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ORIGINAL ARTICLE

Evaluation of the Protective Effects of Arbutin Via Hormonal, Anti-Inflammatory, and Antioxidant Pathways in Experimental Sepsis Induced Ovarian Damage

Gökhan UYANIK[1*], İshak GÖKÇEK[2], Murat ABAY[3], Hamdullah Suphi BAYRAKTAR[4]

[1]Hatay Mustafa Kemal University Faculty of Veterinary Medicine, Department of Obstetrics and Gynaecology, Hatay, Türkiye.

[2]Hatay Mustafa Kemal University Faculty of Veterinary Medicine, Department of Physiology, Hatay, Türkiye.

[3]Erciyes University Faculty of Veterinary Medicine, Department of Obstetrics and Gynaecology, Kayseri, Türkiye.

[4]Hatay Mustafa Kemal University Experimental Researches Application and Research Center, Hatay, Türkiye.

Gökhan UYANIK, Hatay Mustafa Kemal University Faculty of Veterinary Medicine, Department of Obstetrics and Gynaecology, Hatay, Türkiye.

E-mail: gokhan.uyanik@mku.edu.tr

ORCID ID: 0000-0003-4488-3055

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ABSTRACT

The present study evaluated the dose-dependent protective effects of arbutin against sepsis-induced ovarian damage and to compare its prophylactic and post-sepsis adjuvant administration in rats. Forty-nine female Wistar albino rats were randomly assigned to seven groups (n=7): Control, Sham, pre-sepsis arbutin 50 mg/kg (Pre50), pre-sepsis arbutin 100 mg/kg (Pre100), Sepsis (SPS), post-sepsis arbutin 50 mg/kg (Post50), and post-sepsis arbutin 100 mg/kg (Post100). Sepsis was induced via cecal puncture. All sepsis groups received intramuscular amikacin (20 mg/kg/day) for five consecutive days. Arbutin was administered orally for seven days prior to sepsis (prophylactic protocol) or concurrently with antibiotics (post-sepsis protocol). Serum anti-Müllerian hormone (AMH) and estradiol (E2) levels were measured, and ovarian tissue concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), malondialdehyde (MDA), and glutathione (GSH) were determined. Sepsis significantly decreased serum AMH, E2, and ovarian GSH levels, while markedly increasing TNF-α, IL-6, and MDA concentrations. In arbutin-treated groups, both prophylactic and post-sepsis administration increased GSH and reduced TNF-α, IL-6, and MDA levels compared with the sepsis group. Although hormonal parameters improved partially, AMH and E2 did not return to control values within the experimental period. Protective effects were similar across both doses 50 and 100 mg/kg, suggesting a dose-independent response. In conclusion, arbutin alleviated sepsis-induced inflammatory and oxidative ovarian damage through antioxidant and anti-inflammatory mechanisms; however, complete endocrine recovery was not achieved.

Keywords: Arbutin, inflammation, ovarian damage, oxidative stress, sepsis

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Introduction

Sepsis is a complex clinical syndrome that resulting from a dysregulated systemic inflammatory response to infection and may progress to multiple organ dysfunction (Vincent et al., 2013). The associated cytokine storm and, endothelial dysfunction, microcirculatory disturbances, and oxidative stress lead to functional impairment and structural damage in organs (Hoesel & Schmid, 2013; Taşdemir et al., 2020). Increased inflammation, endotoxin exposure, and reactive oxygen species (ROS) may target physiologically sensitive tissues such as the reproductive system (Selli et al., 2023). Although cytokines are known to play roles in the regulation of folliculogenesis, ovulation, and corpus luteum function under normal physiological conditions, elevated inflammatory cytokines and endotoxin burden during sepsis may suppress the hypothalamic-pituitary-ovarian axis, leading to decreased gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion, impaired steroid hormone synthesis, and disrupted follicular development (Wasyluk et al., 2021; Ying et al., 2020). In particular, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) have been reported to suppress steroid hormone synthesis, reduce luteal progesterone secretion, and increase apoptosis in follicular cells (Silva et al., 2020). Furthermore, increased oxidative stress markers in sepsis models have been shown to be associated with cellular damage in ovarian tissue, follicular apoptosis, and impaired oocyte-granulosa cell communication (Taşdemir et al., 2020). These findings indicate that sepsis is not limited to acute systemic effects but may also cause persistent damage to reproductive functions and represent a significant risk factor for fertility. Therefore, in addition to infection control, reducing inflammation- and oxidative stress-induced organ damage represents a critical secondary therapeutic target that warrants investigation in sepsis treatment.

