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Original Research

Therapeutic Effect of Thymoquinone on Melatonin, Ferritin, and Renal Function in Renal Ischemia/Reperfusion Injury in Rats

Ahmet Sarper Bozkurt[1, *], Şenay Görücü Yılmaz[2]

[1] Department of Physiology, University of Gaziantep, Faculty of Medicine, Gaziantep, Türkiye
[2] Department of Nutrition and Dietetics, University of Gaziantep, Faculty of Health Science, Gaziantep, Türkiye

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Corresponding Author
Ahmet Sarper Bozkurt, PhD
Address: Department of Physiology Gaziantep University, Medicine Faculty, Gaziantep, Türkiye
E-mail: asbozkurt@gantep.edu.tr

ABSTRACT

Objective: Ischemia/reperfusion (I/R) injury is the period of tissue or organ damage that develops after the tissue's blood flow is restored. The extent of damage varies according to the severity of tissue and cell damage. Thymoquinone (TQ) has a wide therapeutic spectrum. The effect of thymoquinone on melatonin and ferritin in I/R can regulate renal function by combining these two mechanisms to improve damage. Therefore, the effect of thymoquinone on melatonin and ferritin levels in renal I/R as well as its regulatory role in renal functions have been investigated.

Methods: Thirty-six male *Sprague Dawley* rats were included in the study (250-300 g, 8-10 weeks). The rats were randomly assigned to 6 groups with 6 animals in each group. Groups; 1- Control, 2- Sham, 3- Solvent, 4- Renal ischemia/reperfusion injury (I/R), 5- I/R+ Thymoquinone (TQ) (5 mg/kg/day), 6- TQ (5 mg/kg/day). The dorsal region of the rats was surgically opened, and the left renal artery was clamped for 30 minutes and then reperfused for 24 hours. TQ (i.p) was applied to the treatment groups for 15 days. At the end of the experiment, blood samples were taken from all groups, and kidney function tests (Na^+, K^+, Creatinine, urea, BUN) were performed. Melatonin and ferritin levels were analyzed by the ELISA method from kidney tissue samples.

Results: Data showed that short-term TQ treatment was effective on serum K^+ ($P = 0.010$) and melatonin and ferritin levels in kidney tissue. Melatonin and iron activity, which were normal in healthy groups, melatonin decreased and ferritin increased significantly in the I/R group. TQ treatment positively regulated the dysregulation of these two molecules in I/R.

Conclusion: TQ may contribute to the healing of the damage by improving the K^+ levels, which indicates the insufficiency of kidney functions in I/R damage. Melatonin and ferritin, as interacting molecules in I/R, are regulated by TQ, indicating that they may contribute to the management of I/R damage.

Keywords: Ischemia/reperfusion injury, melatonin, ferritin, thymoquinone.

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INTRODUCTION

Ischemia/reperfusion (I/R) injury is the damage that occurs after the blood flow to a specific organ or tissue is interrupted and blood flow is restored [1]. I/R can occur in many organs or tissues. I/R seen in renal tissue is the major cause of acute kidney injury. A sudden and temporary decrease in kidney function results in inflammation, oxidative stress, fluid, and electrolyte dysregulation [2]. Even if the tissue is reperfused, the damage may be permanent. Thymoquinone (TQ) is a compound with a rich therapeutic potential in many aspects. The compound contained in *Nigella sativa* has given positive results in similar injuries such as ovarian injury [3], renal transplantation [4], spinal cord [5], and intestinal I/R [6]. Although melatonin treatment is applied in renal I/R, the effect of TQ application on melatonin and ferritin levels is not clear. Melatonin is a powerful antioxidant. Meta-analyses indicate the therapeutic and protective properties of melatonin [7]. Additionally, melatonin treatment is suggested to have prophylactic and therapeutic effects against acute kidney injury in I/R patients with obesity. Studies mostly show its preventive effect. In the treatment of the damage with TQ, an improvement that can occur through melatonin and ferritin can provide the regulation of many renal functions together. Ferroptosis is an iron-dependent cell death mechanism and a source of cellular iron load. Ferroptosis is an important mechanism in cerebral I/R [8]. Ferritin is also the largest source of cellular oxidative stress. The increase in oxidative load after I/R contributes to kidney damage. Cellular iron overload is among the causes of many diseases. Iron chelators are one of the treatments used to reduce iron overload. Side effects of chelators and patient compliance are disadvantages. Studies have shown that melatonin can chelate iron and scavenge free radicals. At the same time, melatonin's inhibition of lipid peroxidation indicates its effective role in the ferritin process [9]. Function tests in renal I/R provide information about the kidney's working discipline. These tests, which play an important role in diagnosis and treatment, also provide important data in drug trials [10]. Studies have found that urea and creatinine levels increase and electrolyte values deteriorate in renal I/R [11]. In this study, we investigated the effects of TQ on melatonin and ferritin renal functions in the I/R rat model. In addition to its many properties, TQ is likely to have the functionality of repairing damage via melatonin and ferritin.

