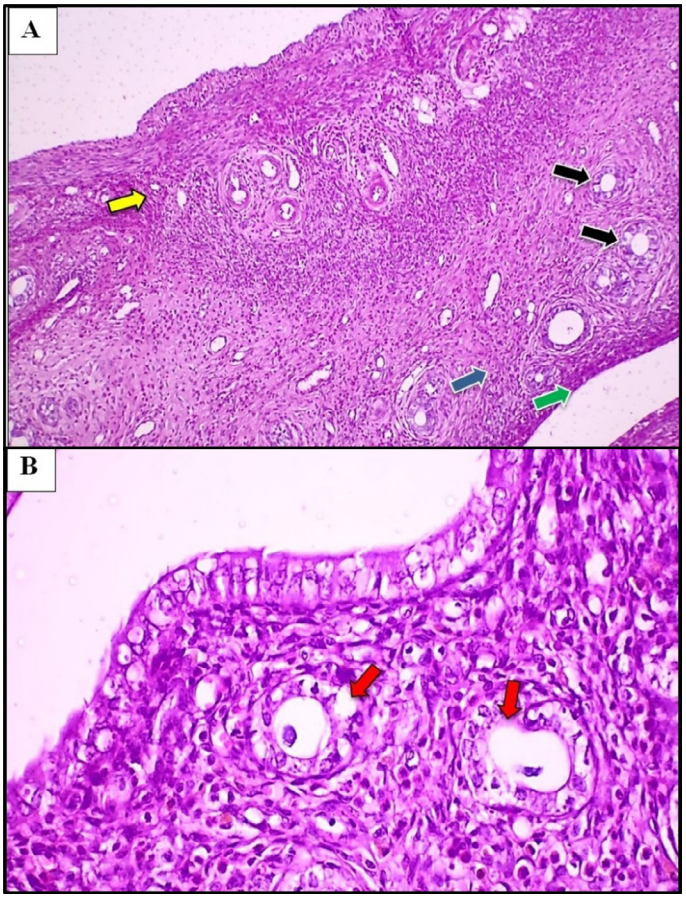

Figure 7: Photomicrograph sections in uterine horn of END+RES rats (A and B). Normal myometrium (yellow arrow), normal endometrial glands (black arrows), normal endometrium (blue arrow), and well-organized luminal epithelium (green arrow). Mild destruction of some epithelial cells lining uterine glands (red arrows). All sections are stained with H and E. A: examined under 100x and B: examined under 400x.

these pathways possible targets for treatment (Zhou *et al*., 2019). Although cancer antigen 125 (CA-125) exhibits limited sensitivity and specificity and is elevated in multiple disorders, it remains a recognized biomarker. When utilized alongside other diagnostic methods, it assists in differentiating individual with endometriosis from those without the condition (Tian *et al*., 2020; Zamzam *et al*., 2023; Feduniw *et al*., 2024). Our observation of elevated CA-125 in END-related groups, particularly those untreated with resveratrol, supports its continued relevance in preclinical evaluation of disease progression (Irungu *et al*., 2019; Szubert *et al*., 2023). Histological examination revealed marked abnormalities in the END, END+AhR^{-}, and END+DMSO groups, including vacuolar degeneration, irregular glandular architecture, and pronounced infiltration of inflammatory cells (especially eosinophils and monocytes). These findings reflect the oxidative stress and cytokine-driven inflammation associated with END (Ansariniya *et al*., 2022; Sumera *et al*., 2022). As well as the histological distortions that

may be associated with elevated TGF-β levels, further implicating this cytokine in immune responses and fibrotic remodeling in the tissue of the uterine horn (Szubert *et al.*, 2023; Kula *et al.*, 2024). Interestingly, this study showed that the used vehicle, DMSO has no distinct biological effects in endometriotic rats, this streamed with previous studies (Dawood and Alghetaa, 2023).

