

Endurance training and MitoQ attenuate renal injury in ovariectomized rats with unilateral ureteral obstruction



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ABSTRACT

Introduction: Oxidative stress and inflammation are recognized as key contributors to the unilateral ureteral obstruction (UVO). The present study aimed to evaluate the potential effect of endurance training (ET) and the mitochondria-targeted antioxidant MitoQ, administered separately or in combination, in ovariectomized (OVX) rats subjected to UVO-induced renal damage.

Methods: Fifty-six OVX female Wistar rats were randomly assigned to eight groups (n = 7/group): Sham, Sham+ET, Sham+MitoQ, Sham+ET+MitoQ, UVO, UVO+ET, UVO+MitoQ, and UVO+ET+MitoQ. ET was performed on a treadmill for four weeks, while MitoQ (5 mg/kg/day, IP) was administered throughout the intervention period. Histopathological alterations, oxidative stress markers, antioxidant status, and inflammatory cytokines were evaluated in obstructed kidneys.

Results: Histological analysis demonstrated significant tubular injury, fibrosis, glomerulosclerosis, and inflammation in UVO rats ($P < 0.001$). Moreover, UVO increased renal malondialdehyde (MDA), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β) levels, while significantly reducing total antioxidant capacity (TAC) and superoxide dismutase (SOD) activity ($P < 0.001$). ET or MitoQ treatment significantly attenuated these pathological alterations, whereas combined therapy exerted greater protective effects than either intervention alone.

Conclusion: ET and MitoQ supplementation effectively ameliorated UVO injury in OVX rats by suppressing oxidative stress and inflammation. Combined intervention produced superior renoprotective effects, compared with either intervention alone. These findings suggest that ET and MitoQ may represent a promising therapeutic approach within the experimental ovariectomized UVO model.

Keywords:

Endurance training

MitoQ

Unilateral ureteral obstruction

Oxidative stress

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Introduction

Ureteral obstruction is a significant global health concern and a common clinical condition affecting both adults and children. This condition can lead to kidney damage and chronic kidney disease (CKD) (Martínez-Klimova et al., 2020). Ureteral obstruction induces a series of hemodynamic changes in the kidney and increased oxidative stress and inflammation. It also triggers inflammatory mediators, leading to interstitial inflammatory cell infiltration, which ultimately contributes to interstitial fibrosis and tubular cell death via necrosis and apoptosis (Martínez-Klimova et al., 2019).

The unilateral ureteral obstruction (UUO) model has been extensively employed in experimental research to examine the molecular pathways and histopathological alterations involved in obstructive kidney injury (Klahr and Pukerson 1994). UUO initiates a cascade of pathological events in the affected kidney, including oxidative stress, interstitial inflammation, tubular apoptosis, cellular atrophy, interstitial fibrosis, and necrosis (Chevalier et al., 2009). Therefore, targeting oxidative stress and inflammation is considered a promising therapeutic strategy to attenuate kidney damage (Dendooven et al., 2011). Despite recent advances, the effective therapeutic interventions for UUO remains a major challenge.

Among modifiable lifestyle factors, physical activity is well recognized as a protective factor that can prevent or ameliorate many risk conditions associated with CKD (Stump 2011). In addition, reduced aerobic capacity has been identified as a strong predictor of mortality in patients with CKD and end stage renal diseases (ESRD) (Cheema 2008). Castaneda et al. have been reported that a 12-week resistance training intervention significantly decreased systemic inflammatory biomarkers and enhanced the nutritional status of patients with CKD (Castaneda et al., 2004). Likewise, Pei et al. demonstrated that exercise training led to improvements in maximal oxygen uptake (VO_2 peak) and contributed to better quality of life among CKD patients (Pei et al., 2019). The protective effects of exercise have also been reported in various studies, including cardiotoxicity (Roshan et al., 2011), liver disease (Melo et al., 2021), lung toxicity (So et al., 2021), and estrogen-deficiency (Masoumi-Ardakani et al., 2022a).

Mitoquinone mesylate (MitoQ) is a mitochondria-targeted antioxidant with potent antioxidant effects (Kelso et al., 2001). The ubiquinone moiety of MitoQ facilitates

its rapid uptake and accumulation within mitochondria, thereby preventing mitochondrial oxidative damage. MitoQ restores antioxidant capacity by reducing lipid peroxidation and scavenging free radicals (Graham et al., 2009). Numerous studies have been demonstrated its antioxidant effects in cardiovascular disease (Xiao et al., 2017), diabetic kidney disease (Rostamzadeh et al., 2024), myocardial injury (Masoumi-Ardakani et al., 2022b), hypertension (Zadeh et al., 2023) and estrogen-deficient conditions, such as ovariectomy (Askaripour et al., 2022a; Zadeh et al., 2023).