Phytochemical compounds have attracted attention as potential supportive therapeutic options against sepsis- and inflammation-associated tissue damage due to their strong antioxidant and anti-inflammatory properties (Selli et al., 2023). Arbutin (hydroquinone-β-D-glucopyranoside) is a diet-derived soluble phenolic compound that exhibits biological effects such as scavenging ROS, reducing lipid peroxidation, increasing intracellular antioxidant enzyme activities (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GSH-Px]), and preserving mitochondrial integrity (Ebrahim-Tabar et al., 2020). In addition, arbutin has been reported to suppress the production of key inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), modulate inflammatory signalling pathways including nuclear factor kappa B (NF-κB) and Janus kinase/signal transducer and activator of transcription (JAK/STAT), and regulate apoptotic processes (Lee & Kim, 2012; Zhang et al., 2021). Moreover, the ability of arbutin to inhibit caspase activation and exert anti-apoptotic effects by regulating the B-cell lymphoma 2 (BCL-2)/BCL-2-associated X (BAX) ratio (Zhang et al., 2021) suggests that it may reduce the increased cleaved caspase-3 activity and follicular cell loss observed in sepsis models. In addition to these effects, its high toxic dose threshold and ability to act on oxidative stress without excessively suppressing the systemic immune response make arbutin a safe candidate for tissue protection in sepsis models (Bian et al., 2022; Birdal et al., 2024; Demir et al., 2023; Zhang et al., 2021). However, the potential role of arbutin in persistent inflammatory and oxidative damage following antibiotic treatment in sepsis has not been sufficiently investigated in the current literature.

We hypothesized that the inflammatory and oxidative damage induced by sepsis in ovarian tissue could be attenuated by arbutin through both pre-sepsis prophylactic approaches and supportive administration concurrent with antibiotic treatment. To the best of our knowledge, no comprehensive study has evaluated the comparative effects of prophylactic arbutin administration before sepsis and its adjuvant use during sepsis treatment on ovarian damage. Therefore, the present study aimed to evaluate, in a dose-dependent manner, whether prophylactic

arbutin administration can protect ovarian tissue in a sepsis model and whether its addition to standard antibiotic therapy can enhance therapeutic efficacy.

Material and Methods

Animals

A total of forty-nine healthy female Wistar albino rats, aged 10-12 weeks and weighing 200-250 g, were obtained from the Experimental Research Application and Research Center of Hatay Mustafa Kemal University (10.02.2026, 2026/02-12 Number Ethics Committee Decision). Throughout the experimental period, animals were housed in polycarbonate cages under controlled environmental conditions (ambient temperature 20-22°C, 12 h light/12 h dark photoperiod). Rats were fed a standard pelleted rodent diet and had ad libitum access to drinking water.

Experimental design

The female Wistar albino rats (n=49) were randomly divided into seven groups, with an equal number of animals in each group: Control , Sham, pre-sepsis arbutin 50 mg/kg (Pre50), pre-sepsis arbutin 100 mg/kg (Pre100), Sepsis (SPS), post-sepsis arbutin 50 mg/kg (Post50), and post-sepsis arbutin 100 mg/kg (Post100). During the 7-day period preceding sepsis induction, arbutin (Purity ≥ 98.0 %, Ambeed, USA, Cat No: A309050) was administered orally at doses of 50 mg/kg and 100 mg/kg to the Pre50 and Pre100 groups, respectively. During the same period, no intervention was applied to the Control group, whereas the Sham, SPS, Post50, and Post100 groups were administered 1 mL of 0.9% saline via oral gavage.(0.9% NaCl Isotonic, Polifleks, Türkiye) (Figure 1). On day 8 of the experiment, experimental sepsis was induced in the Pre50, Pre100, SPS, Post50, and Post100 groups using the cecal puncture method (Cai et al., 2023). All surgical procedures were performed under general anesthesia. For anesthesia, ketamine (80 mg/kg; Ketasol® 10%, VetViva Richter GmbH, Austria) and xylazine (10 mg/kg; Xylazinbio® 2%, Bioveta, Czech Republic) were administered intraperitoneally (Luca et al., 2018). Following a midline incision, the abdominal cavity was accessed via midline laparotomy (Figure 2A-B). The cecum was then exteriorized and punctured at two separate points on the antimesenteric surface, distal to the ileocecal valve, using a 22G needle (Cai et al., 2023). After confirming the extrusion of fecal content, the cecum was gently returned to the peritoneal cavity (Figure 2C). The abdominal wall was closed in two layers using 4/0 sterile synthetic absorbable suture material (Figure 2D-E). In the Sham group, only a midline incision was performed, and the abdomen was subsequently closed without cecal puncture, whereas no surgical procedure was applied to the Control group (Figure 1).

