

Olivetol Mitigates Ovarian Ischemia/Reperfusion-Induced Oxidative and Inflammatory Damage via Enhancement of Antioxidant Defense

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ABSTRACT

Ovarian torsion leads to ischemia and subsequent reperfusion injury, resulting in oxidative stress, inflammation, and tissue damage that may impair ovarian function. Olivetol, a natural resorcinol derivative with known antioxidant and anti-inflammatory properties, has not been previously evaluated for its protective potential in ovarian ischemia/reperfusion (I/R) injury. In this experimental study, rats were divided into eight groups: Sham, Sham + Olivetol (100 mg/kg), Ischemia, Ischemia + Olivetol (50 mg/kg), Ischemia + Olivetol (100 mg/kg), I/R, I/R + Olivetol (50 mg/kg), and I/R + Olivetol (100 mg/kg). Ischemia was induced by clamping the ovarian pedicle for 3 hours' period, followed by reperfusion in relevant groups. Olivetol was administered orally before ischemia or reperfusion induction. Superoxide dismutase (SOD), glutathione (GSH), myeloperoxidase (MPO), and malondialdehyde (MDA) levels were analyzed in ovarian tissues to assess oxidative and inflammatory changes. SOD activity and GSH levels were significantly decreased in ischemia and I/R groups compared to the Sham group, whereas Olivetol administration dose-dependently restored these antioxidant parameters. In contrast, MPO and MDA levels were markedly elevated following ischemia and reperfusion, indicating increased oxidative stress and inflammation; these parameters were significantly reduced by Olivetol treatment, particularly at the 100 mg/kg dose ($p < .001$). High-dose Olivetol showed no toxic effects in healthy rats. Olivetol exerted significant protective effects against ovarian ischemia/reperfusion injury by enhancing antioxidant defenses and reducing oxidative and inflammatory damage. These findings suggest that Olivetol may represent a promising therapeutic candidate for preventing reperfusion-induced ovarian injury and preserving ovarian function.

Keywords: Antioxidant, Inflammation, Olivetol, Ovarian ischemia/reperfusion, Oxidative stress.

Introduction

Ovarian torsion represents a gynecological emergency caused by twisting of the ovary on its ligamentous axis, leading to diminished or absent ovarian perfusion. The restoration of blood supply following detorsion, although essential for tissue survival, paradoxically induces further tissue damage known as I/R injury (Bridwell et al., 2022; Kilkenny & Wilson, 2023). This process triggers the generation of excessive reactive oxygen species (ROS), lipid peroxidation, inflammatory cytokine release, and cellular apoptosis, ultimately impairing ovarian function and fertility potential (Bayir et al., 2016; Okur et al., 2025). Understanding the mechanisms underlying ovarian I/R injury is therefore crucial for developing effective pharmacological strategies to protect ovarian tissue integrity.

Several antioxidants and anti-inflammatory agents have been investigated to mitigate I/R-induced ovarian damage. Substances such as melatonin, resveratrol, and N-acetylcysteine have shown protective effects by reducing oxidative stress and inhibiting inflammatory cascades (Bodur et al., 2016; Kılıç et al., 2016). However, the search for novel and more potent compounds continues, particularly those that can exert both antioxidant and anti-inflammatory activities with minimal toxicity.

Olivetol (5-pentylresorcinol) is a naturally occurring resorcinol derivative found in certain species of lichens and plants. The compound has been shown to exert multiple biological effects, including antioxidative, anti-inflammatory, antimicrobial, and neuroprotective actions. (Taura et al., 2009; Ün & Ugan, 2021). Olivetol serves as a biosynthetic precursor of cannabinoids, but it also exhibits independent pharmacological actions unrelated to cannabinoid receptor modulation. Research findings have demonstrated that Olivetol can counteract oxidative processes by neutralizing free radicals and preventing lipid peroxidation, thereby indicating its possible utility in oxidative stress-mediated conditions (Reshma et al., 2023).

Given the pivotal role of oxidative stress and inflammation in the pathogenesis of ovarian I/R injury, Olivetol may represent a promising candidate for reducing reperfusion-associated tissue damage. However, to date, no experimental studies have investigated the protective effects of Olivetol on ovarian ischemia and reperfusion injury.

