Clinical and Experimental Health Sciences

Therapeutic Potential of Irisin in Ovarian Torsion-Detorsion: Mitigating Oxidative Stress and Inflammatory Response

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Received: February 10, 2025 **Accepted:** June 23, 2025

ABSTRACT

Objective: Ovarian torsion (OT) is a critical gynecological emergency marked by partial or complete rotation of the ovary around its ligamentous supports, resulting in impaired blood flow and potential ischemic injury or necrosis if not treated promptly. This study explores the potential of irisin in mitigating ischemia-reperfusion (I/R) injury following ovarian torsion-detorsion (T/D), with a focus on oxidative stress and inflammatory mediators.

Methods: Twenty-four female Sprague-Dawley rats were allocated into three groups: Sham, T/D, and irisin 10 μg/kg. Oxidative stress markers—total oxidant status (TOS), oxidative stress index (OSI), malondialdehyde (MDA), and myeloperoxidase (MPO)—were measured to assess tissue damage. Antioxidant parameters, including superoxide dismutase (SOD) activity and total antioxidant status (TAS) were evaluated. Serum levels of tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) were analyzed to assess systemic inflammation and irisin's modulatory role.

Results: The T/D group showed elevated MPO and MDA levels relative to the sham group ($p<.05$), alongside significant reductions in SOD activity and TAS levels ($p<.05$). Irisin administration reversed these imbalances, decreasing MPO and MDA levels and enhancing SOD and TAS levels ($p<.05$ vs. T/D group). TNF-α and IL-1β levels, which were significantly elevated in the T/D group, were reduced by irisin treatment ($p < .05$ vs. T/D group), indicating its anti-inflammatory efficacy.

Conclusion: The findings support the potential of irisin as a therapeutic agent for mitigating oxidative stress and inflammation in ovarian I/R injury. Irisin may offer clinical benefits in preserving ovarian function during conditions related to T/D.

Keywords: Ovarian torsion-detorsion, ischemia-reperfusion injury, irisin, oxidative stress, inflammatory response

1. INTRODUCTION

Ovarian torsion (OT) refers to the rotation of an ovary around its pedicle, typically occurring during gynecological events (1). This rotation can disrupt normal ovarian blood flow, leading to vascular compromise and potentially severe clinical outcomes (2). Although OT is relatively uncommon, it predominantly affects women of reproductive age and can have serious implications. Notably, 15% of OT cases occur during adolescence (3). This condition is often associated with underlying ovarian masses or cysts. Despite its rarity, OT accounts for approximately 3% of all gynecological emergencies (4, 5).

Detorsion procedures are employed to restore blood flow and preserve ovarian viability (6). However, the reperfusion that follows detorsion induces an overproduction of reactive oxygen species (ROS) and promotes lipid peroxidation (7). These processes can damage follicles and contribute to the development of atretic bodies within the ovarian tissue. Prompt diagnosis and treatment are crucial for distinguishing OT from other conditions and protecting reproductive function (8). Recent investigations aim to mitigate the damage caused by T/D, with a particular focus on minimizing cell damage resulting from reperfusion injury following ischemia (9-11).

How to cite this article: Güler CM, Bircan B, Eraslan E, Akdemir Ekinci NF, Yazıcı Ş, Erdoğan Güzel D, Öztürk D, Polat E, Tanyeli A. Therapeutic Potential of Irisin in Ovarian Torsion-Detorsion: Mitigating Oxidative Stress and Inflammatory Response. Clin Exp Health Sci 2025; 15: 434-439. https://doi.org/10.33808/clinexphealthsci.1636484

Irisin is a myokine secreted primarily by adipose tissue in response to physical activity, and it exerts numerous biological effects, especially in muscle metabolism. It enhances metabolic rate, increases energy expenditure, and facilitates fat oxidation (12). There is growing scientific interest in irisin's anti-inflammatory, anti-apoptotic, and antioxidative properties, which are implicated in the pathogenesis of various diseases, including liver disorders, myocardial infarction, pulmonary injury, renal diseases, cancer, and atherosclerosis (13, 14).