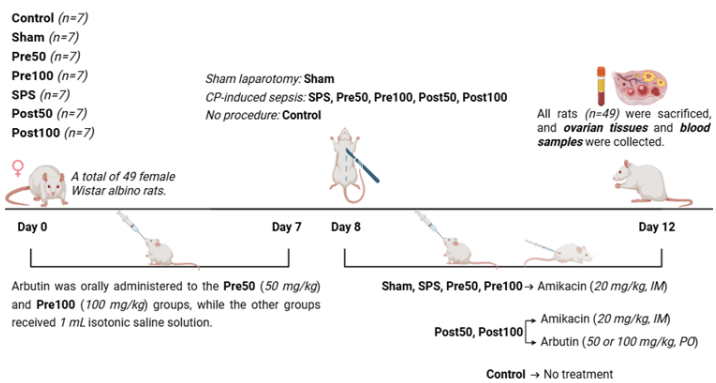


Figure 1. Experimental design and treatment protocol. Forty-nine female Wistar albino rats were divided into seven groups (n=7): Control, Sham, arbutin pre-treatment (Pre50, Pre100), Sepsis (SPS), and post-treatment (Post50, Post100). Sepsis was induced by cecal puncture on Day 8. Arbutin (50 or 100 mg/kg, PO) was given either pre- or post- sepsis induction, while amikacin (20 mg/kg, IM) was administered from Day 8 to Day 12. Animals were sacrificed on Day 12, and ovarian tissues and blood samples were collected

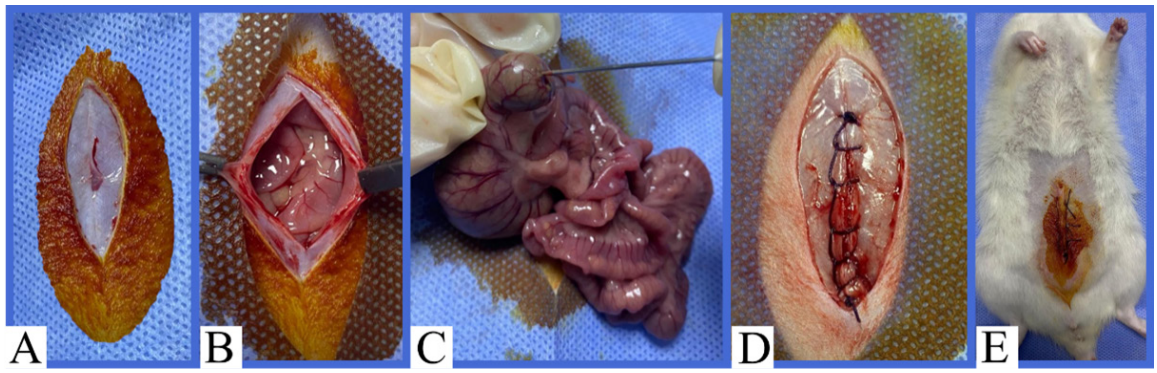


Figure 2. Cecal puncture procedure for experimental sepsis induction: (A) skin incision; (B) exposure of the abdominal cavity; (C) exteriorization of the cecum followed by cecal puncture; (D) closure of the abdominal wall; (E) skin suturing

Between days 8 and 12 of the study, all groups except the Control group received intramuscular 20 mg/kg/day amikacin (100 mg/2 mL, Amikozit®, Avixa İlaç, Türkiye) for five consecutive days (Staneva et al., 1994). In addition to amikacin treatment, oral arbutin was administered to the Post50 and Post100 groups at doses of 50 mg/kg and 100 mg/kg, respectively. Except for the Control group, the remaining groups received an equal volume (1 mL) of isotonic saline solution (Figure 1). At the end of the experimental period, on day 12, all animals were euthanized under general anesthesia. Bilateral ovarian tissues were excised under aseptic conditions, carefully cleared of surrounding connective tissues, and stored at -20°C until analysis. For the determination of serum estradiol (E2) and anti-Müllerian hormone (AMH) levels, blood samples were collected via cardiac puncture into clot activator gel tubes (Vacusera®, Disera, Türkiye). Samples were centrifuged at 5000 × g for 3 minutes to separate serum, and sera were stored at -20°C until hormone analyses were performed.

Hormonal, oxidative stress and inflammatory cytokine analyses

Serum AMH (ng/mL) and E2 (pg/mL) concentrations were determined using commercially available AMH (Rat AMH, Elabscience, USA, Cat. No: E-EL-R3022) and E2 (Rat Estrogen, Finetest, China, Cat. No: ER1505) enzyme immunoassay (EIA) kits in accordance with the manufacturer's instructions. All serum samples were brought to room temperature prior to analysis, and measurements were performed within the same assay run to minimize analytical variability. Following completion of the reaction, microplate absorbance values were measured photometrically at 450 nm using a microplate reader (Erba LisaScan EM Absorbance Microplate Reader; Erba Diagnostics, Mannheim, Germany). AMH and E2 concentrations were calculated based on the corresponding standard curves.