The objective of the present investigation was to evaluate the biochemical and histopathological effects of Olivetol using an experimental ovarian I/R injury model in rats. We hypothesized that Olivetol administration would attenuate oxidative stress, suppress inflammatory responses, and preserve ovarian tissue architecture following I/R insult.

Methods

Animals and Ethical Statement

Totally 48 female albino Wistar rats weighing 200–220 g were used in this study and were supplied by the Medical Experimental Research and Application Center of Atatürk University following ethical authorization. The animals were maintained under controlled lighting conditions (12 h light/12 h dark) with unrestricted access to standard laboratory chow and water. Ethical permission for all animal experiments was obtained from the Local Ethics Committee for Animal Experiments of Atatürk University (Date: August 17, 2023, approval no. 2300251381), and all procedures complied with the approved protocol.

Animal Grouping and Surgical Procedures

Totally 48 female albino Wistar rats were randomly divided into eight experimental groups (n=6), as outlined in Table 1. Animals in the sham groups (Groups 1 and 2) underwent laparotomy without the induction of I/R. The absence of toxicity at the high dose of Olivetol (100 mg/kg; CAS No. 500–66–3; Sigma, Germany) was assessed by measuring ovarian SOD, GSH, and MDA levels in healthy rats (Group 2) and comparing them with the Sham group. No significant differences were observed, indicating that Olivetol did not induce oxidative stress-related tissue damage at this dose. However, histopathological examination and additional systemic toxicity markers were not evaluated, which represents a limitation of the toxicity assessment.

On the experimental day, anesthesia was induced in all animals using sodium thiopental (25 mg/kg, intraperitoneally). In the ischemia and I/R groups, the ovaries were accessed through a midline abdominal incision. Ischemia was established by placing atraumatic vascular clamps on the ovarian vessels for 3 hours in Groups 3–8. Reperfusion was subsequently achieved by

removing the clamps and restoring blood flow for an additional 3 hours in Groups 6–8. All surgical procedures were conducted following the standard techniques and

experimental protocols described in previous studies on ovarian ischemia and reperfusion models (Oral et al., 2017; Toktay et al., 2022).

Table 1.

Groups and Experimental Procedures

Groups	30 min before Ischemia	Ischemia	2.5h after Ischemia	3h after Ischemia	6h after Ischemia
1. Sham	water	Sham operation	-	-	sacrificed
2. Sham + Oli100	100 mg/kg Oli	Sham operation	-	-	sacrificed
3. I	water	Ischemia	-	sacrificed	-
4. I + Oli50	50 mg/kg Oli	Ischemia	-	sacrificed	-
5. I + Oli100	100 mg/kg Oli	Ischemia	-	sacrificed	-
6. I/R	-	Ischemia	water	Reperfusion	sacrificed
7. I/R + Oli50	-	Ischemia	50 mg/kg Oli	Reperfusion	sacrificed
8. I/R + Oli100	-	Ischemia	100 mg/kg Oli	Reperfusion	sacrificed

Olivetol dosing was determined based on preliminary dose-finding experiments and literature review. In pilot studies, Olivetol was administered at 25, 50, 100, and 200 mg/kg, and oxidative stress parameters (SOD, GSH, and MDA) were evaluated. Similar biochemical responses were observed between 25 and 50 mg/kg doses and between 100 and 200 mg/kg doses. Therefore, 50 mg/kg and 100 mg/kg were selected as representative low and high doses for the main experiments.

To evaluate the protective role of Olivetol against ovarian I/R injury, the compound was administered orally at doses of 50 or 100 mg/kg to four experimental groups, 30 minutes before the onset of ischemia. Following completion of the experimental protocol, the animals were sacrificed using an overdose of sodium thiopental. Both ovaries were then carefully excised and preserved at -80°C until biochemical analyses were performed.

Biochemical Analyses

Collected ovarian tissue samples were preserved at -80°C until biochemical evaluation. For each animal, approximately 100 mg of ovarian tissue was rinsed with

phosphate-buffered saline containing heparin and subsequently processed. Tissue homogenization was performed in liquid nitrogen using a TissueLyser II system with a grinding jar set (Qiagen, Hilden, Germany), followed by centrifugation in accordance with the manufacturers' protocols.