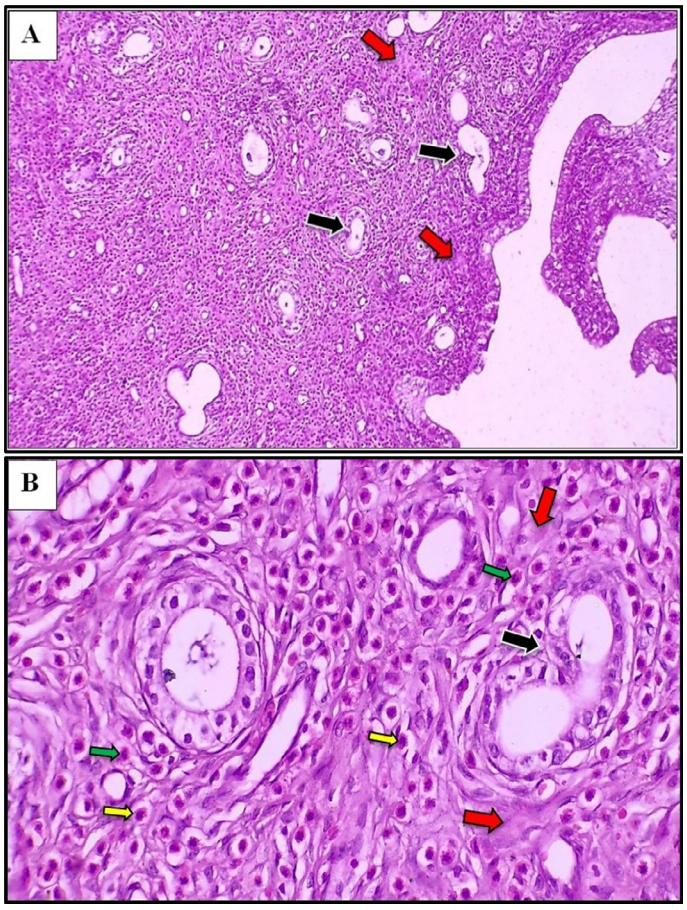

Figure 8: Photomicrograph sections in uterine horn of END+AhR^{-} rats (A and B). Irregular dilated endometrial glands (black arrows), endometrial and stromal hyperplasia (red arrows) with highly infiltrated inflammatory cells especially monocytes (green arrows) and eosinophils (yellow arrows). All sections are stained with H and E. A: examined under 100x and B: examined under 400x.

The present study employed CH223191, a selective AhR antagonist (AhR^{-}), and resveratrol (RES), a natural polyphenolic compound known to function as AhR agonist, to evaluate the effects of AhR modulation on key pathophysiological parameters associated with endometriosis. The utilization of AhR agonist or antagonist molecules influences several hallmarks of distinct diseases and modifies their progression (Abdulla *et al.*, 2021; Rejano-Gordillo *et al.*, 2022). By disrupting and controlling several critical pathophysiological processes, including immunological responses, inflammation, xenobiotic metabolism, angiogenesis, cell survival, and proliferation