Main Points

- This study suggests that TQ may affect melatonin and ferritin molecules separately or may play a role in compensating for I/R injury by acting in a melatonin-ferritin or ferritin-melatonin direction.
- This study is the first to evaluate the relationship between melatonin and ferritin with renal function tests in rats with a renal ischemia model.

MATERIAL AND METHODS

Ethical standards and laboratory condition

Ethical permissions for the study were obtained from the Gaziantep University Experimental Animals local ethics committee (decision number:2024/49, protocol number:398). Thirty-six adult male Sprague Dawley rats (250-300 g, 8-10 weeks) were included in the study. The rats were randomly assigned to 6 groups with 6 rats in each group. The rats were housed individually in standard cages at 22-24 °C under a 12h dark/12h light cycle until the end of the study. The rats had ad libitum access to water and food. Injections and sampling were performed at 9-11 am.

Experimental groups and treatments

Rats were anesthetized with 75 mg/kg (Ketalar, 002038, Eczacıbaşı Health Products Industry and Trade Inc., Lüleburgaz, Turkey) ketamine and 10 mg/kg (Alfazyne, 0804125-11, Alfasan, Woerden, Holland) xylazine intraperitoneally before the surgical procedure. The rats were shaved with a shaver on the left renal area under anesthesia and the skin, fascia, and muscle layer were cut 1.5 cm vertically-laterally with surgical scissors. The kidney was removed and the renal artery was clamped. The kidney was observed for a few minutes to change color for ischemia and was reperfused for 24 hours after waiting for 30 minutes. Finally, TQ was applied.

Experimental groups

Control group (n= 6); Ad-libitum feeding without any intervention. No surgical procedure was performed.

Sham group (n=6); The back regions were opened and closed without any procedure.

Solvent group (n = 6); 2 ml i.p applied for 15 days (Ethanol: PBS (pH 7.2) (1:1) (Cayman, 15039). No surgical procedure was performed.

Ischemia/Reperfusion injury (I/R); After the back region of the rats was opened, clamping was performed on the left renal artery for 30 minutes. Immediately after the 30 minutes, reperfusion was performed for 24 hours [12].

Ischemia/reperfusion injury (IR) + Thymoquinone (TQ) group (IR+TQ) (n=6); After the rats' back region was opened as surgical, the left renal artery was clamped for 30 minutes. Immediately after the 30 minutes, reperfusion was performed for 24 hours [12]. The incision was closed with a surgical suture and after post-operative care, TQ was dissolved according to the manufacturer's recommendation (Cayman, 15039, USA). Rats were treated with 5 mg/kg/day TQ (i.p) for 15 days [13].

Thymoquinone (TQ) group (n=6); TQ was administered (i.p) for 15 days at 5 mg/kg/day [13].

Renal function tests

Following TQ treatment, 6 ml intracardiac blood samples were taken from rats under anesthesia into gel tubes, and renal function tests were performed from the serum samples obtained Levels of serum urea, BUN, creatinine, Na^+, and K^+ activity were determined by enzymatic-kinetic method in Beckman Coulter AU5400 (Gaziantep University, Sahinbey Research and Practice Hospital Biochemistry Laboratory).