Ovarian tissue samples were homogenized in phosphate-buffered saline (PBS; 0.01 M, pH 7.4) at a weight/volume ratio of 1:9. The homogenates were centrifuged at 5000 × g for 10 minutes, and the supernatants were collected for biochemical analyses. Ovarian MDA (Rat MDA, Finetest China, Cat. No: ER1878), TNF-α (Rat TNF-α, Finetest China, Cat. No: ER1393), and IL-6 (Rat IL-6, Finetest, China, Cat. No: ER0042) levels were measured in the supernatants using commercially available ELISA kits. Total protein levels in ovarian tissue were also determined, and MDA, TNF-α, and IL-6 concentrations were expressed relative to protein content.

Statistical analysis

Prior to statistical analysis, the assumptions of parametric testing were evaluated. Normality was assessed using the Shapiro-Wilk test, and homogeneity

of variances was examined with Levene's test. Intergroup comparisons were performed using one-way analysis of variance (one-way ANOVA). When a statistically significant difference was detected by ANOVA, Tukey's post-hoc multiple comparison test was applied. All data are presented as mean±standard error of the mean (SEM). A value of $p<0.05$ was considered statistically significant. IBM SPSS 23 (IBM SPSS Corp., Armonk, NY, USA) was used in all statistical analyses.

Results

Ovarian TNF-α and IL-6 levels varied significantly among groups ($p<0.001$). TNF-α was markedly elevated in the SPS group (34.885±3.438 pg/mg protein) compared with Control (13.958±0.639 pg/mg protein) and Sham (14.895±1.200 pg/mg protein). Pre-sepsis arbutin groups showed lower TNF-α levels (Pre50: 19.321±1.657; Pre100: 17.233±1.546 pg/mg protein) than SPS, whereas post-sepsis arbutin groups (Post50: 24.279±1.565; Post100: 25.151±1.517 pg/mg protein) remained higher than controls but significantly reduced compared with SPS (Figure 3A). Similarly, IL-6 was highest in the SPS group (52.489±3.944 pg/mg protein) compared with Control (18.630±1.521 pg/mg protein) and Sham (19.453±0.939 pg/mg protein). Pre-sepsis arbutin (34.899±3.617 and 33.192±4.852 pg/mg protein) and post-sepsis arbutin groups (31.896±2.567 and 32.873±1.944 pg/mg protein) showed significantly lower IL-6 levels than SPS but did not return to control values (Figure 3B).

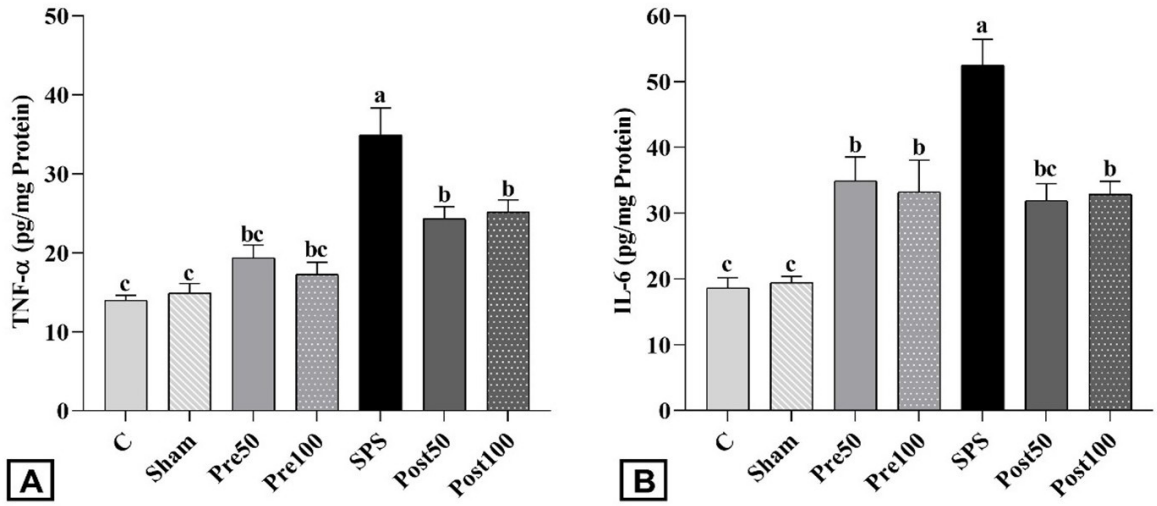


Figure 3. Effects of different treatment protocols on ovarian inflammatory cytokine levels. (A) Tumor necrosis factor-α (TNF-α, pg/mg protein) and (B) interleukin-6 (IL-6, pg/mg protein) concentrations in Control, Sham, Pre-sepsis arbutin 50 mg/kg (Pre50), Pre-sepsis arbutin 100 mg/kg (Pre100), sepsis (SPS), Post-sepsis arbutin 50 mg/kg (Post50), and Post-sepsis arbutin 100 mg/kg (Post100) groups. *Data are presented as mean±SEM. Different lowercase letters (a, b, c) above the bars indicate statistically significant differences among groups ($p<0.001$)