Given the established protective effects of irisin in ischemic models, we hypothesize that exogenous irisin administration could attenuate oxidative stress and inflammation in ovarian I/R injury, thereby preserving ovarian structural integrity. This study aims to assess the therapeutic potential of irisin in a rat model of ovarian T/D by evaluating its impact on oxidative stress markers (malondialdehyde [MDA], oxidative stress index [OSI], total oxidant status [TOS], and myeloperoxidase [MPO]), antioxidant defense mechanisms (superoxide dismutase [SOD] and total antioxidant status [TAS]), and proinflammatory cytokines (interleukin-1 beta [IL-1β] and tumor necrosis factor-alpha [TNF-α]). These findings aim to provide new insights into the clinical applicability of irisin for preventing ovarian injury in gynecological settings.

2. METHODS

2.1. Ethical Approval

This study was approved by the Animal Experiments Local Ethics Committee of Atatürk University (Approval Date: 30.06.2017; Protocol No: 5). All procedures adhered to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines to ensure ethical conduct, transparency, and reproducibility.

2.2. Chemicals

A 10% povidone-iodine solution (Batticon, Adeka) was used for disinfection. Anesthesia was achieved using a combination of ketamine (Ketalar®, Pfizer, Istanbul) and xylazine hydrochloride (Rompun®, Bayer, Istanbul). Irisin (CAS 1465928-51-1, purity ≥95.0%) was obtained from Sigma-Aldrich (St. Louis, MO, USA).

2.3. Animals

Female Wistar albino rats (12–16 weeks old, 200–250 g) were sourced from the Atatürk University Laboratory Animals Research and Application Center. Rats were housed under standard conditions with a 12-hour light/dark cycle, controlled temperature, and relative humidity (55 ± 5%). Standard pellet feed and water were provided *ad libitum*. Animals were fasted overnight before procedures, with water available throughout.

2.4. Experimental Groups

The experimental animals were prepared for the experimental process. They were supine positioned. The abdominal areas were shaved and disinfected with 10% povidone-iodine. For anesthesia, intraperitoneal (i.p.) ketamine (100 mg/kg) and xylazine (15 mg/kg) were preferred based on previous research (15). A total of 24 female Wistar albino rats (12–16 weeks old, 200–250 g) were randomized into three experimental groups (n=8 per group):

Group I (sham): Underwent laparotomy (1–2 cm incision) without any ovarian manipulation.

Group II (T/D): The T/D model is represented in Figure 1, based on a previous study (16). Following laparotomy, bilateral ovarian torsion was induced by rotating the ovaries 360° in a clockwise direction and securing them with atraumatic microvascular clamps for three hours. Following the torsion phase, the clamps were carefully removed, allowing blood circulation to resume for another three hours before the surgical site was closed.

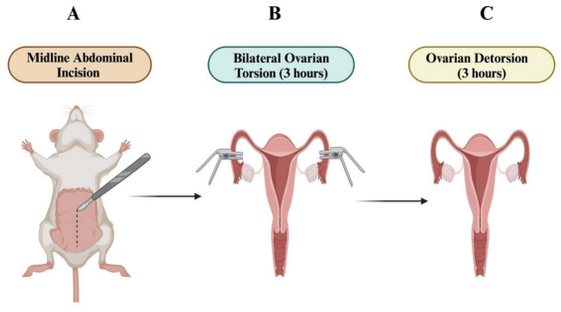

Figure 1. *Schematic representation of the ovarian torsion/detorsion (T/D) experimental model. A) Midline abdominal incision (1–2 cm) for surgical access. B) Induction of bilateral ovarian torsion via 360° clockwise rotation, stabilized with atraumatic vascular clamps for a 3-hour ischemic phase. C) Initiation of the reperfusion phase by clamp removal, restoring blood circulation during detorsion (Created in https://BioRender.com).*

Group III (Irisin 10 µg/kg): Underwent the same procedure as Group II, with the addition of intravenous irisin (10 µg/kg) administered via tail vein 30 minutes before detorsion. The irisin dose was selected based on prior research (17).

Following a 3-hour detorsion period, rats were humanely euthanized via intraperitoneal (i.p.) ketamine (100 mg/kg) and xylazine (15 mg/kg) administration to induce deep anesthesia, followed by cervical dislocation to ensure death.