Melatonin and Ferritin Analysis

The clamped left kidney tissue was removed and used for melatonin (Fine Test, ER116) and ferritin (Fine Test, ER0947) analyses by ELISA method. According to the commercial kit protocol for melatonin and ferritin analysis, tissues were immediately dissected on ice (tissue: PBS (1:9)) and homogenized in cold PBS in a homogenizer (IKA) (IKA T25 digital ultra turrax, Germany) at 12.000 rpm for 1 min. Samples were centrifuged at 5000xg for 5 min and the supernatant was analyzed spectrophotometrically by ELISA method. To determine the optical density (OD), 2 replicate measurements were performed at a wavelength of 450 nm. Data were calculated according to a standard curve.

Statistical Analysis

To detect a difference of 0.50 between groups based on historical data, the required minimum sample size was calculated as 6 animals in each group under the conditions of 5% Type I error and 80% power (Type II error 0.20). Power analysis was performed using the MedCalc v.11.3.5 package program. In the statistical evaluation of the data, categorical data were summarized as frequency and percentage, and continuous data were summarized as mean ± standard deviation. Data were presented as the mean ± SD/SEM of at least three independent measurements. Statistical significance was accepted as $P < 0.05$. One-way ANOVA was used for comparisons. Correlations were tested with Pearson. Data were normalized using the Shapiro-Wilk test. Post-hoc analyses were performed using the Tukey test. Statistical significance was accepted as $P < 0.05$.

RESULTS

TQ Improved Renal Function in Renal I/R

K^+ levels measured in serum samples decreased in the I/R+TQ group compared to the I/R group ($P<0.05$) (Figure 1E). TQ treatment may have a regulatory effect on K^+ levels in renal functions. In the comparative analysis between the groups, it was found that the K^+ value was significantly higher in the I/R group than in the control, sham, and solvent groups (Mean differences = 1.778, SE = 0.192, 95% CI = 1.710-2.877, $P<0.001$). Renal function tests showed that TQ had a functional effect on the K^+ levels in renal I/R. Other parameters were not significant ($P<0.05$).

Melatonin and Ferritin Levels Associated with TQ Treatment

The significance between the groups was tested with One-Way ANOVA. Melatonin (SS = 3.204, df = 5, MS = 0.641, F = 351.960) and ferritin (SS = 3.745, df = 5, MS = 0.749, F = 24.847) levels were significant between the groups ($P<0.001$). Melatonin levels decreased in I/R injury, and an increase was detected after TQ treatment (Figure 2).

For melatonin, a statistically significant relationship was found between control, sham, and PBS with I/R and I/R+TQ. I/R and I/R+TQ showed significant relationships in all groups. Significance was also found between the TQ treatment group and the I/R and I/R+TQ groups (Table 1). Multiple comparative analyses demonstrated the functional effect of TQ on melatonin and ferritin levels. Ferritin levels were significant among control-I/R, sham-I/R, solvent-I/R, I/R-all groups, I/R+TQ-I/R and TQ-I/R ($P<0.001$). In the correlation analyses performed to determine the direction of significance, it was determined that melatonin and ferritin were in mutual interaction (Table 2).