Considering the pivotal contribution of oxidative stress and inflammation in the pathogenesis of ureteral obstruction, along with the recognized antioxidant and anti-inflammatory effects of endurance training (ET) and MitoQ, this study was designed to evaluate the effects of ET and MitoQ, alone and in combination, on histopathological damage, oxidative stress, and inflammation in ovariectomized (OVX) female rats subjected to UUO as a model of postmenopausal obstructive nephropathy.

Material and Methods

Animals

Fifty-six adult female Wistar rats ($n=7$ per group), weighing between 180 and 220 g, were included in the present investigation. The animals were supplied by the institutional animal facility and maintained under normal controlled laboratory conditions. The sample size ($n=7$ per group) was determined based on previous studies using similar experimental UUO models that employed comparable group sizes and reported adequate statistical power to detect significant differences in renal histopathological and biochemical outcomes (Askaripour et al., 2022a). All experimental procedures were approved by the Institutional Animal Ethics Committee of Kerman University of Medical Sciences (Ethics Approval No. IR.KMU.AEC.1401.002) and were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

OVX and UUO procedures

All animals were subjected to bilateral ovariectomy surgery two weeks before experiments. Anesthesia was induced by intraperitoneal administration of a ketamine/xylazine combination (80/10 mg/kg). After transverse incision in the lower abdominal area, ovaries were sur-

TABLE 1: Endurance training schedule.

Week	1	2	3	4
Speed (m/min)	15 60% Vmax	20 65% Vmax	27 75% Vmax	27 75% Vmax
Time (min)	20	30	45	50

**FIGURE 1.** The final morphology of the non-obstructed right kidney and the obstructed left kidney is illustrated using two distinct color indicators. In the UUO groups, the obstructed left kidney exhibited marked enlargement, distension, and swelling as a result of urine retention, ultimately leading to hydronephrosis.

gically removed. Finally, the incision sites were closed using sterile 4-0 sutures (Askaripour et al., 2022a). After completion of the recovery phase, OVX rats were subjected to UUO surgery. A left lateral flank incision was performed to access the left ureter. Subsequently, the ureter was ligated at two separate locations using 4-0 silk sutures and transected between the ligation points. In the sham groups, surgical procedures were carried out except for ureteral ligation (Askaripour et al., 2022b). Figure 1 presents the final dimensions of both the non-obstructed right kidney and the obstructed left kidney.

Endurance training protocol

Endurance training was conducted in the training groups over a period of four weeks, five days per week, between 11 AM and 4 PM daily (Aminizadeh et al., 2021). Maximal oxygen consumption ($\text{VO}_{2\text{max}}$) was measured using the Vmax system. Lactate levels were measured using a lactometer (Lønbro et al., 2019). Subsequently, $\text{VO}_{2\text{max}}$ was calculated, and the ET protocol was performed according to the guidelines outlined in Table 1 (Zoladz et al., 2016). The control (CTL) and MitoQ-treated groups were placed on the treadmill during

each training session without undergoing active exercise.

Experimental groups and protocol

A total of fifty-six OVX female Wistar rats were randomly placed into eight groups ($n = 7$ per group): Sham, Sham + ET, Sham + MitoQ, Sham + MitoQ + ET, UUO, UUO + ET, UUO + MitoQ, and UUO + MitoQ + ET. Endurance training was performed through regular treadmill exercise for four weeks, following the protocol outlined in Table 1. MitoQ was administered intraperitoneally (IP) at a dose of 5 mg/kg/day, prepared in saline, from the first day of the experiment and continued for the full 4-week duration (Chacko et al., 2011; Huang et al., 2022). For the UUO groups that received exercise, treadmill sessions began 24 hours post-surgery. The non-MitoQ groups received saline injections of the same volume as the MitoQ dose. On day 43, the animals were weighed and anesthetized. After that, the animals were euthanized, and left kidney tissues were harvested and weighed. One portion of the kidney was fixed in 10% formalin for histopathological evaluation, and the other was preserved at -80°C for the measurement of antioxidant and inflammatory biomarkers. The left kid-