Ovarian MDA and GSH levels differed significantly among groups ($p<0.001$). MDA levels were markedly elevated in the SPS group (92.894±5.447 pg/mg protein) compared with the Control (45.866±3.234 pg/mg protein) and Sham (44.175±4.435 pg/mg protein) groups. Pre-treatment with arbutin significantly reduced MDA levels, particularly in the Pre100 group (47.847±2.877 pg/mg protein), which was comparable to controls. The Pre50 group showed intermediate values (52.638±2.395 pg/mg protein). Although post-sepsis arbutin administration also reduced MDA levels (Post50: 69.608±5.968; Post100: 68.403±5.691 pg/

mg protein) compared with the Sepsis group, these values remained significantly higher than those of the Control and Sham groups (Figure 4A). In contrast, GSH levels were significantly decreased in the SPS group (4.719±0.258 nmol/g protein) compared with the Control (7.201±0.435 nmol/g protein) and Sham (6.930±0.381 nmol/g protein) groups. All arbutin-treated groups demonstrated significantly higher GSH levels than the SPS group. GSH concentrations were 6.605±0.318 (Pre50), 6.461±0.343 (Pre100), 7.174±0.299 (Post50), and 7.252±0.176 nmol/g protein, and these values were statistically comparable to the Control and Sham groups (Figure 4B).

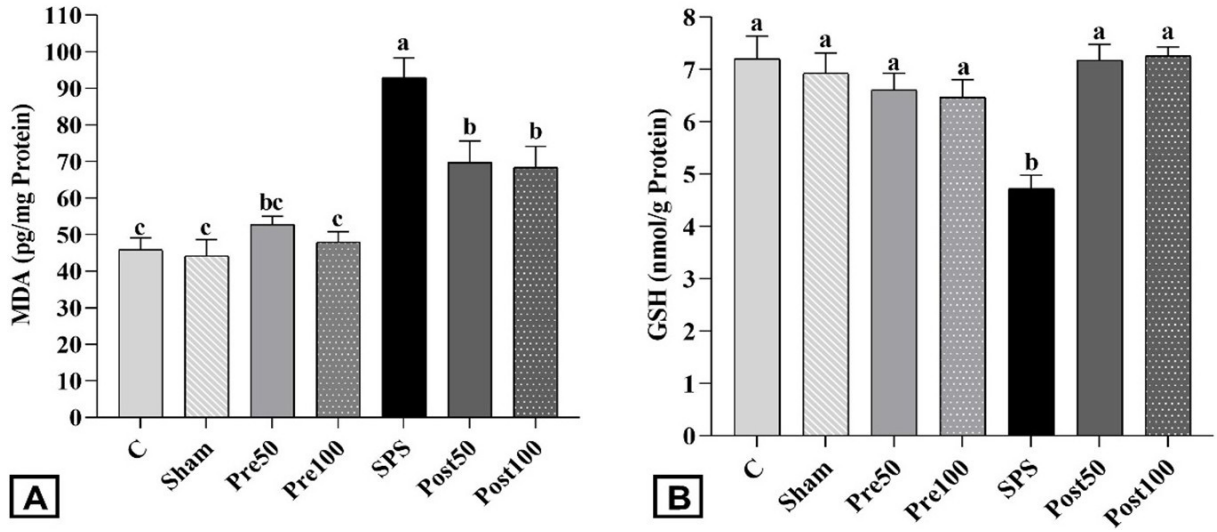


Figure 4. Effects of different treatment protocols on ovarian oxidative stress parameters. (A) Ovarian malondialdehyde (MDA) levels (pg/mg protein) and (B) glutathione (GSH) levels (mmol/g protein) in Control, Sham, Pre-sepsis arbutin 50 mg/kg (Pre50), Pre-sepsis arbutin 100 mg/kg (Pre100), sepsis (SPS), Post-sepsis arbutin 50 mg/kg (Post50), and Post-sepsis arbutin 100 mg/kg (Post100) groups.*Different lowercase letters (a, b, c) above the bars indicate statistically significant differences among groups ($p<0.001$)