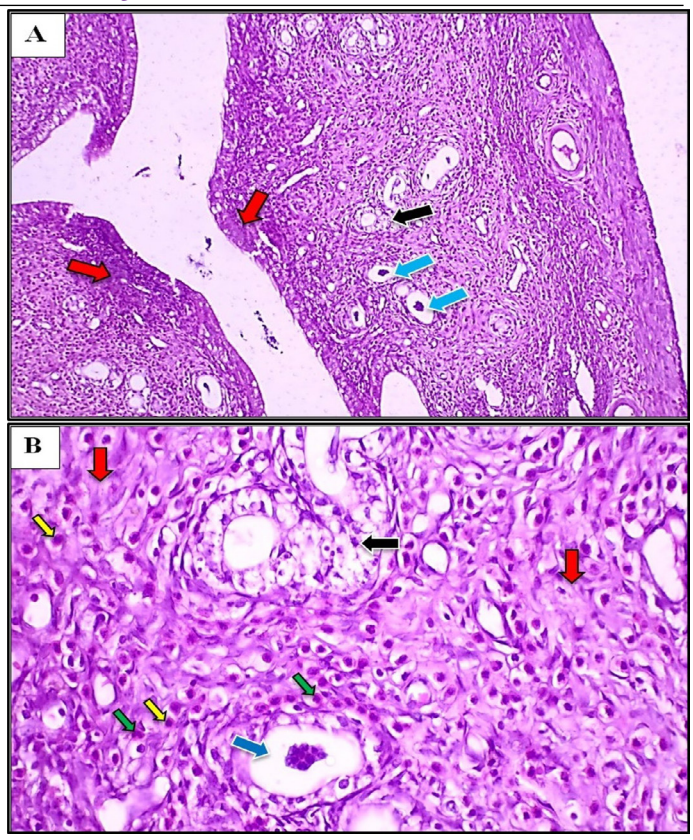

Figure 9: Photomicrograph sections in uterine horn of END+DMSO rats (A and B). Vacuolar degeneration in some stromal cells lining the endometrial glands (black arrows), endometrium hyperplasia (red arrows) with inflammatory cells infiltration, particularly monocytes (green arrows) and eosinophil (yellow arrows) and aggregation of neutrophils in the lumen of affected glands (blue arrows). H and E stains. A: Examined under 100x and B: examined under 400x.

(Neamah *et al.*, 2019; Hu *et al.*, 2023; Ichisaka *et al.*, 2024; Stockinger *et al.*, 2024). CH223191 binds to the AhR ligand-binding domain, competing with other ligands for AhR binding and also suppressing AhR signaling pathways (Kim *et al.*, 2022; Bustani *et al.*, 2024, 2025). By contrast, some research suggests that RES has a high affinity to bind with AhR and compete with other ligands to regulate AhR signaling as well as modulate the effects of AhR activation and offer a protective mechanism against potential detrimental effects (Lee *et al.*, 2020; Pinto *et al.*, 2023; Szaefer *et al.*, 2024). RES exerted marked protective effects, including reductions in TGF-β and CA-125 levels, histological restoration of uterine horn, and improved reproductive outcomes. These findings are consistent with prior research demonstrating that the RES can inhibit TGF-β signaling to suppress the proliferation and migration of cancer cells (Ashrafizadeh *et al.*, 2020). RES can decrease levels of IL-17 and interferon-gamma (IFN-γ) as well as suppress the angiogenesis-related genes such as VEGF and MMP-9, so obstructing the formation of new blood vessels and limiting the growth and proliferation of

endometrial cells (Alghetaa *et al*., 2018; Jiang *et al*., 2023; Al-Khaqani and Mohammed, 2024; Sienko *et al*., 2024). Moreover, the efficacy of RES as an anti-inflammatory, anti-oxidative, anti-proliferative, anti-angiogenic, anti-invasive, anti-adhesive, and pro-apoptotic agent can inhibit disease progression and prevent dissemination of endometrial lesions (Alharris *et al*., 2018, 2022; Khudair and Al-Okaily, 2022). Finally, our findings align with recent evidence indicating that AhR-targeted therapeutics, contingent upon ligand specificity and context, may either worsen or improve disease, highlighting the intricacy of this signaling pathway.

CONCLUSION

The findings of this study suggest that TGF-β signaling dysregulation implicated in the progression of endometriosis, as evidenced by increased *Tgfβ* gene expression and elevated inflammatory markers in END-induced rats. Additionally, the noted decrease in litter size among END and END+DMSO rats may indicate a considerable influence of systemic inflammation on reproductive outcomes. Resveratrol administration exhibited effectively reduced *Tgfβ* gene expression in splenocytes and lowered TGF-β and CA-125 levels in both serum and peritoneal fluid, underscoring its potential attenuated inflammatory, fibrotic, and angiogenic hallmarks of endometriosis. These results support the concept that focused modulation of AhR activity may be an effective method for controlling endometriosis, especially through agents that exhibit anti-inflammatory, anti-proliferative, and pro-apoptotic characteristics. Further investigations are necessary to clarify the molecular relationships between AhR and critical cytokine signaling pathways, as well as to examine the therapeutic applicability of AhR-targeted therapy. Furthermore, the integration of AhR modulators with existing or novel medications may produce synergistic effects that improve disease resolution and reproductive recovery in endometriosis.

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NOVELTY STATEMENT

This research article provides deep insight into the mechanistic roles of resveratrol in modulation of endometriosis pathophysiology.

AUTHOR'S CONTRIBUTION

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.

Data availability

The data is available from the corresponding author in reasonable request.