The resulting supernatants were utilized for the assessment of SOD activity, MDA level, GSH level, and MPO activity. Analyses were conducted using rat-specific, high-sensitivity assay kits (Cayman-706002, Cayman-10009055, Cayman-703002 [USA], and Sunredbio-21-11-0575 [China]). All assays were carried out in duplicate. Protein content was quantified using the Lowry method with a commercial total protein kit (Sigma-Aldrich, TP0300-1KT, USA). Biochemical results were expressed as per milligram of protein.

Statistical Analyses

All statistical evaluations were conducted using IBM SPSS Statistics software version 20.0 (IBM SPSS Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances was

evaluated using Levene's test. All datasets satisfied the assumptions for parametric analysis. Therefore, intergroup comparisons were performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Data are presented as mean $\pm$ standard error (SE). A p value $< .05$ was considered statistically significant.

Results

Biochemical Results

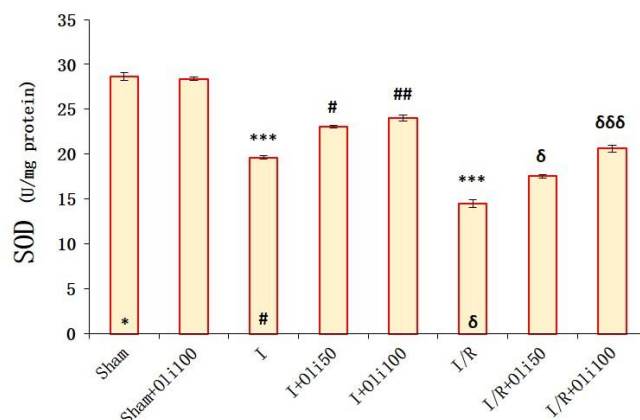
High-dose Olivetol (100 mg/kg) did not show any toxic effects in healthy rats, as confirmed in Group 2, where Olivetol was administered to assess potential toxicity. Evaluation of antioxidant parameters revealed that Olivetol treatment increased SOD activity and GSH levels, both of which were significantly reduced following ischemia and reperfusion injury. In contrast, Olivetol administration decreased the pro-oxidant enzyme MPO activity in both ischemia and ischemia/reperfusion groups. Similarly, MDA levels, an indicator of lipid peroxidation, were also reduced by Olivetol treatment. These findings suggest that Olivetol exhibits potent antioxidant and protective effects against ischemia- and reperfusion-induced oxidative damage in ovarian tissues.

SOD activities

The SOD activity levels in ovarian tissues of the experimental groups are presented as follows: Sham group: 28 U/mg, Ischemia group: 19 U/mg, Ischemia + Olivetol 50 mg/kg group: 23 U/mg, Ischemia + Olivetol 100 mg/kg group: 25 U/mg, I/R group: 14 U/mg, I/R + Olivetol 50 mg/kg group: 17 U/mg, and I/R + Olivetol 100 mg/kg group: 20 U/mg (Figure 1). SOD activity was significantly decreased in both the ischemia and I/R groups compared to the Sham group, indicating oxidative stress due to ischemic damage. Administration of Olivetol markedly increased SOD activity in a dose-dependent manner. In the ischemia groups, Olivetol at 50 mg/kg significantly increased SOD activity ($p < .05$), while 100 mg/kg Olivetol resulted in a more pronounced increase ($p < .01$) compared to the ischemia group. Similarly, in the I/R groups, Olivetol at 50 mg/kg significantly elevated SOD activity ($p < .01$), and 100 mg/kg Olivetol produced a further significant increase ($p < .001$) relative to the I/R group. These results suggest that Olivetol

administration effectively enhanced antioxidant defense mechanisms and alleviated ischemia- and reperfusion-induced oxidative damage in ovarian tissues.

Figure 1: SOD: Superoxide Dismutase, Oli: Olivetol, I: Ischemia, I/R: Ischemia/Reperfusion. Each bar expressed as mean value $\pm$ SE. Significant differences were detected between all groups, compared to Sham group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$), compared to I group (# $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$) and compared to I/R group ($\delta p < 0.05$, $\delta\delta p < 0.01$, $\delta\delta\delta p < 0.001$) by one-way ANOVA followed by Tukey test. Within the same column, group means sharing identical symbols were considered not significantly different, whereas distinct symbols indicated statistically significant differences according to Tukey's test.