Serum AMH and E2 concentrations differed significantly among groups ($p<0.05$). Control (2.795±0.126 ng/mL) and Sham (2.762±0.118 ng/mL) groups exhibited significantly higher AHM levels than all treatment groups ($p<0.001$). The SPS group showed the lowest AMH value (2.059±0.162 ng/mL), and no significant difference was detected between SPS and the pre- or post-sepsis arbutin groups (Pre50: 2.224±0.100; Pre100: 2.188±0.098; Post50: 2.139±0.094; Post100: 2.226±0.131 ng/mL) (Figure 5A). Similarly, E2 levels were significantly higher in the Control (48.466±3.821 pg/mL) and Sham (46.807±3.812 pg/mL) groups compared with the SPS group (31.354±3.207 pg/mL) ($p=0.004$). Although the pre- and post-sepsis groups (38.271±2.613; 37.960±3.000; 36.913±2.188; 37.311±2.301 pg/mL) showed intermediate values, no statistically significant differences were obserwed between these groups and SPS (Figure 5B).

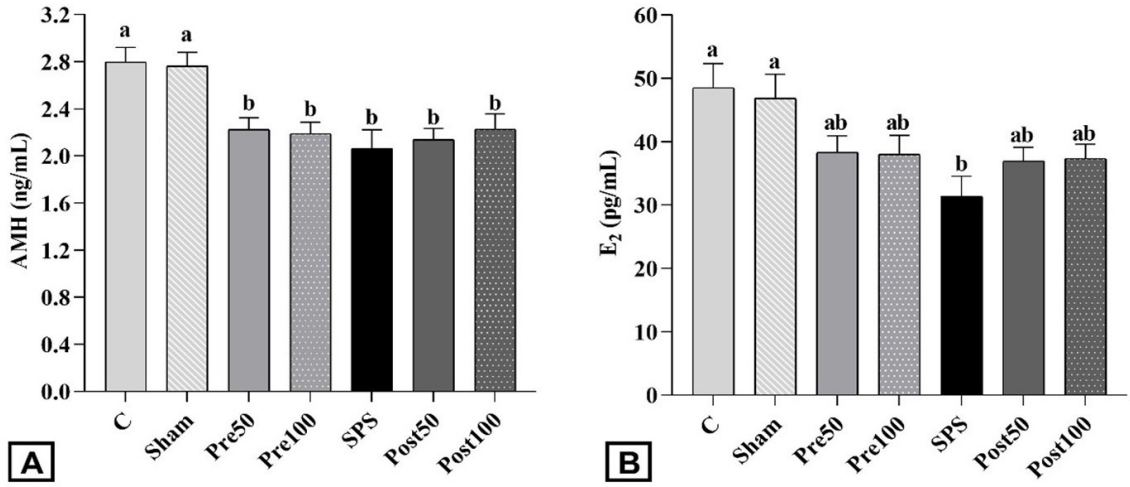


Figure 5. Effects of different treatment protocols on serum reproductive hormone levels. (A) Serum anti-Müllerian hormone (AMH, ng/mL) and (B) estradiol (E2, pg/mL) concentrations in Control, Sham, Pre-sepsis arbutin 50 mg/kg (Pre50), Pre-sepsis arbutin 100 mg/kg (Pre100), sepsis (SPS), Post-sepsis arbutin 50 mg/kg (Post50), and Post-sepsis arbutin 100 mg/kg (Post100) groups. *Data are expressed as mean±SEM. Different lowercase letters (a, b) above the bars indicate statistically significant differences among groups ($p<0.05$)

Discussion

Sepsis is a complex syndrome characterized by an exaggerated inflammatory response and multiple organ dysfunction. In sepsis, uncontrolled release of inflammatory cytokines leads to endothelial injury, microcirculatory disturbances, and oxidative stress-related structural and functional damage (Hoesel & Schmid, 2013; Taşdemir et al., 2020; Vincent et al., 2013). In this study, sepsis was induced using a standardized cecal puncture-based intraperitoneal polymicrobial sepsis model. Previous studies have shown that this model successfully induces sepsis, as evidenced by decreased white blood cell counts, thrombocytopenia, hypotension, elevated pro-inflammatory cytokine levels, and impaired organ functions (Cai et al., 2023). Consistent with these reports, the significant increase in ovarian pro-inflammatory cytokines (TNF-α and IL-6) levels in the SPS group compared with the Control and Sham groups supports the successful induction of sepsis in the present study. In addition, owing to inflammatory processes and redox imbalance, impairments also develop in the reproductive system during sepsis, particularly in ovarian function (Silva et al., 2020). Consistently, in the present study, sepsis-related biological processes caused decreases in reproductive hormones and ovarian reserves, whereas arbutin administered in addition to antibiotic therapy in sepsis exerted prophylactic and therapeutic antioxidant and anti-inflammatory effects on the ovaries.