2.5. Biochemistry Methods

For biochemical analyses, 100 mg of ovarian tissue was homogenized in 2 mL of 10% phosphate-buffered saline (PBS) using a homogenizer (IKA, Staufen, Germany) at 10,000 rpm for 5 minutes while kept on ice. The homogenate was centrifugated at 3,000 × g for 30 minutes at 4°C and utilized for biochemical assays. The analyses included measurements of MDA, MPO, SOD, TAS, and TOS. Additionally, proinflammatory cytokines, like TNF-α and IL-1β, were quantified using a rat-specific ELISA kit (Elabscience, Wuhan, China).

MDA levels were determined following a modified thiobarbituric acid (TBA) assay, initially described by Ohkawa et al. (1979) (18). In this assay, tetramethoxypropane was used as an external standard, and the concentration of lipid peroxidation products was expressed in MDA nanomoles. The reaction between TBA and MDA was measured spectrophotometrically (PowerWave™ XS Biotek). The assay involved incubating the sample with butylated hydroxytoluene (BHT) in methanol and adding phosphoric acid and TBA reagents. The mixture was heated for 60 minutes at 95°C. Following the cooling, the sample was centrifuged for 3 minutes at 10,000×g.

MPO activity was assessed using the method outlined by Bradley et al. (19). This method quantifies the oxidation of o-dianisidine in the presence of hydrogen peroxide (H_2O_2), forming a yellow-orange complex. After centrifuging the tissue suspension at 40,000×g for 15 minutes, the supernatant was analyzed with a spectrophotometer (PowerWave XS Biotek).

SOD activity was determined using a method adapted from Sun et al. (20). This technique assesses the inhibitory effect of SOD on nitro blue tetrazolium (NBT). The optical density was recorded using a spectrophotometer (PowerWave XS Biotek).

Total protein concentrations in the tissue homogenates were determined using the Bradford protein assay (Bio-Rad, USA), with bovine serum albumin (BSA) as the standard. All biochemical parameters (MDA, MPO, SOD, and cytokines) were normalized to the protein content and expressed as units per milligram of protein.

TAS and TOS levels were determined using commercial kits (Rel Assay Diagnostics, Gaziantep, Turkey), where TAS was expressed in terms of Trolox equivalents (mmol Trolox Eq/L) and TOS in hydrogen peroxide equivalents (µmol H_2O_2 Eq/L). The oxidative stress index (OSI) was calculated as the ratio of TOS to TAS, following normalization to the same unit (Arbitrary unit) (21).

2.6. Statistics

All data are represented as mean±standard error of the mean (SEM). Statistical analyses were completed using SPSS version 16.0 (SPSS Inc. and Lead Tech. Inc., Chicago, IL). Before analysis, the normality of the data was evaluated to determine the appropriate statistical methods. Group comparisons were conducted using the Kruskal-Wallis test for nonparametric data. In cases where significant differences were observed, the Mann-Whitney U test was employed to pinpoint the specific groups responsible for the variation. A p-value of ≤ .05 was the threshold for statistical significance.

3. RESULTS

3.1. Assessment of Oxidative Stress and Antioxidant Markers

Biochemical analyses revealed notable differences in oxidative stress parameters among the experimental groups (Figure 2). The T/D group exhibited significantly elevated MPO activity and MDA levels compared to the sham group (p<.05). Conversely, irisin administration (10 µg/kg) significantly reduced both MPO activity and MDA levels relative to the T/D group (p<.05), indicating a protective effect against oxidative stress.

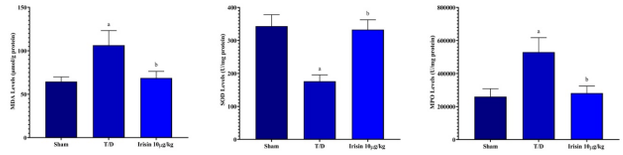

Figure 2. *Effects of irisin on oxidative stress markers. Superoxide dismutase (SOD) activity, malondialdehyde (MDA) levels, and myeloperoxidase (MPO) activity across experimental groups. Data represent mean±SEM. [a]p<.05 vs. sham group, [b]p<0.05 vs. D/T group (one-way ANOVA with Tukey's post-hoc test). Irisin (10 µg/kg) administration significantly reduced MDA and MPO levels while restoring SOD activity, demonstrating its antioxidant efficacy in mitigating oxidative damage.*

In contrast, SOD activity, an essential antioxidant enzyme, was significantly decreased in the T/D group compared to the sham group (p < .05). Irisin treatment effectively restored SOD activity to levels comparable to those of the sham group (p < .05 vs. T/D), underscoring its antioxidative efficacy.