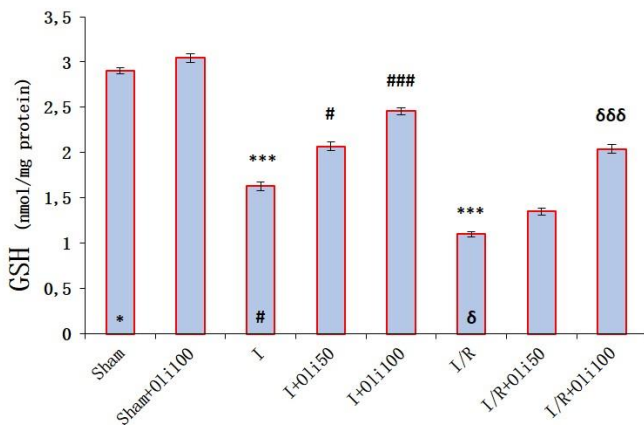


GSH levels

The GSH levels in ovarian tissues of the experimental groups were measured as follows: Sham group: 2.90 nmol/mg protein, Ischemia group: 1.69 nmol/mg protein, Ischemia + Olivetol 50 mg/kg group: 2.06 nmol/mg protein, Ischemia + Olivetol 100 mg/kg group: 2.45 nmol/mg protein, I/R group: 1.10 nmol/mg protein, I/R + Olivetol 50 mg/kg group: 1.35 nmol/mg protein, and I/R + Olivetol 100 mg/kg group: 2.04 nmol/mg protein (Figure 2). GSH levels were significantly decreased in both the ischemia and I/R groups compared to the Sham group, indicating a marked reduction in antioxidant capacity following ischemic and reperfusion injury. In the ischemia groups, Olivetol treatment resulted in a dose-dependent increase in GSH levels; 50 mg/kg Olivetol significantly elevated GSH ($p < .05$), while 100 mg/kg Olivetol led to a more pronounced increase ($p < .001$) compared to the ischemia group. In the

I/R groups, 50 mg/kg Olivetol caused a mild but non-significant rise in GSH levels, whereas 100 mg/kg Olivetol significantly increased GSH content ($p < .001$) relative to the I/R group. These results indicate that Olivetol effectively enhanced the antioxidant defense system and mitigated oxidative stress induced by ischemia and reperfusion in ovarian tissue.

Figure 2: GSH: Glutathione, Oli: Olivetol, I: Ischemia, I/R: Ischemia/Reperfusion. Each bar expressed as mean value $\pm$ SE. Significant differences were detected between all groups, compared to Sham group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$), compared to I group (# $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$) and compared to I/R group ($\delta p < 0.05$, $\delta\delta p < 0.01$, $\delta\delta\delta p < 0.001$) by one-way ANOVA followed by Tukey test. Within the same column, group means sharing identical symbols were considered not significantly different, whereas distinct symbols indicated statistically significant differences according to Tukey's test.

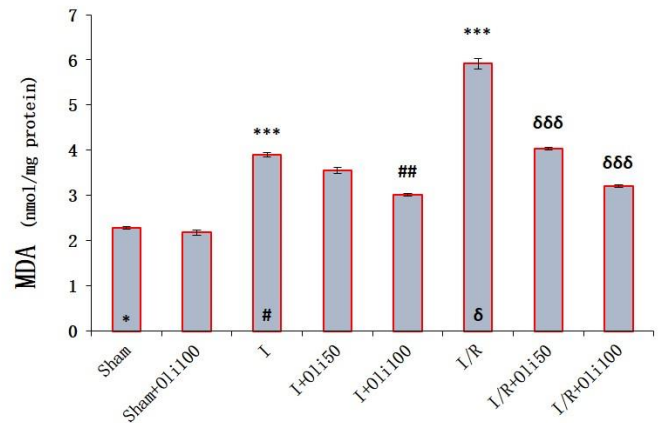


MDA levels

The MDA levels in ovarian tissues of the experimental groups were measured as follows: Sham group: 2.28 nmol/mg protein, Ischemia group: 3.90 nmol/mg protein, Ischemia + Olivetol 50 mg/kg group: 3.55 nmol/mg protein, Ischemia + Olivetol 100 mg/kg group: 3.02 nmol/mg protein, I/R group: 5.91 nmol/mg protein, I/R + Olivetol 50 mg/kg group: 4.03 nmol/mg protein, and I/R + Olivetol 100 mg/kg group: 3.21 nmol/mg protein (Figure 3). MDA levels were significantly increased in both the ischemia and I/R groups compared to the Sham group, indicating enhanced lipid peroxidation and oxidative stress resulting from ischemic and reperfusion injury. In the ischemia groups, Olivetol administration reduced MDA levels in a dose-