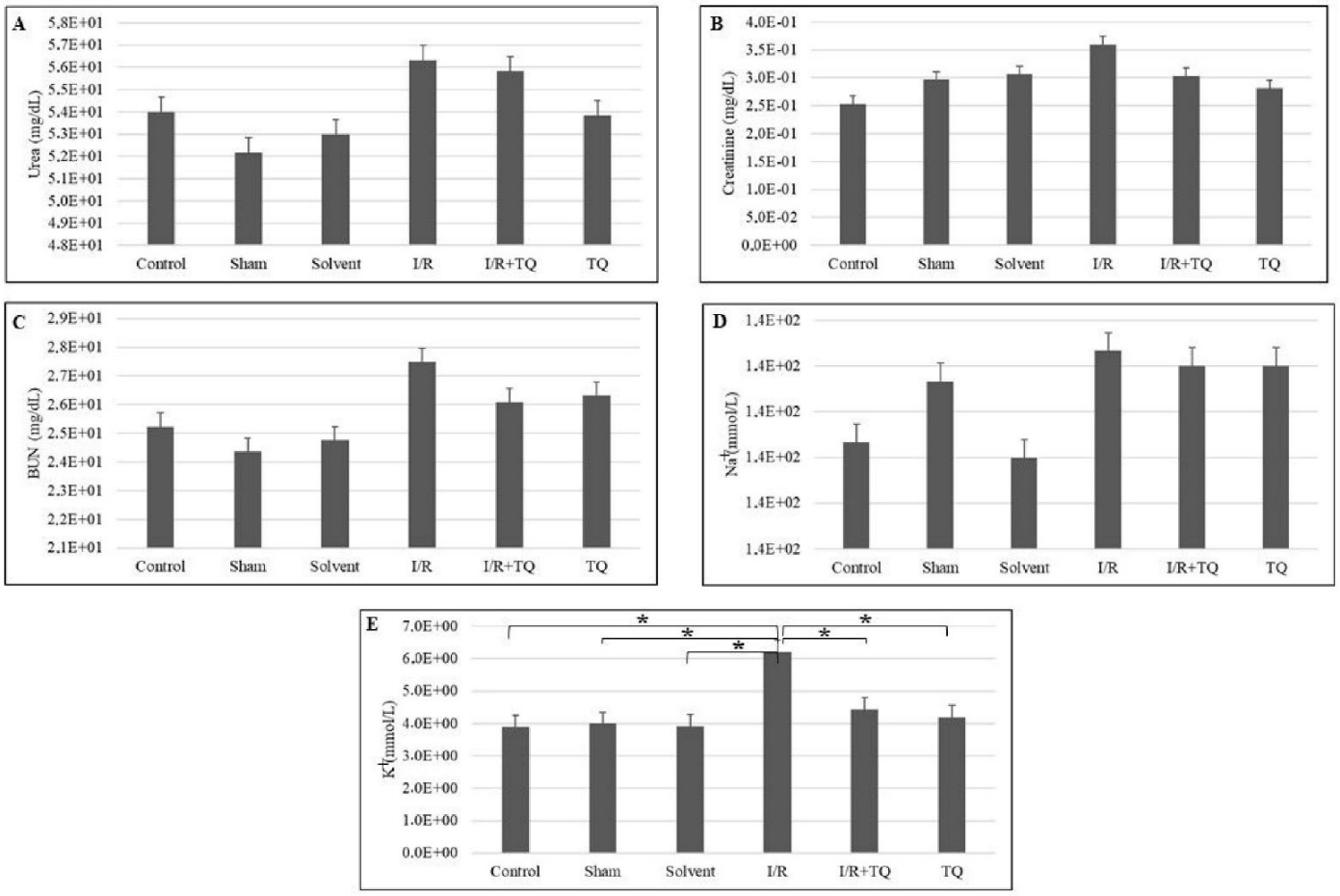

Figure 1. The serum levels of urea, BUN, creatinine, Na^+, and K^+ in the experimental groups. Error bars represent standard error. Urea, BUN, creatinine, and Na^+ were higher in the I/R group and lower after TQ treatment in all groups. The results were not statistically significant except for K^+. Potassium levels were significant in the I/R+TQ group compared to the I/R group. *P<0.05 is significant. **A.** Urea (mg(dL), **B.** Creatinine (mg/dL), **C.** BUN (mg/dL), **D.** Na^+ (mmol/L), **E.** K^+ (mmol/L).