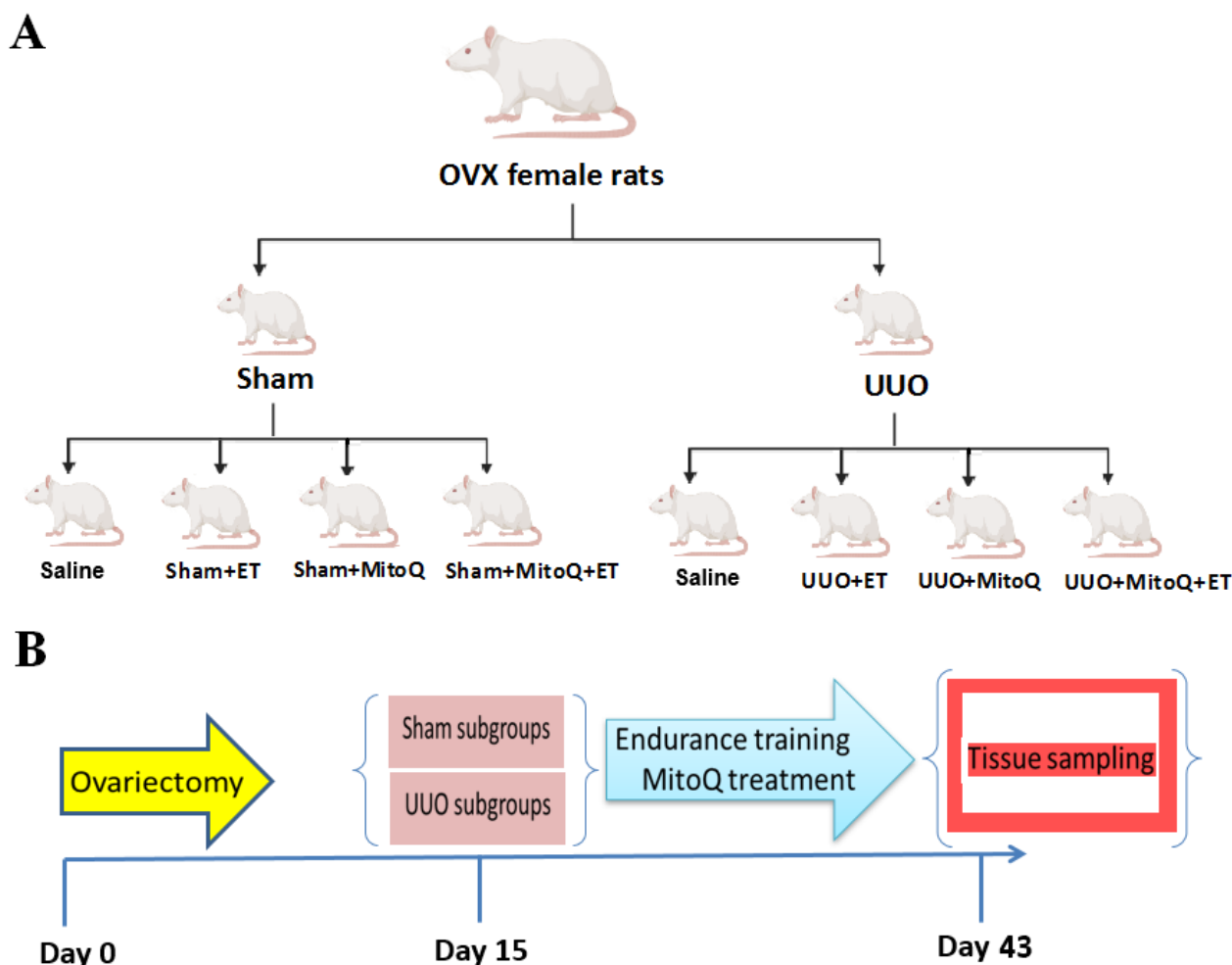


FIGURE 2. Schematic illustration of the experimental groups (A) and study timeline (B). UUO: Unilateral ureteral obstruction; ET: Endurance training; MitoQ: Mitochondria-targeted antioxidant MitoQ.

ney was analyzed because unilateral ureteral obstruction was induced in the left ureter, and the ipsilateral kidney is the primary site of pathological changes in the UUO model. The experimental design and study timeline are presented in Figures 2A and 2B.

Histological evaluation

Hematoxylin and eosin (H&E) and Masson's trichrome staining were employed for histological evaluation. A blinded pathologist scored the experimental groups using an Olympus microscope (CX33, Tokyo, Japan). Tubular injury scoring system was defined as follows: score 0 indicated the absence of abnormalities; score 1 represented involvement of 1–25% of the tissue; score 2 corresponded to 26–50% involvement; score 3 reflected 51–75% abnormality; and score 4 indicated tissue involvement from 76% to 100% (Hammad et al.,

2023). Inflammatory changes were graded according to the following criteria: score 0 indicated normal without evidence of inflammation; score 1 represented inflammatory cell infiltration in less than 25%; score 2 corresponded to involvement of less than 50% of the fields; score 3 reflected inflammatory changes in less than 75%; and score 4 indicated inflammation affecting more than 75% (Askaripour et al., 2022a). Fibrotic lesions in the interstitium detected by collagen deposition and scored from 0 to 3 under: 0 = up to 5% area affected, score 1 = 6–25%, 2 = 26–50%, and 3 = more than 50% of the area (Racusen et al., 1999). Glomerulosclerosis scored from 0 to 4. score 0 = no sclerosis of the glomeruli, score 1 = sclerosis up to 25%, score 2 = sclerosis 25% to 50%, score 3 = sclerosis 50% to 75%, and score 4 = sclerosis > 75% (Askaripour et al., 2022b).