3.2. Ovarian Tissue Oxidative Status

The T/D group demonstrated a significant reduction in TAS compared to the sham group (p<.05), reflecting diminished antioxidant capacity. Treatment with irisin resulted in a statistically significant increase in TAS (p<.05 vs. T/D), suggesting enhanced antioxidant defense.

Conversely, TOS and OSI values were significantly elevated in the T/D group (p<.05 vs. sham), indicating increased oxidative stress. Irisin administration normalized these values, significantly reducing both TOS and OSI compared to the T/D group (p < .05), further highlighting its role in reestablishing redox balance (Figure 3).

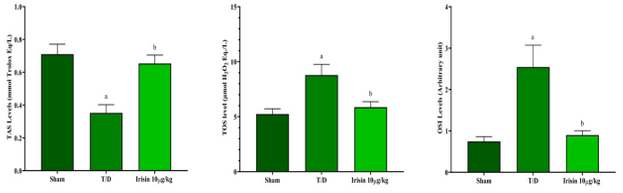

Figure 3. *Modulation of systemic oxidative stress indices by irisin. Total antioxidant status (TAS), oxidative stress index (OSI), and total oxidant status (TOS) in sham, D/T, and irisin-treated groups. Values are expressed as mean±SEM. [a]p<.05 vs. sham group, [b]p<.05 vs. D/T group (one-way ANOVA with Tukey's post-hoc test). Irisin (10 µg/kg) treatment normalized TAS, TOS, and OSI levels, counteracting the oxidative imbalance induced in the D/T group.*

3.3. Proinflammatory Cytokine Modulation

Serum concentrations of TNF-α and IL-1β were significantly higher in the T/D group compared to the sham group (p<.05), confirming the presence of a robust inflammatory

response following reperfusion injury. Irisin administration significantly reduced the levels of both cytokines (p<.05 vs. T/D), demonstrating its anti-inflammatory potential in this model (Figure 4).

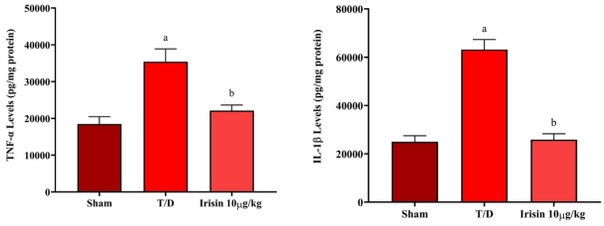

Figure 4. *Irisin attenuates proinflammatory cytokine Levels. Concentrations of tumor necrosis factor-alpha (TNF-α) and interleukin-1ß (IL-1ß) in serum samples from sham, D/T, and irisin-treated groups. Data are presented as mean±SEM. [a]p<.05 vs. sham group, [b]p<.05 vs. D/T group (one-way ANOVA with Tukey's post-hoc test). Irisin (10 µg/kg) notably attenuated the elevation of IL-1ß and TNF-α, highlighting its anti-inflammatory role in the experimental model.*

4. DISCUSSION

Ovarian torsion represents a significant threat to female fertility due to the risk of ischemia and subsequent tissue necrosis if not managed promptly (22). Although detorsion is a commonly employed intervention to restore perfusion, it is paradoxically associated with reperfusion injury mediated by excessive ROS generation (23, 24). ROS overproduction leads to lipid peroxidation by converting metabolic by-products into free radicals in ischemic tissues (25). Increased MDA concentrations during I/R injury are recognized as biomarkers of lipid peroxidation, reflecting oxidative damage to cellular membranes (26). MPO, a substance secreted by neutrophils and macrophages, is crucial in oxidative stress-related tissue damage by generating hydroxyl radicals (27). Our research supports the accuracy of these findings by demonstrating a substantial rise in MDA and MPO levels, which suggests the presence of I/R injury due to ovarian T/D, consistent with prior studies on ovarian I/R injury.