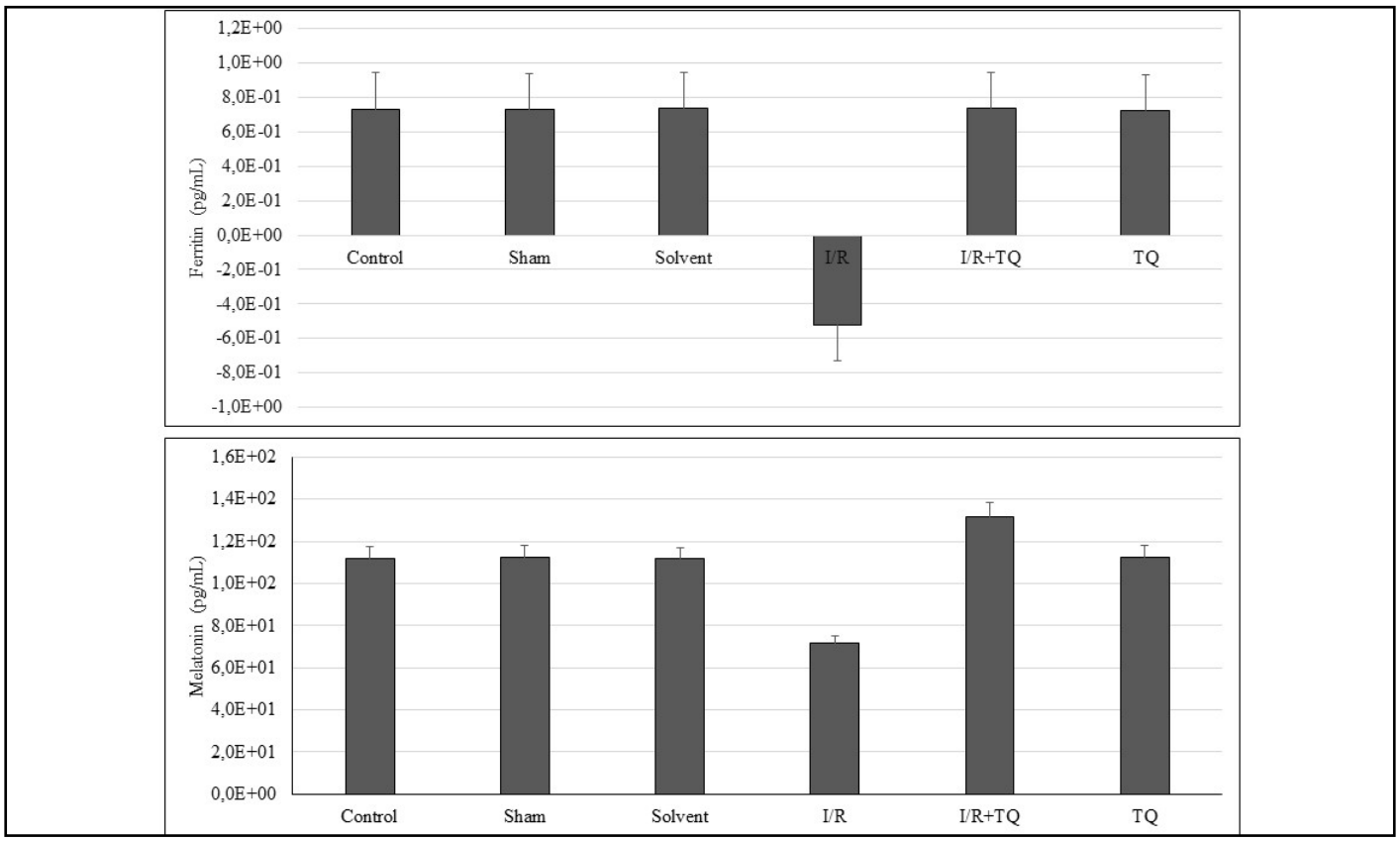

Figure 2. Renal tissue melatonin and ferritin levels in experimental groups. Melatonin levels were low after I/R injury in kidney tissue and increased after TQ treatment. Ferritin levels were high after I/R injury in kidney tissue and decreased after TQ treatment.

Table 1. Multiple comparisons of groups for kidney tissue melatonin and ferritin levels.

Parameters	Experimental Groups	Experimental Groups	Mean Difference	SE	P-value	95% CI
Melatonin	Control	Sham	-0.012	0.025	0.997	-0.087-0.063
		Solvent	0.001	0.025	1.000	-0.074-0.076
		I/R	0.661	0.025	**<0.001***	0.586-0.736
		I/R+TQ	-0.335	0.025	**<0.001***	-0.410--0.260
		TQ	-0.011	0.025	0.998	-0.086-0.064
	Sham	Control	0.012	0.025	0.997	-0.063-0.087
		Solvent	0.013	0.025	0.995	-0.062-0.088
		I/R	0.673	0.025	**<0.001***	0.598-0.748
		I/R+TQ	-0.323	0.025	**<0.001***	-0.398--0.248
		TQ	0.001	0.025	1.000	-0.074-0.076
	Solvent	Control	-0.001	0.025	1.000	-0.076-0.074
		Sham	-0.013	0.025	0.995	-0.088-0.062
		I/R	0.660	0.025	**<0.001***	0.585-0.735
		I/R+TQ	-0.336	0.025	**<0.001***	-0.411--0.261
		TQ	-0.012	0.025	0.996	-0.087-0.063
	I/R	Control	-0.661	0.025	**<0.001***	-0.736--0.586
		Sham	-0.673	0.025	**<0.001***	-0.748--0.598
		Solvent	-0.660	0.025	**<0.001***	-0.735--0.585