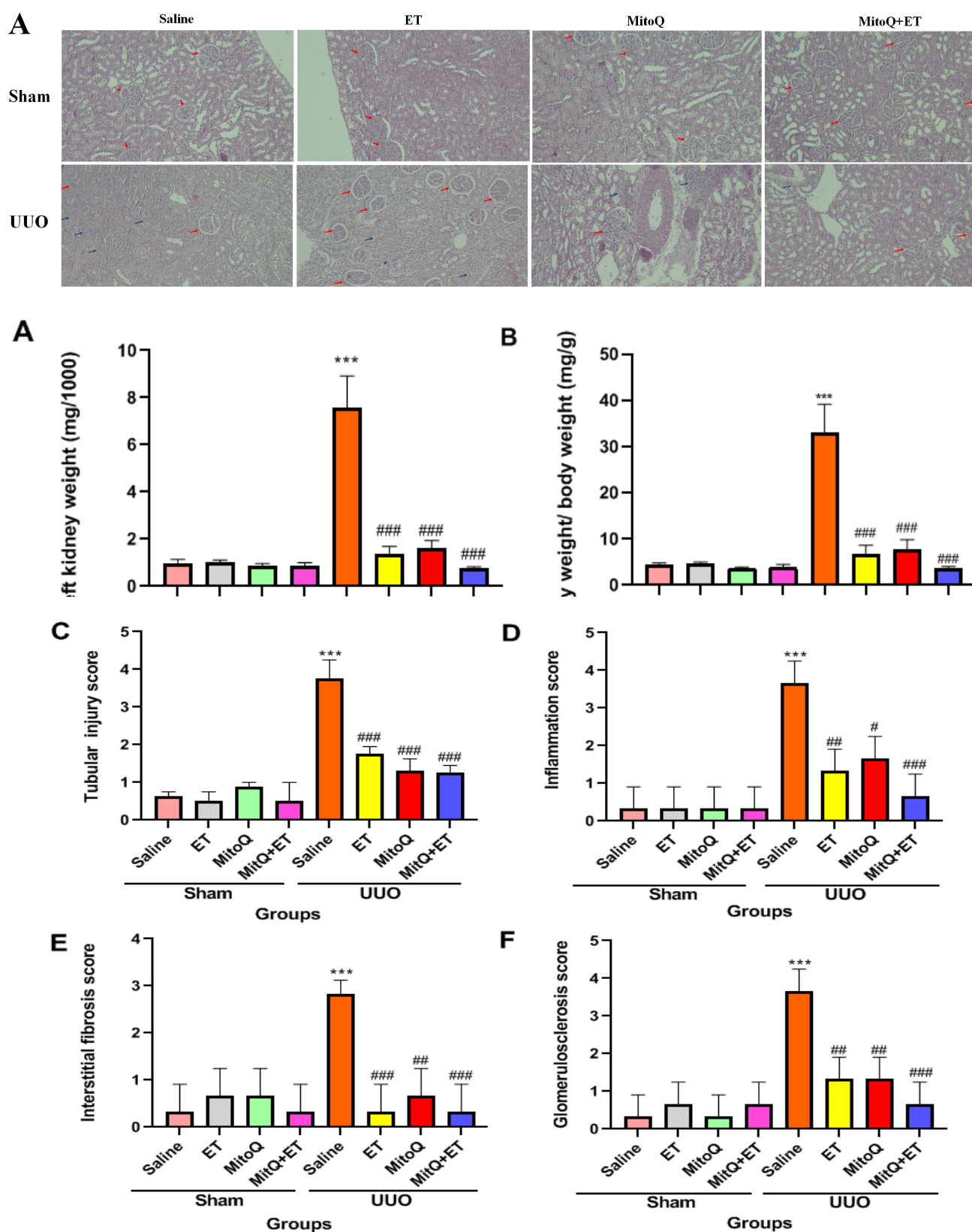


FIGURE 3. Histological assessment and semi-quantitative scoring of left kidney tissues across the experimental groups. H&E (A) and Masson's trichrome staining (B) of the left kidneys (original magnification $\times 100$; Scale bar: 200 μm). Quantitative scoring of tubular injury (C), inflammation (D), interstitial fibrosis (E), and glomerulosclerosis (F) in the left kidneys of studied groups. (mean $\pm$ SD, $n=7$). *** $P<0.001$ versus Sham + saline group. # $P<0.05$, ## $P<0.01$, ### $P<0.001$ versus UUO + saline group. Red arrows show preserved architecture and normal glomeruli in the left kidney tissue. Blue arrows show marked glomerulosclerosis, interstitial fibrosis, tubular injury, and chronic inflammation in the left kidney tissue.