Abbreviations

AhR, Aryl Hydrocarbon Receptor; AhR^{-}, Aryl Hydrocarbon Receptor knocked down; Bcl-2, B-cell lymphoma 2; CA-125, cancer antigen-125; DMSO, dimethyl sulfoxide; EMT, epithelial-mesenchymal transition; END, Endometriosis; ERK 1/2, Extracellular Signal-Regulated Kinases 1/2; Gapdh, glyceraldehyde-3-phosphate dehydrogenase; IFN-γ, interferon-gamma; MCL1, myeloid cell leukemia-1; MCT, Monocarboxylate Transporters; MMP, matrix metalloproteinase; NF-kB, Nuclear Factor Kappa; NK, Natural Killer Cell; PE, Peritoneal exudate; RES, Resveratrol; VEGF, Vascular Endothelial Growth Factor.

Generative AI and AI-assisted technology statement

Authors disclose that they have not used any generative artificial intelligence or AI-assisted technology in forming this manuscript nor in generating its data.

Conflict of interest

The authors have declared no conflict of interest.

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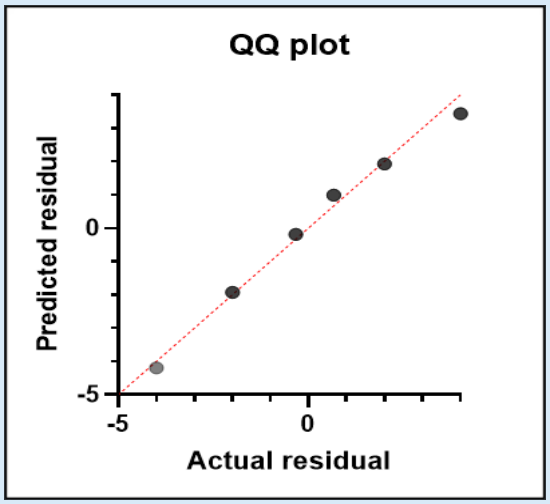
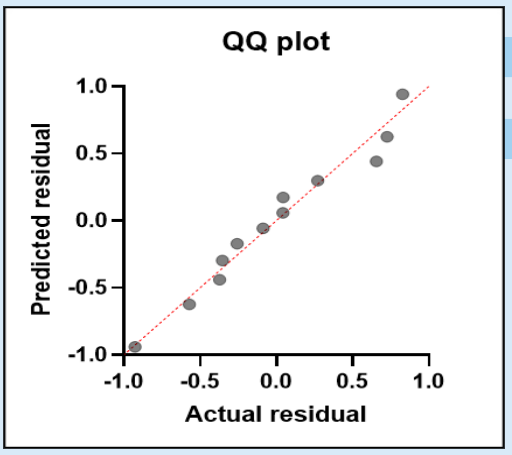
Supplementary Table S1: Statistical analysis of litter size.

Number of families	**1**							
Number of comparisons per family	**10**							
Alpha	**0.05**							
Tukey's multiple comparisons test	**Mean Diff.**	**95.00% CI of diff.**	**Below threshold?**	**Summary**	**Adjusted P value**			
Naive vs. END	7.333	0.05648 to 14.61	Yes	*	0.0481	A-B		
Naive vs. END+RES	0	-7.277 to 7.277	No	ns	>0.9999	A-C		
Naive vs. END+AhR$^-$	5.333	-1.944 to 12.61	No	ns	0.189	A-D		
Naive vs. END+DMSO	7.333	0.05648 to 14.61	Yes	*	0.0481	A-E		
END vs. END+RES	-7.333	-14.61 to -0.05648	Yes	*	0.0481	B-C		
END vs. END+AhR$^-$	-2	-9.277 to 5.277	No	ns	0.8888	B-D		
END vs. END+DMSO	0	-7.277 to 7.277	No	ns	>0.9999	B-E		
END+RES vs. END+AhR$^-$	5.333	-1.944 to 12.61	No	ns	0.189	C-D		
END+RES vs. END+DMSO	7.333	0.05648 to 14.61	Yes	*	0.0481	C-E		
END+AhR$^-$ vs. END+DMSO	2	-5.277 to 9.277	No	ns	0.8888	D-E		
Test details	**Mean 1**	**Mean 2**	**Mean Diff.**	**SE of diff.**	**n1**	**n2**	**q**	**DF**
Naive vs. END	9.333	2	7.333	2.211	3	3	4.69	10
Naive vs. END+RES	9.333	9.333	0	2.211	3	3	0	10
Naive vs. END+AhR$^-$	9.333	4	5.333	2.211	3	3	3.411	10
Naive vs. END+DMSO	9.333	2	7.333	2.211	3	3	4.69	10
END vs. END+RES	2	9.333	-7.333	2.211	3	3	4.69	10
END vs. END+AhR$^-$	2	4	-2	2.211	3	3	1.279	10
END vs. END+DMSO	2	2	0	2.211	3	3	0	10
END+RES vs. END+AhR$^-$	9.333	4	5.333	2.211	3	3	3.411	10
END+RES vs. END+DMSO	9.333	2	7.333	2.211	3	3	4.69	10
END+AhR$^-$ vs. END+DMSO	4	2	2	2.211	3	3	1.279	10
Compact letter display								
Naive	A							
END+RES	A							
END+AhR$^-$	A B							
END	B							
END+DMSO	B							