Melatonin		I/R+TQ	-0.996	0.025	**<0.001***	-1.071--0.921
		TQ	-0.672	0.025	**<0.001***	-0.747--0.597
	I/R+TQ	Control	0.335	0.025	**<0.001***	0.260-0.410
		Sham	0.323	0.025	**<0.001***	0.248-0.398
		Solvent	0.336	0.025	**<0.001***	0.261-0.411
		I/R	0.996	0.025	**<0.001***	0.921-1.071
		TQ	0.324	0.025	**<0.001***	0.249-0.399
	TQ	Control	0.011	0.025	0.998	-0.064-0.086
		Sham	-0.001	0.025	1.000	-0.076-0.074
		Solvent	0.012	0.025	0.996	-0.063-0.087
		I/R	0.672	0.025	**<0.001***	0.597-0.747
		I/R+TQ	-0.324	0.025	**<0.001***	-0.399--0.249
Ferritin	Control	Sham	0.005	0.100	1.000	-0.300-0.310
		Solvent	-0.001	0.100	1.000	-0.306-0.304
		I/R	0.867	0.100	**<0.001***	0.562-1.172
		I/R+TQ	0.000	0.100	1.000	-0.305-0.305
		TQ	0.007	0.100	1.000	-0.298-0.312
	Sham	Control	-0.005	0.100	1.000	-0.310-0.300
		Solvent	-0.006	0.100	1.000	-0.311-0.299
		I/R	0.863	0.100	**<0.001***	0.558-1.168
		I/R+TQ	-0.005	0.100	1.000	-0.310-0.300
		TQ	0.002	0.100	1.000	-0.303-0.307
	Solvent	Control	0.001	0.100	1.000	-0.304-0.306
		Sham	0.006	0.100	1.000	-0.299-0.311
		I/R	0.868	0.100	**<0.001***	0.564-1.173
		I/R+TQ	0.001	0.100	1.000	-0.304-0.306
		TQ	0.008	0.100	1.000	-0.297-0.313
	I/R	Control	-0.867	0.100	**<0.001***	-1.172--0.562
		Sham	-0.863	0.100	**<0.001***	-1.168--0.558
		Solvent	-0.868	0.100	**<0.001***	-1.173--0.564
		I/R+TQ	-0.868	0.100	**<0.001***	-1.173--0.563
		TQ	-0.861	0.100	**<0.001***	-1.166--0.556
	I/R+TQ	Control	0.000	0.100	1.000	-0.305-0.305
		Sham	0.005	0.100	1.000	-0.300-0.310
		Solvent	-0.001	0.100	1.000	-0.306-0.304
		I/R	0.868	0.100	**<0.001***	0.563-1.173
		TQ	0.007	0.100	1.000	-0.298-0.312
	TQ	Control	-0.007	0.100	1.000	-0.312-0.298
		Sham	-0.002	0.100	1.000	-0.307-0.303
		Solvent	-0.008	0.100	1.000	-0.313-0.297
		I/R	0.861	0.100	**<0.001***	0.556-1.166
		I/R+TQ	-0.007	0.100	1.000	-0.312-0.298

*The mean difference is significant at the 0.05 level. SE; standard error, CI; confidence interval.

Table 2. Correlation analysis of kidney melatonin and ferritin levels.