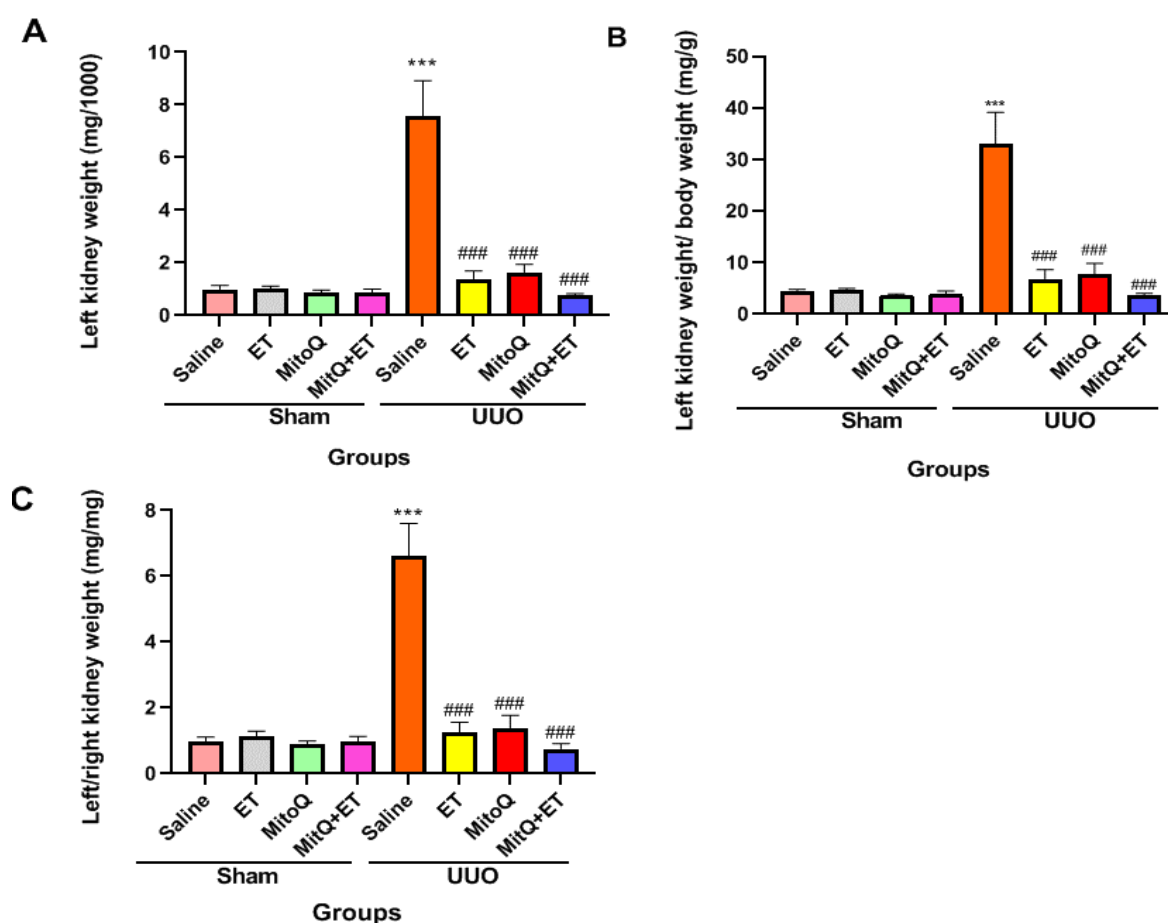


FIGURE 4. Effect of ET and MitoQ on the left kidney weight (A), the ratio of left kidney weight to body weight (B), and left/right kidney weight (C) in the experimental groups. The data are presented as the mean $\pm$ SD. With $n = 7$ per group. UUO: Unilateral ureteral obstruction; ET: Endurance training; MitoQ: Mitochondria-targeted antioxidant MitoQ. *** $P < 0.001$ versus Sham + saline group. ### $P < 0.001$ versus UUO + saline group.

Assessment of kidney lipid peroxidation and antioxidant enzymatic activity

Lipid peroxidation in left kidney tissue was determined by MDA levels (Rao et al., 1989). After the protocol, the absorbance of the resulting pink supernatant was then measured at 534 nm. Additionally, tissue superoxide dismutase (SOD) and total antioxidant capacity (TAC) activities were measured using commercial assay kits (Navand Salamat Company, Urmia, Iran).

Enzyme-Linked Immunosorbent Assay (ELISA)

Tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) levels were quantified in left kidney tissue using commercially available ELISA kits (Immutopics, San Clemente, CA, USA) according to the manufacturer's instructions. The optical density was measured at 450 nm using a Thermo Scientific Multiskan FC microplate reader (Thermo Fisher Scientific, Vantaa, Finland).