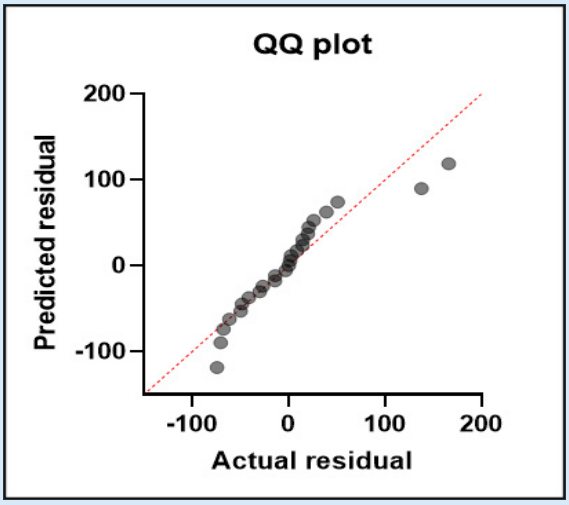
Supplementary Table S2: Statistical analysis of Tgfb gene expression.

Number of families	**1**						
Number of comparisons per family	**6**						
Alpha	**0.05**						
Tukey's multiple comparisons test	**Mean Diff.**	**95.00% CI of diff.**	**Below threshold?**	**Summary**	**Adjusted P Value**		
Naive vs. END	-3.599	-5.264 to -1.934	Yes	***	0.0006	A-B	
Naive vs. END+RES	0.1777	-1.487 to 1.842	No	ns	0.9853	A-C	
Naive vs. END+AhR$^-$	0.01767	-1.647 to 1.682	No	ns	>0.9999	A-D	
END vs. END+RES	3.777	2.112 to 5.441	Yes	***	0.0004	B-C	
END vs. END+AhR$^-$	3.617	1.952 to 5.281	Yes	***	0.0005	B-D	
END+RES vs. END+AhR$^-$	-0.16	-1.825 to 1.505	No	ns	0.9891	C-D	
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	n1	n2	q
Naive vs. END	0.9743	4.573	-3.599	0.5199	3	3	9.79
Naive vs. END+RES	0.9743	0.7967	0.1777	0.5199	3	3	0.4833
Naive vs. END+AhR$^-$	0.9743	0.9567	0.01767	0.5199	3	3	0.04806
END vs. END+RES	4.573	0.7967	3.777	0.5199	3	3	10.27
END vs. END+AhR$^-$	4.573	0.9567	3.617	0.5199	3	3	9.838
END+RES vs. END+AhR$^-$	0.7967	0.9567	-0.16	0.5199	3	3	0.4352
Compact letter display							
END	A						
Naive	B						
END+AhR$^-$	B						
END+RES	B						