In the present study, significantly increased ovarian TNF-α and IL-6 levels in the SPS group compared with the control and sham groups (Figure 3) indicate that sepsis elicited a pronounced local inflammatory response in ovarian tissue. Indeed, it is well established that microbial products such as lipopolysaccharide (LPS) activate the myeloid differentiation primary response 88 (MyD88)/NF-κB signaling pathway via toll-like receptor 4 (TLR4) during sepsis, resulting in a rapid rise in pro-inflammatory cytokines, particularly TNF-α and IL-6 (Hoesel & Schmid, 2013; Mansouri et al., 2025; Vincent et al., 2013). In this context, Gökçek and Uyanık (2025) demonstrated that LPS significantly increased TNF-α and IL-6 expression in ovarian tissue and that this increase was associated with suppression of steroidogenesis. Similarly, Magata (2020) reported that endotoxin exposure adversely affects ovarian function by increasing cytokine levels within the follicular microenvironment. In the arbutin-treated groups, however, the significant decreases in TNF-α

and IL-6 levels compared with the SPS group (Figure 3) suggest that arbutin can modulate the ovarian inflammatory response at the molecular level. In experimental inflammation models, arbutin has been reported to suppress the TLR4/NF-κB pathway, reduce IκB phosphorylation, and consequently decrease the expression of TNF-α, IL-6, and IL-1β (Lee & Kim, 2012; Zhang et al., 2021). Moreover, arbutin has been shown to limit cytokine production by modulating JAK/STAT signalling and to reduce leukocyte infiltration at the tissue level (Demir et al., 2023). Therefore, the reductions in cytokine levels observed in both pre- and post-sepsis arbutin protocols in our study are consistent with the anti-inflammatory profile reported in the literature.

On the other hand, increased MDA levels and decreased GSH levels in the SPS group (Figure 4) indicate that sepsis disrupted redox homeostasis in ovarian tissue. Experimental sepsis and LPS models have likewise reported increased lipid peroxidation products and weakened antioxidant defences in the ovary (Gökçek & Uyanık, 2025; Selli et al., 2023). This condition has been emphasized to be associated with mitochondrial stress, impaired energy metabolism, and cellular damage in follicular cells (Qin et al., 2024; Taşdemir et al., 2020). It has also been reported that oxidative stress and endocrine suppression develop concomitantly in sepsis-related ovarian dysfunction and that these two processes may potentiate one another (Taşdemir et al., 2020).

Notably, the significant decreases in serum AMH and E2 levels in the SPS group (Figure 5) suggest that sepsis may adversely affect not only oxidative balance but also follicular reserve indicators and steroidogenesis. It has been shown that endotoxin and pro-inflammatory cytokine exposure at the ovarian level can impair granulosa cell function (Gökçek & Uyanık, 2025). In this process, increased TLR4-mediated inflammatory responses and activation of the NF-κB pathway may reduce the expression and activity of steroidogenesis-related enzymes, particularly aromatase (CYP19A1) (Price et al., 2013). TNF-α has been reported to increase caspase-mediated apoptotic signalling in granulosa cells and compromise cellular integrity (Silva et al., 2020). IL-6, in turn, is suggested to contribute to the persistence of the inflammatory response via JAK/STAT and NF-κB pathways and to increase oxidative damage through redox-sensitive mechanisms (Hoesel & Schmid, 2013). Therefore, under septic conditions, it is an expected outcome that increased inflammation and oxidative stress together suppress granulosa cell functions, reduce aromatase activity, and decrease E2 production (Qin et al., 2024; Tabandeh et al., 2022). Because AMH is primarily secreted by granulosa cells of preantral and small antral follicles, increased follicular loss and atresia may lead to a decrease in AMH levels (Iwase et al., 2023). The adverse effects of oxidative stress and inflammation on the follicular pool and ovarian reserve have also been discussed in different studies (Gökçek & Uyanık, 2025; Gökçek et al., 2025; Magata, 2020). In addition, systemic mechanisms such as suppression of the HPG axis during sepsis have been reported to further deepen gonadal dysfunction (Ma et al., 2025). Accordingly, the pattern of increased cytokine burden and impaired redox balance observed in the SPS group in our study is consistent with suppression of steroidogenesis and decreases in follicular reserve indicators at the ovarian level.

Demir et al. (2023) reported that arbutin reduces markers related to oxidative stress, inflammation, and apoptosis in ovarian injury and strengthens protective responses. In the present study, arbutin administration significantly alleviated sepsis-induced ovarian disturbances, particularly at the level of oxidative stress (Figure 4). Regardless of dose, the decrease in MDA and the increase in GSH toward control values in the pre- and post-sepsis arbutin groups compared with the SPS group suggest that lipid peroxidation was limited and antioxidant defences were re-supported in ovarian tissue. Mechanistically, arbutin has been reported to enhance antioxidant responses via the Nrf2/HO-1 axis, contributing to preservation of the GSH pool, maintenance of redox balance, and increased ROS scavenging capacity (Ebrahim-Tabar et al., 2020). Therefore, the GSH restoration observed in our study appears biologically consistent with reinforcement of Nrf2-associated antioxidant gene expression.