Statistical Analysis

Data are expressed as mean $\pm$ Standard Deviation (SD). GraphPad Prism® software (version 9.0; California, USA) was used for statistical analyses. Differences among groups were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. A P -value < 0.05 was considered statistically significant.

Results

Effect of ET and MitoQ on the renal histology

The results of H&E staining of the left kidney showed that UUO significantly increased tubular damage and inflammation (Figure 3 A, C, D; $P < 0.001$). Both ET and MitoQ treatment, as well as their combination, reversed the effects of UUO ($P < 0.05$). Additionally, the results in Masson's trichrome staining demonstrated that UUO significantly increased interstitial fibrosis and glomeru-

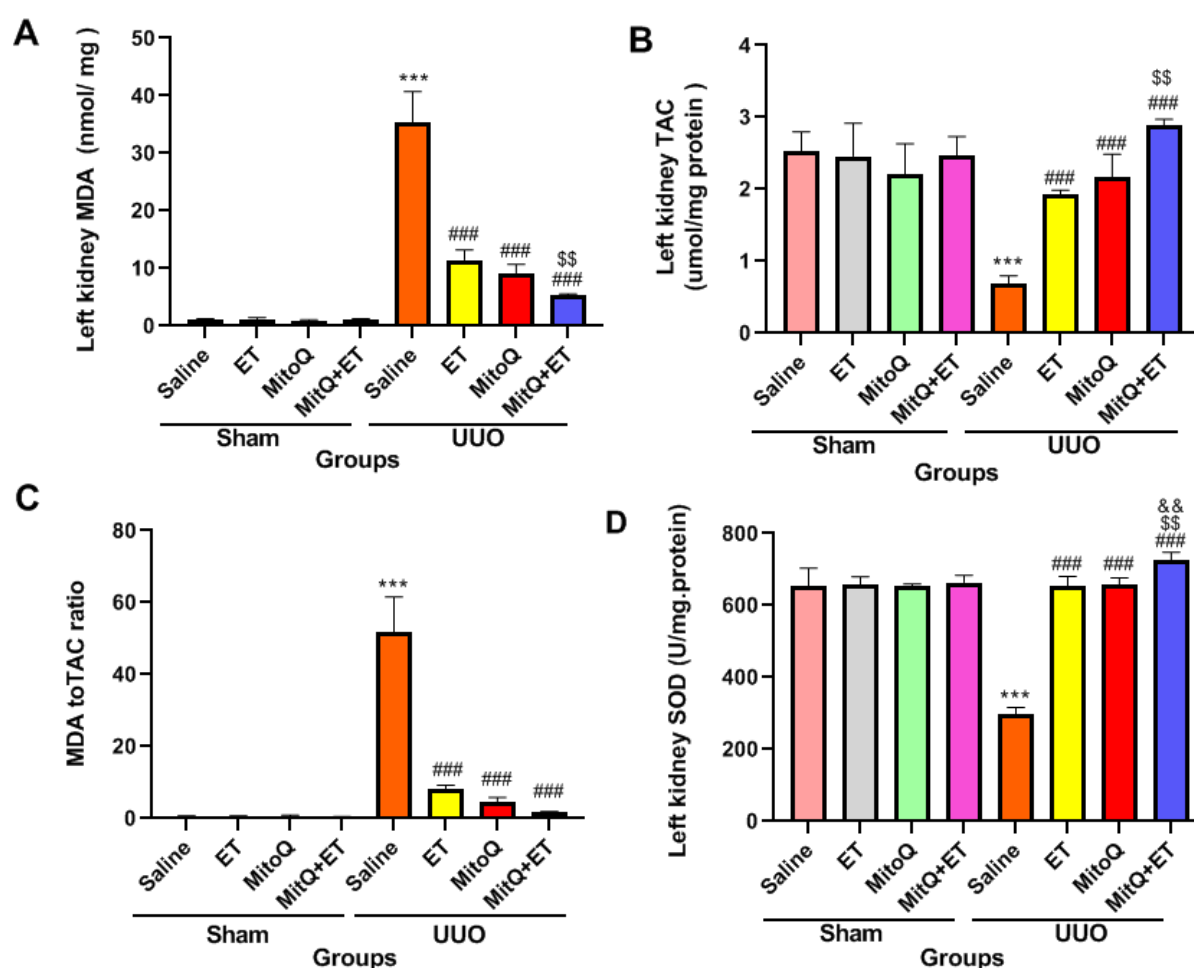


FIGURE 5. Effect of ET and MitoQ on MDA (A), TAC (B), MDA to TAC ratio (C), and SOD (D) levels in the left kidney across the experimental groups. The data are presented as the mean $\pm$ SD. With $n = 7$ per group. UUO: Unilateral ureteral obstruction; ET: Endurance training; MitoQ: Mitochondria-targeted antioxidant MitoQ. *** $P < 0.001$ versus Sham + saline group. ### $P < 0.001$ versus UUO + saline group. \$\$ $P < 0.01$ versus UUO + ET group. && $P < 0.01$ versus UUO + MitoQ group.

losclerosis in the left kidney of OVX rats (Figure 3 B, E, F; $P < 0.001$). Four weeks of ET or MitoQ administration, along with their combination, effectively reversed these parameters in the obstructed kidney ($P < 0.001$).