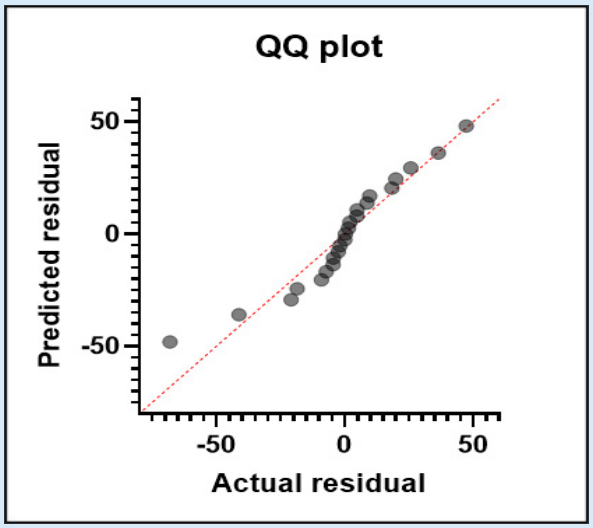
Supplementary Table S3: Statistical analysis of circulatory *Tgfb* concentration.

Number of families	**1**							
Number of comparisons per family	**10**							
Alpha	**0.05**							
Tukey's multiple comparisons test	**Mean Diff.**	**95.00% CI of diff.**	**Below threshold?**	**Summary**	**Adjusted P Value**			
Naive vs. END	-157.7	-268.5 to -46.78	Yes	**	0.0032	A-B		
Naive vs. END+RES	41.39	-69.49 to 152.3	No	ns	0.7958	A-C		
Naive vs. END+AhR$^-$	23.72	-87.17 to 134.6	No	ns	0.9665	A-D		
Naive vs. END+DMSO	-151.9	-282.6 to -21.22	Yes	*	0.0179	A-E		
END vs. END+RES	199.1	79.29 to 318.8	Yes	***	0.0006	B-C		
END vs. END+AhR$^-$	181.4	61.61 to 301.1	Yes	**	0.0017	B-D		
END vs. END+DMSO	5.765	-132.5 to 144.1	No	ns	>0.9999	B-E		
END+RES vs. END+AhR$^-$	-17.68	-137.4 to 102.1	No	ns	0.9915	C-D		
END+RES vs. END+DMSO	-193.3	-331.6 to -54.99	Yes	**	0.0037	C-E		
END+AhR$^-$ vs. END+DMSO	-175.6	-313.9 to -37.32	Yes	**	0.0088	D-E		
Test details	**Mean 1**	**Mean 2**	**Mean Diff.**	**SE of diff.**	**n1**	**n2**	**q**	**DF**
Naive vs. END	580.9	738.6	-157.7	37.06	7	5	6.017	20
Naive vs. END+RES	580.9	539.5	41.39	37.06	7	5	1.58	20
Naive vs. END+AhR$^-$	580.9	557.2	23.72	37.06	7	5	0.9051	20
Naive vs. END+DMSO	580.9	732.8	-151.9	43.67	7	3	4.919	20
END vs. END+RES	738.6	539.5	199.1	40.02	5	5	7.033	20
END vs. END+AhR$^-$	738.6	557.2	181.4	40.02	5	5	6.409	20
END vs. END+DMSO	738.6	732.8	5.765	46.22	5	3	0.1764	20
END+RES vs. END+AhR$^-$	539.5	557.2	-17.68	40.02	5	5	0.6246	20
END+RES vs. END+DMSO	539.5	732.8	-193.3	46.22	5	3	5.915	20
END+AhR$^-$ vs. END+DMSO	557.2	732.8	-175.6	46.22	5	3	5.374	20
Compact letter display								
END	A							
END+DMSO	A							
Naive	B							
END+AhR$^-$	B							
END+RES	B							



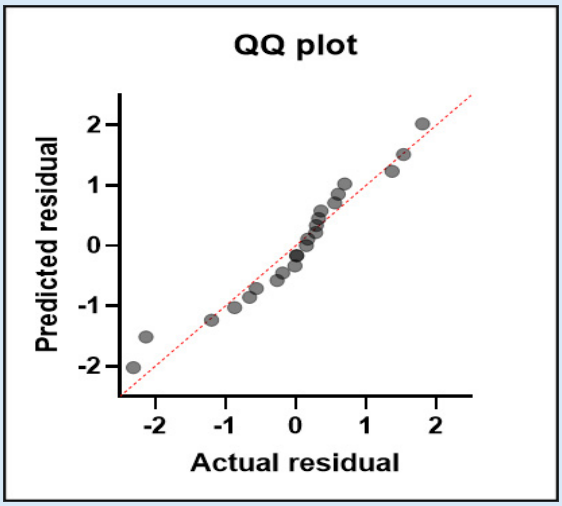
Supplementary Table S4: Statistical analysis of peritoneal exudate Tgfb concentration.