In addition, pre- and post-sepsis arbutin administration consistently reduced TNF-α and IL-6 levels in a dose-independent manner (Figure 3). In this context, evidence indicating that arbutin can reduce the oxidative-inflammatory burden by suppressing pro-inflammatory pathways such as TNF-α/NF-κB/iNOS supports its potential to limit the damage created by the inflammation-oxidative stress interplay within the ovarian microenvironment in sepsis (Okkay et al., 2024). In an LPS-induced sepsis model, arbutin was reported to suppress NF-κB-mediated inflammatory responses, reduce the production of pro-inflammatory cytokines such as TNF-α and IL-6, strengthen antioxidant defence systems, and limit oxidative stress-related cellular damage, thereby exerting a marked protective effect in tissues through these mechanisms (Bian et al., 2022). Similarly, in an LPS-induced acute kidney injury model, arbutin was reported to activate the PI3K/Akt/Nrf2 signalling pathway, suppress inflammatory and apoptotic processes, reduce oxidative stress burden, and confer prominent tissue protection via these molecular mechanisms (Zhang et al., 2021). These findings are consistent with studies reporting that arbutin decreases oxidative stress and inflammatory markers and restores the antioxidant system (Birdal et al., 2024; Wang & Mu, 2021).

Despite the marked reduction in oxidative stress and inflammatory activity following prophylactic (Pre50 and Pre100) or therapeutic (Post50 and Post100) arbutin administration in addition to antibiotic therapy, the failure of AMH and E2 levels to return fully to normal within the experimental period (Figure 5) supports the view that endocrine suppression in sepsis is multifactorial and cannot be explained solely by redox imbalance. Even if arbutin reduces oxidative damage, re-establishment of steroidogenesis may require time when inflammatory signalling persists or granulosa cell function is compromised, thereby limiting the E2 response during the study period (Guan et al., 2021). Moreover, because AMH is secreted mainly by granulosa cells of preantral and small antral follicles and reflects the growing follicle pool, rapid AMH recovery may not be biologically expected if sepsis-induced inflammation increases follicular atresia or causes early follicle loss (Iwase et al., 2023; Moolhuijsen & Visser, 2020). Another important point is that sepsis creates a pan-endocrine stress state affecting not only the ovarian microenvironment but also central endocrine regulation; in critical illness, inflammation and stress can suppress the HPG axis at the hypothalamic-pituitary level, reducing gonadotropin dynamics and consequently gonadal steroid responses (Ma et al., 2025; Wasyluk et al., 2021). In addition, bactericidal antibiotics used for infection control may transiently increase free LPS release in sepsis models (Lepper et al., 2002). Thus, antibiotic-related endotoxin dynamics may contribute to the persistence of cytokine burden, prolong inflammation-mediated suppression of steroidogenesis, and delay AMH/E2 recovery despite improvement in redox balance with arbutin. Nevertheless, clarification of this relationship requires further studies evaluating free LPS kinetics, cytokine timing, antibiotic class and treatment window together with ovarian TLR4/NF-κB activation and steroidogenesis markers such as CYP19A1.

Conclusion

Experimental sepsis induced ovarian dysfunction through inflammatory and oxidative stress pathways. Arbutin reduced these alterations in both prophylactic and post-sepsis protocols, with similar efficacy at 50 and 100 mg/kg but did not fully restore AMH and E2 levels. These findings suggest that arbutin may serve as a supportive agent against sepsis-induced ovarian damage, although further studies are needed to confirm its reproductive effects and underlying mechanisms.

Conflict of Interest

The authors stated that they did not have anyreal, potential or perceived conflict of interest.

Ethical Approval

This study were obtained from the Experimental Research Application and Research Center of Hatay Mustafa Kemal University (10.02.2026, 2026/02-12 Number Ethics Committee Decision).

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Similarity Rate

We declare that the similarity rate of the article is 5% as stated in the report uploaded to the system.

Author Contributions

Motivation/Concept: G.U., İ.G., M.A., H.S.B., Design: G.U., İ.G., M.A., H.S.B., Control/Supervision: M.A., Data Collection and/or Processing: G.U., H.S.B., Analysis and/or Interpretation: İ.G., Literature Review: G.U., İ.G., Writing the Article: G.U., İ.G., Critical Review: G.U., İ.G., M.A., H.S.B.

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