Oxidative stress triggers endogenous defense mechanisms, such as SOD, which neutralizes superoxide radicals, and non-enzymatic antioxidants like glutathione GSH, a critical cellular reductant. These antioxidant systems act synergistically to mitigate oxidative damage and restore redox homeostasis at the cellular level (28). Although cells have their defense mechanisms, in the case of ischemia, this balance is disrupted by oxidative stress (29). The imbalance between oxidants and antioxidants intensifies tissue damage during I/R injury. Thus, identifying pharmacological agents with potent antioxidant and anti-inflammatory properties is crucial for mitigating ovarian damage and improving the management of I/R injury (30). Our research reveals a significant decline in SOD activity in the T/D group, consistent with the existing literature.

I/R injury is associated with elevated levels of pro-inflammatory cytokines, notably IL-1β and TNF-α. Elevated levels of these cytokines have been observed in ovarian tissues subjected to I/R injury, contributing to tissue damage (31). Our findings also supported high proinflammatory cytokine levels (IL-1β and TNF-α) in the T/D group, indicating inflammatory response during I/R injury.

Irisin has attracted attention because of its protective effects against I/R injury. Research indicates that irisin mitigates myocardial I/R injury by preserving mitochondrial function and reducing oxidative stress. Specifically, it enhances the activity of SOD 2, thereby decreasing ROS production and subsequent cellular damage (32). Additionally, irisin has been shown to activate the AMP-activated protein kinase (AMPK) pathway, leading to enhanced mitochondrial biogenesis and function, which are crucial in maintaining cellular energy homeostasis during ischemia-reperfusion (I/R) events (33). Beyond its mitochondrial protective roles, irisin exerts anti-inflammatory effects by modulating gut microbiota composition and enhancing intestinal barrier integrity, thereby reducing systemic inflammation associated with myocardial I/R injury (34). In another study, I/R-related ROS production and proinflammatory parameters (IL-1β, IL-6, etc.) can be diminished by irisin (35).

The collective data from our study reinforce the hypothesis that irisin exerts both antioxidative and anti-inflammatory effects, thereby conferring tissue protection in ovarian T/D injury. These effects may be mediated through multiple mechanisms, including modulation of ROS production, preservation of antioxidant enzyme activity, and suppression of proinflammatory cytokine release.

Future studies should explore the molecular pathways underpinning these protective effects, such as irisin's interaction with the AMPK and SOD2 pathways, and evaluate its translational potential in clinical gynecology.

5. CONCLUSION

Ovarian torsion remains a gynecological emergency requiring swift intervention to prevent irreversible damage. This study provides experimental evidence that irisin effectively attenuates oxidative stress and inflammation associated with T/D-induced I/R injury. The observed reductions in oxidative biomarkers and pro-inflammatory cytokines, along with the restoration of antioxidant capacity, underscore the therapeutic promise of irisin. Further investigations are warranted to elucidate its molecular mechanisms and assess its clinical applicability in preserving ovarian function.

Acknowledgements: *We would like to thank Marmara University for providing access to academic databases.*

Funding: *The author(s) received no financial support for the research.*

Conflicts of interest: *The authors declare that they have no conflict of interest.*

Ethics Committee Approval: *This study was approved by Atatürk University Animal Experiments Local Ethics Committee (Approval date: 30.06.2017; Number: 5).*

Peer-review: *Externally peer-reviewed.*

Author Contributions: (Initials only)

Research idea: MCG, BB, EE, AT

Design of the study: MCG, BB, EE, FNEA, ŞY, DGE, DÖ, EP, AT

Acquisition of data for the study: EE, EP

Analysis of data for the study: EE, EP

Interpretation of data for the study: EE, MCG

Drafting the manuscript: MCG, BB, EE, ŞY, AT

Revising it critically for important intellectual content: MCG, EE, ŞY, AT

Final approval of the version to be published: MCG, BB, EE, FNEA, ŞY, DGE, DÖ, EP, AT

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