dependent manner; 50 mg/kg Olivetol produced a non-significant decrease, while 100 mg/kg Olivetol significantly lowered MDA levels ($p < .01$) compared to the ischemia group. Similarly, in the I/R groups, both 50 mg/kg and 100 mg/kg Olivetol treatments markedly decreased MDA levels with high significance ($p < .001$ for both) relative to the I/R group. These findings suggest that Olivetol effectively reduced lipid peroxidation and oxidative damage in ovarian tissues following ischemia and reperfusion.

Figure 3: MDA: Malondialdehyde, Oli: Olivetol, I: Ischemia, I/R: Ischemia/Reperfusion. Each bar expressed as mean value $\pm$ SE. Significant differences were detected between all groups, compared to Sham group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$), compared to I group (# $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$) and compared to I/R group ($\delta p < 0.05$, $\delta\delta p < 0.01$, $\delta\delta\delta p < 0.001$) by one-way ANOVA followed by Tukey test. Within the same column, group means sharing identical symbols were considered not significantly different, whereas distinct symbols indicated statistically significant differences according to Tukey's test.

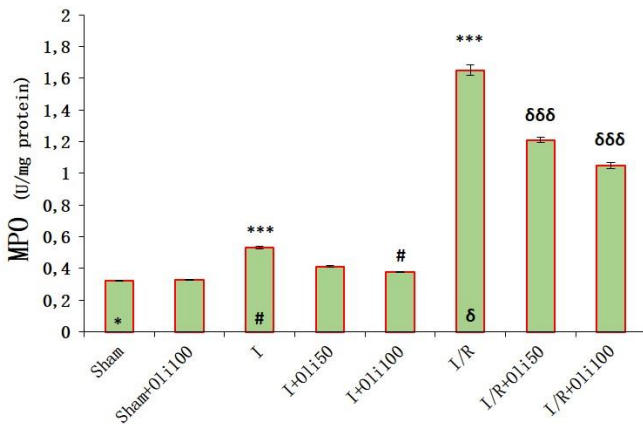


MPO activities

The MPO activity levels in ovarian tissues of the experimental groups were determined as follows: Sham group: 0.32 U/mg, Ischemia group: 0.53 U/mg, Ischemia + Olivetol 50 mg/kg group: 0.41 U/mg, Ischemia + Olivetol 100 mg/kg group: 0.38 U/mg, I/R group: 1.65 U/mg, I/R + Olivetol 50 mg/kg group: 1.21 U/mg, and I/R + Olivetol 100 mg/kg group: 1.04 U/mg (Figure 4). MPO activity was significantly increased in both the ischemia and I/R groups compared to the Sham group, indicating enhanced neutrophil infiltration and inflammatory response following ischemic and reperfusion injury. In the ischemia

groups, Olivetol treatment led to a dose-dependent reduction in MPO activity; while 50 mg/kg Olivetol caused a non-significant decrease, 100 mg/kg Olivetol significantly reduced MPO levels ($p < .05$) compared to the ischemia group. Similarly, in the I/R groups, Olivetol at 50 mg/kg and 100 mg/kg significantly decreased MPO activity ($p < .001$ for both) relative to the I/R group. These findings demonstrate that Olivetol effectively attenuated ischemia- and reperfusion-induced inflammatory responses in ovarian tissue by reducing MPO activity.

Figure 4: MPO: Myeloperoxidase, Oli: Olivetol, I: Ischemia, I/R: Ischemia/Reperfusion. Each bar expressed as mean value $\pm$ SE. Significant differences were detected between all groups, compared to Sham group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$), compared to I group (# $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$) and compared to I/R group ($\delta p < 0.05$, $\delta\delta p < 0.01$, $\delta\delta\delta p < 0.001$) by one-way ANOVA followed by Tukey test. Within the same column, group means sharing identical symbols were considered not significantly different, whereas distinct symbols indicated statistically significant differences according to Tukey's test.