Parameters	Correlations	Melatonin	Ferritin
Melatonin (pg/mL)	Pearson Correlation	1	0.825*
	Sig. (2-tailed)		**<0.001***
Ferritin (ng/mL)	Pearson Correlation	0.825	1
	Sig. (2-tailed)	**<0.001***	

*Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

Hypoxic damage to the tissue resulting from ischemia results in the loss of cell integrity and ultimately cell death, depending on the duration of ischemia. In this process, the beginning of tissue reperfusion changes the extent of the damage. Free oxygen radicals released by polymorphonuclear leukocytes settling in the area after reperfusion increase tissue destruction and trigger reperfusion-related damage [14]. This defect may progress to acute kidney injury in the future. Renal function impairment is a known result of I/R. The underlying mechanism of this problem is inflammation-related. The inflammatory response in I/R further exacerbates the damage. Serum renal function tests can provide insight into the extent of the damage. In I/R, where optimal tissue oxygenation cannot be provided, suboptimal oxygenation cannot completely reverse the damage. This situation is reflected in serum markers and provides data about the onset of damage. These biological quantitative data are a signature of metabolic markers that compromise kidney function. Serum urea levels are filtered back to the plasma via the tubular epithelium and predict kidney disease as a clinical outcome by affecting factors such as the rate of hepatic production and protein intake [15]. Studies have determined that TQ reduces K accumulation in cerebral I/R [16]. In addition, TQ has a protective effect against toxicity caused by chemotherapeutic agents [17]. Among the urea, BUN, creatinine, Na^+, and K^+ used to analyze kidney functions, only K^+ was significant (Figure 1A-D). In terms of metabolic activities, potassium showed a more dominant difference in the groups. Renal excretion of potassium prevents toxic amounts from accumulating. A decrease in renal function is associated with increasing K^+ levels. In our study, TQ had no statistically positive/negative effect on parameters other than K in rats with I/R damage. At the same time, the obtained K^+ data suggest that TQ may have therapeutic potential in reducing elevated potassium levels in I/R.

Melatonin is a pineal hormone that is central to the biological clock and energy metabolism. Ferritin is an important protein that provides iron storage. As shown in this study, there is a metabolic link between the two molecules. Studies show that this link is achieved by triggering the degradation of ferroportin via hepcidin [18]. In this study, which showed that the molecular link is at the level of gene expression, it was shown that the expression of melatonin in hepatocytes induces hepcidin gene expression, promotes Fpn degradation, and thus causes cellular iron accumulation. In our study, we propose a mutual interaction between melatonin and ferritin in the renal tissue in I/R, similar to the regulation of iron homeostasis under the influence of melatonin in hepatocytes. Although an effect from melatonin to ferritin is suggested in hepatocytes, a flux from ferritin to melatonin may also be possible, as in our study. Ferritin is the only molecule taken up by the ferroportin receptor in cells. Its advantages and disadvantages are experienced in I/R. A previous study demonstrated that ferroptosis, a ferritin-dependent cell death mechanism, may be effective in reducing neuronal losses and regaining cognitive functions under the influence of TQ in a mouse Alzheimer's model [19]. Under normal conditions, the melatonin lost in the body can be compensated by other organs that adapt to the environment. A study has shown that iron overload. One study shows that iron overload reduces melatonin production [20]. In a recent study, melatonin was shown to be a ferroptosis inhibitor [21].

Limitations

The limiting factor in this study is that the effect on different organs in rats with a renal ischemia model was not demonstrated. Revealing the effects of the renal ischemia model on different organs in rats may contribute to the literature.

CONCLUSION

Our results indicate that TQ may affect both molecules separately or may play a role in the compensation of I/R damage by acting in the melatonin-ferritin direction or the ferritin-melatonin direction. TQ has the potential to a therapeutic in the regulation of I/R injury, and K^+ levels can be used as a marker in testing

renal function and response to treatment.

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Conflict of interest: No conflict of interest.

Authors' contributions: Conception: ASB, ŞGY- Design: ASB., ŞGY. - Supervision: ASB., ŞGY. Fundings: ASB., ŞGY. Data Collection and/or Processing: ASB., ŞGY. - Analysis and/or Interpretation: ASB., ŞGY. - Literature Review: ASB., ŞGY. - Writing: ASB., ŞGY. - Critical Review: ASB., ŞGY.

Ethics approval: This study was approved by Gaziantep University Experimental Animals Local Ethics Committee (decision number:2024/49, protocol number: 398).

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