Effect of ET and MitoQ on left kidney weight

In Figure 4, we present the result of the kidney weight indices. Our findings indicate that UUO significantly increased the weight of the left kidney, the ratio of left kidney weight to body weight, and the left/right kidney weight ratio compared to the Sham + saline group ($P < 0.001$). Furthermore, ET or MitoQ treatment in UUO groups, as well as their combination, resulted in a significant decrease in these parameters compared to the UUO + saline group ($P < 0.001$).

Effect of ET and MitoQ on oxidative stress

The levels of oxidant and antioxidant parameters in left kidney tissue are presented in Figure 5A–D. Compared to the Sham + saline group, the MDA and the MDA to TAC ratio levels significantly increased in the UUO group. Conversely, the levels of TAC and SOD significantly decreased ($P < 0.001$). After four weeks of ET or MitoQ administration, as well as their combination, these parameters were reversed in the obstructed kidney ($P < 0.001$). The ET and MitoQ combination notably exhibited a more pronounced effect ($P < 0.05$).

Effect of ET and MitoQ on inflammatory biomarkers

The level of TNF- α and IL-1 β increased in the UUO group (Figure 6, $P < 0.001$). Four weeks of ET or MitoQ treatment and their combination significantly reduced

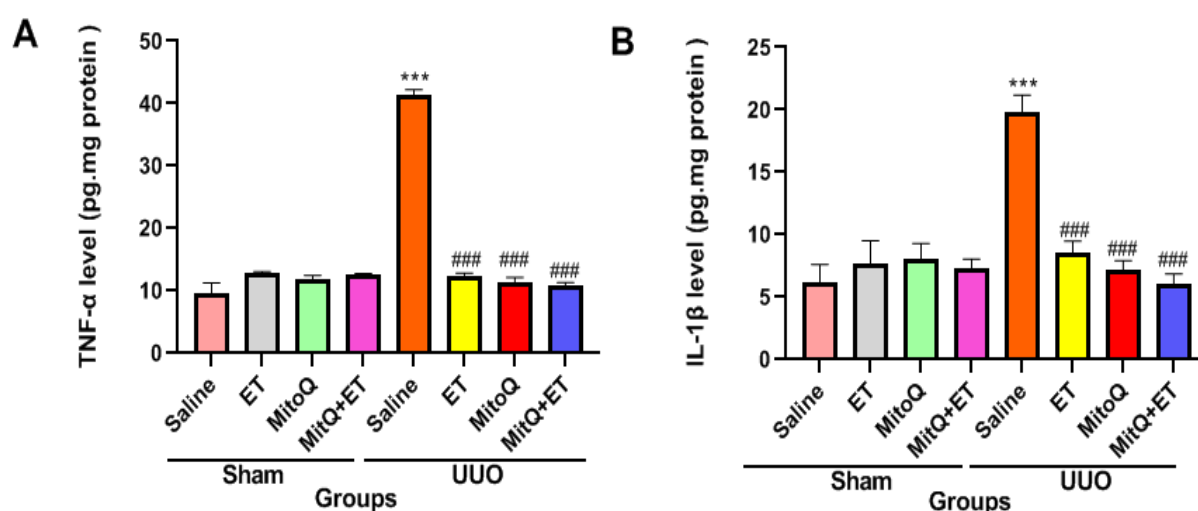


FIGURE 6. The effect of ET and MitoQ on the levels of TNF- α (A) and IL-1 β (B) in the left kidney in the experimental groups. The data are presented as the mean $\pm$ SD, with $n=7$ for each group. UUO: Unilateral ureteral obstruction; ET: Endurance training; MitoQ: Mitochondria-targeted antioxidant MitoQ. *** (Statistical significance) $P<0.001$ versus Sham + saline group. ### $P<0.001$ versus UUO + saline group.

the level of these inflammatory cytokines in the UUO group (Figure 6, $P<0.001$).

Discussion

The current study demonstrated that four weeks of ET and MitoQ supplementation, individually or in combination, significantly attenuated oxidative stress and inflammation in OVX rats with UUO. In addition, these interventions ameliorated histopathological alterations. The observed renoprotective effects are likely mediated through the antioxidant and anti-inflammatory properties of ET and MitoQ.