Discussion

In the present study, we investigated the potential protective effects of Olivetol on ovarian I/R injury in rats by evaluating oxidative stress and inflammation-related biochemical parameters. Our results demonstrated that ischemia and subsequent reperfusion significantly disrupted the oxidant-antioxidant balance in ovarian tissue, as evidenced by decreased SOD and GSH levels and increased MPO and MDA activities. Treatment with Olivetol, particularly at higher doses, effectively restored antioxidant capacity and reduced oxidative damage,

indicating its potent cytoprotective potential against I/R-induced ovarian injury.

Ovarian torsion followed by detorsion represents a classic I/R injury. Although ischemia initiates cellular damage through oxygen deprivation, reperfusion paradoxically exacerbates tissue injury by triggering excessive production of reactive oxygen species (Bayir et al., 2016). The total tissue damage therefore reflects the combined effects of both ischemic and reperfusion phases (Kalogeris et al., 2016). During reperfusion, mitochondrial dysfunction and activation of oxidant-generating enzymes lead to a burst of ROS production, which has been demonstrated in several organs, including the kidney, heart, muscle, and ovaries (Li & Jackson, 2002). Excessive ROS induces lipid peroxidation, disrupts cellular and endothelial membrane integrity, and impairs cellular homeostasis. In addition, ROS inactivates endogenous antioxidant enzymes and promotes neutrophil recruitment and activation, resulting in increased cytokine release and amplification of inflammatory responses, ultimately contributing to ovarian tissue injury (Bayir et al., 2016).

Significant reductions in SOD activity and GSH concentrations in the ischemia and I/R groups demonstrate impairment of antioxidant defense pathways, likely attributable to overproduction of ROS. (Bircan et al., 2025; Öztürk et al., 2025; Un et al., 2015). Restoration of these parameters by Olivetol suggests that it enhances the antioxidant defense mechanism, likely through free radical scavenging and inhibition of lipid peroxidation. These findings are consistent with previous studies reporting the antioxidative and ROS-scavenging abilities of Olivetol in various experimental models of oxidative stress (Cascio et al., 2006; Divya & Narayanan, 2022; Özkan et al., 2025; Shanmugasundaram & Jayasankar, 2025; Zabolotneva et al., 2025).

Neutrophil activation and MPO release contribute to excessive reactive oxygen species production, thereby linking inflammation and oxidative stress in the pathogenesis of I/R injury (Tang et al., 2022). MPO activity, an indicator of neutrophil infiltration and inflammation, was markedly elevated following ischemia and reperfusion, supporting the role of inflammatory cell activation in ovarian I/R injury (Yilmaz et al., 2020). Olivetol administration significantly reduced MPO activity,

indicating that it may suppress neutrophil-mediated oxidative and inflammatory responses. However, inflammation is a complex, multifactorial process involving multiple cytokines and signaling pathways, and the assessment of inflammation based on a single biochemical marker such as MPO represents a limitation of the present study. Nevertheless, MPO is widely accepted as a reliable indicator of neutrophil-driven inflammatory responses in ischemia/reperfusion injury (Ciortan et al., 2025; Rizo-Tellez et al., 2022). Similarly, MDA levels—a key marker of lipid peroxidation and cellular membrane damage—were significantly increased after ischemia and reperfusion but were effectively decreased by Olivetol in a dose-dependent manner. The reduction of both MPO and MDA levels by Olivetol highlights its dual antioxidant and anti-inflammatory properties.

Taken together, these findings suggest that Olivetol mitigates oxidative and inflammatory damage by enhancing endogenous antioxidant defenses and attenuating lipid peroxidation and neutrophil activation. The observed effects are comparable to those of other well-known antioxidants, such as melatonin and resveratrol, which have also been reported to protect ovarian tissues against I/R-induced damage. Importantly, administration of high-dose Olivetol (100 mg/kg) did not produce any toxic effects in healthy rats, supporting its safety profile at the doses tested.

Conclusion

In conclusion, our study provides the first experimental evidence that Olivetol exerts protective effects against ovarian ischemia/reperfusion injury through its potent antioxidant and anti-inflammatory activities. By improving the redox balance and reducing tissue inflammation, Olivetol may preserve ovarian function and structure following ischemic insult. Further studies, including molecular and histopathological evaluations, are warranted to elucidate the precise mechanisms underlying its protective effects and to explore its potential therapeutic application in clinical settings of ovarian torsion and other ischemic conditions.

Ethics Committee Approval: This project was approved by the Local Ethics Committee for Animal Experiments of Atatürk University (approval number: 2300251381, Date: 17.08.2023).

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