Number of families	**1**							
Number of comparisons per family	**10**							
Alpha	**0.05**							
Tukey's multiple comparisons test	**Mean Diff.**	**95.00% CI of diff.**	**Below threshold?**	**Summary**	**Adjusted P Value**			
Naive vs. END	-164.9	-215.2 to -114.6	Yes	****	<0.0001	A-B		
Naive vs. END+RES	-19.52	-69.84 to 30.80	No	ns	0.766	A-C		
Naive vs. END+AhR$^-$	-73.17	-123.5 to -22.85	Yes	**	0.0028	A-D		
Naive vs. END+DMSO	-161.2	-219.3 to -103.1	Yes	****	<0.0001	A-E		
END vs. END+RES	145.4	95.09 to 195.7	Yes	****	<0.0001	B-C		
END vs. END+AhR$^-$	91.76	41.45 to 142.1	Yes	***	0.0003	B-D		
END vs. END+DMSO	3.688	-54.41 to 61.79	No	ns	0.9997	B-E		
END+RES vs. END+AhR$^-$	-53.64	-104.0 to -3.327	Yes	*	0.0335	C-D		
END+RES vs. END+DMSO	-141.7	-199.8 to -83.62	Yes	****	<0.0001	C-E		
END+AhR$^-$ vs. END+DMSO	-88.08	-146.2 to -29.98	Yes	**	0.0019	D-E		
Test details	**Mean 1**	**Mean 2**	**Mean Diff.**	**SE of diff.**	**n1**	**n2**	**q**	**DF**
Naive vs. END	555.8	720.7	-164.9	16.64	5	5	14.02	18
Naive vs. END+RES	555.8	575.3	-19.52	16.64	5	5	1.659	18
Naive vs. END+AhR$^-$	555.8	629	-73.17	16.64	5	5	6.218	18
Naive vs. END+DMSO	555.8	717.1	-161.2	19.21	5	3	11.87	18
END vs. END+RES	720.7	575.3	145.4	16.64	5	5	12.36	18
END vs. END+AhR$^-$	720.7	629	91.76	16.64	5	5	7.799	18
END vs. END+DMSO	720.7	717.1	3.688	19.21	5	3	0.2714	18
END+RES vs. END+AhR$^-$	575.3	629	-53.64	16.64	5	5	4.559	18
END+RES vs. END+DMSO	575.3	717.1	-141.7	19.21	5	3	10.43	18
END+AhR$^-$ vs. END+DMSO	629	717.1	-88.08	19.21	5	3	6.482	18
Compact letter display								
END	A							
END+DMSO	A							
END+AhR$^-$	B							
END+RES	C							
Naive	C							



Supplementary Table S5: Statistical analysis of circulatory CA-125 concentration.