ROS overproduction critically involved in the progression renal injury (Dendooven et al., 2011) and attenuation of oxidative stress and inflammation are considered key therapeutic approaches for renal injury (Hassan et al., 2021). The ROS scavenging effects of ET and MitoQ have been reported previous studies. Masoumi-Ardakani et al. reported that ET and MitoQ either alone or in combination, enhanced antioxidant capacity in hypertensive individuals by increased TAC levels and reduced MDA concentrations (Masoumi-Ardakani et al., 2022b). Similarly, Jeong et al. reported that both ET and MitoQ mitigated age-associated oxidative stress in the hippocampus of aged rats through the upregulation of SOD and catalase (Jeong et al., 2021).

Moreover, treadmill exercise has been reported to maintain mitochondrial integrity, attenuate oxidative

stress, and mitigate renal damage in hypertensive rats (Gu et al., 2015). Consistent with these observations, our study showed that ET and MitoQ, alone or in combination, markedly improved antioxidant defenses and reduced lipid peroxidation in obstructed kidneys, as evidenced by elevated TAC and SOD activity alongside decreased MDA levels.

Inflammatory responses in injured renal tissue are triggered by the production of cytokines and chemokines (Li et al., 2020). This inflammatory environment further promotes ROS generation and oxidative damage, leading to the expression of inflammatory cytokines such as TNF- α and IL-1 β , mitochondrial dysfunction and tubular injury (Hassan et al., 2021). In our study, four weeks of treadmill exercise combined with MitoQ significantly attenuated renal inflammation in OVX rats subjected to UUO, as demonstrated by reduced levels of TNF- α and IL-1 β . Different studies reported that ET and MitoQ exert significant anti-inflammatory effects across a range of pathological conditions (Escribano-Lopez et al., 2016; Jeong et al., 2021; Masoumi-Ardakani et al., 2022b). These results indicate that the protective effects of ET and MitoQ may, at least in part, be mediated through the inhibition of inflammatory signaling pathways. Although UUO is a well-established inducer of renal oxidative stress and inflammation, the present study was designed to evaluate therapeutic interventions in an ovariectomized UUO model rather than to determine the

independent contribution of estrogen deficiency. Therefore, the specific effect of estrogen deficiency cannot be separated from that of UUO in the current study.

Mitochondrial dysfunction is increasingly recognized as a key contributor to the progression of UUO-induced renal injury through its role in oxidative stress, inflammation, and cell death (Gu et al., 2015). Tubular epithelial cells are particularly rich in mitochondria and are therefore highly susceptible to oxidative stress and mitochondrial dysfunction (Srivastava et al., 2023). Excessive mitochondrial ROS production has been associated with inflammatory responses, tubular injury, and fibrotic remodeling (Srivastava et al., 2023). Supporting this concept, Smith and Murphy reported that MitoQ accumulates several hundred-fold within mitochondria and is effectively distributed to renal tissue in vivo (Smith and Murphy 2010). In the present study, UUO markedly increased oxidative stress and lipid peroxidation in the obstructed kidneys of OVX rats, indicating enhanced oxidative stress. ET and MitoQ supplementation significantly restored the oxidant-antioxidant balance and attenuated inflammatory responses, suggesting that these interventions may have indirectly contributed to preserving mitochondrial function. However, this hypothesis requires confirmation through direct assessment of mitochondrial-specific parameters.

This study has several limitations. The absence of a non-ovariectomized control group precluded distinguishing the specific contribution of estrogen deficiency from the effects of UUO. In addition, only the obstructed kidney was evaluated, and mitochondrial-specific mechanisms were not assessed. Although renal functional parameters such as serum creatinine and urea were not measured, these markers are often preserved in unilateral UUO because the contralateral kidney compensates for overall renal function. Future studies should include non-ovariectomized controls, bilateral kidney evaluation, and direct analyses of mitochondrial function to further clarify the underlying mechanisms.

Conclusion

In conclusion, our study demonstrated that ET and MitoQ, alone or in combination, markedly improved oxidative stress status and inflammation in the obstructed kidneys of ovariectomized female rats. These protective effects were accompanied by attenuation of tubular injury and renal fibrosis. Overall, the findings suggest

that ET and MitoQ may serve as potential therapeutic strategies for preventing or mitigating kidney damage, particularly in postmenopausal conditions characterized by elevated oxidative stress and inflammation.

Acknowledgment

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Conflicts of interest

The authors declare that there is no conflict of interest.

Ethics approval

This study abides by the ARRIVE guideline. Ethical approval was obtained from the Animal Care and Use Committee of the Kerman University of Medical Sciences (Ethics Code: IR.KMU.AEC.1401.002) in accordance with the guidelines provided by the National Institutes of Health for the Care and Use of Laboratory Animals.

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