Number of families	**1**							
Number of comparisons per family	**10**							
Alpha	**0.05**							
Tukey's multiple comparisons test	**Mean Diff.**	**95.00% CI of diff.**	**Below threshold?**	**Summary**	**Adjusted P Value**			
Naive vs. END	-3.173	-5.290 to -1.057	Yes	**	0.0021	A-B		
Naive vs. END+RES	0.315	-1.801 to 2.431	No	ns	0.9908	A-C		
Naive vs. END+AhR$^-$	-3.487	-5.603 to -1.371	Yes	***	0.0008	A-D		
Naive vs. END+DMSO	-2.761	-5.205 to -0.3175	Yes	*	0.0225	A-E		
END vs. END+RES	3.488	1.372 to 5.605	Yes	***	0.0008	B-C		
END vs. END+AhR$^-$	-0.3136	-2.430 to 1.803	No	ns	0.9909	B-D		
END vs. END+DMSO	0.4121	-2.032 to 2.856	No	ns	0.9853	B-E		
END+RES vs. END+AhR$^-$	-3.802	-5.918 to -1.686	Yes	***	0.0003	C-D		
END+RES vs. END+DMSO	-3.076	-5.520 to -0.6326	Yes	**	0.0099	C-E		
END+AhR$^-$ vs. END+DMSO	0.7256	-1.718 to 3.169	No	ns	0.894	D-E		
Test details	**Mean 1**	**Mean 2**	**Mean Diff.**	**SE of diff.**	**n1**	**n2**	**q**	**DF**
Naive vs. END	14.65	17.82	-3.173	0.6999	5	5	6.412	18
Naive vs. END+RES	14.65	14.33	0.315	0.6999	5	5	0.6365	18
Naive vs. END+AhR$^-$	14.65	18.14	-3.487	0.6999	5	5	7.046	18
Naive vs. END+DMSO	14.65	17.41	-2.761	0.8082	5	3	4.832	18
END vs. END+RES	17.82	14.33	3.488	0.6999	5	5	7.049	18
END vs. END+AhR$^-$	17.82	18.14	-0.3136	0.6999	5	5	0.6335	18
END vs. END+DMSO	17.82	17.41	0.4121	0.8082	5	3	0.7211	18
END+RES vs. END+AhR$^-$	14.33	18.14	-3.802	0.6999	5	5	7.682	18
END+RES vs. END+DMSO	14.33	17.41	-3.076	0.8082	5	3	5.383	18
END+AhR$^-$ vs. END+DMSO	18.14	17.41	0.7256	0.8082	5	3	1.27	18
Compact letter display								
END+AhR$^-$	A							
END	A							
END+DMSO	A							
Naive	B							
END+RES	B							



Supplementary Table S6: Statistical analysis of peritoneal exudate CA-125 concentration.

Number of families	**1**						
Number of comparisons per family	**10**						
Alpha	**0.05**						
Tukey's multiple comparisons test	**Mean Diff.**	**95.00% CI of diff.**	**Below threshold?**	**Summary**	**Adjusted P Value**		
Naive vs. END	-9.674	-13.77 to -5.574	Yes	****	<0.0001	A-B	
Naive vs. END+RES	-3.039	-7.138 to 1.060	No	ns	0.2134	A-C	
Naive vs. END+AhR$^-$	-7.254	-11.35 to -3.155	Yes	***	0.0003	A-D	
Naive vs. END+DMSO	-8.382	-12.48 to -4.283	Yes	****	<0.0001	A-E	
END vs. END+RES	6.635	2.535 to 10.73	Yes	***	0.0008	B-C	
END vs. END+AhR$^-$	2.419	-1.680 to 6.519	No	ns	0.4192	B-D	
END vs. END+DMSO	1.291	-2.808 to 5.391	No	ns	0.8768	B-E	
END+RES vs. END+AhR$^-$	-4.215	-8.315 to -0.1160	Yes	*	0.042	C-D	
END+RES vs. END+DMSO	-5.343	-9.443 to -1.244	Yes	**	0.007	C-E	
END+AhR$^-$ vs. END+DMSO	-1.128	-5.227 to 2.971	No	ns	0.9203	D-E	
Test details	**Mean 1**	**Mean 2**	**Mean Diff.**	**SE of diff.**	**n1**	**n2**	**q**	**DF**
Naive vs. END	23.7	33.38	-9.674	1.37	5	5	9.987	20
Naive vs. END+RES	23.7	26.74	-3.039	1.37	5	5	3.137	20
Naive vs. END+AhR$^-$	23.7	30.96	-7.254	1.37	5	5	7.489	20
Naive vs. END+DMSO	23.7	32.08	-8.382	1.37	5	5	8.653	20
END vs. END+RES	33.38	26.74	6.635	1.37	5	5	6.849	20
END vs. END+AhR$^-$	33.38	30.96	2.419	1.37	5	5	2.498	20
END vs. END+DMSO	33.38	32.08	1.291	1.37	5	5	1.333	20
END+RES vs. END+AhR$^-$	26.74	30.96	-4.215	1.37	5	5	4.352	20
END+RES vs. END+DMSO	26.74	32.08	-5.343	1.37	5	5	5.516	20
END+AhR$^-$ vs. END+DMSO	30.96	32.08	-1.128	1.37	5	5	1.164	20
Compact letter display								
END	A							
END+DMSO	A							
END+AhR$^-$	A							
END+RES	B							
Naive	B