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Research Article

Investigation of the Effects of Curcumin-Rich Turmeric Extract on Kidney Damage Caused by Isotretinoin in Rats

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ABSTRACT

Aim: The use of isotretinoin (ISOT) is known as the last step in treatment due to its side effects on the kidneys and other organs. The aim of this study was to evaluate the protective effect of curcumin-rich turmeric extract (CRTE) against kidney damage caused by isotretinoin based on oxidative stress parameters and routine biochemical parameters indicating kidney damage.

Material and Methods: Weighing 220-240 gr gavage to rats for 30 days, the treatment groups and the control group dissolved in sunflower oil ISOT 7.5 mg/kg/day ISOT 50, 100, 200 mg/kg/day extract of turmeric from rich kurkumi was performed. after 30 days, the mice were anesthetized, and then kidney tissues and blood were taken. The experiment was terminated by euthanasia. Finally, BUN and CRT levels of the blood and SOD, GSH and MDA levels in the kidney tissue were determined.

Results: At the end of the study, BUN, CRT levels and kidney MDA levels increased and SOD and GSH levels decreased in the isotretinoin group compared to the healthy control group. (CRTE+ISOT) in the 50, 100 and 200 mg/kg/day groups, on the other hand, showed a statistically BUN, CRT and SOD, GSH and MDA levels, especially in the group with 200 mg/kg/day at all three doses. There was no difference in the groups given CRTE and sunflower oil.

Conclusion: The protective effect of curcumin-rich turmeric extract in eliminating the side effects of kidney damage caused by isotretinoin therapy may suggest it as a herbal medicine.

Keywords: Curcumin, isotretinoin, kidney damage, oxidative stress, turmeric.

INTRODUCTION

Acne is a skin disease with a multifactorial pathogenesis, including increased sebum production, changes in keratinization processes leading to comedone formation, and follicular colonization by *Propionibacterium acnes* (1). This, in turn, leads to increased metabolic activity and the release of inflammatory mediators (2). Acne affects 85% of young people aged 24, 8% of those aged 25-34, and 3% of those aged 35-44 (3). One-third of these cases require serious, long-term treatment.

Retinoids and antibiotics are among the most commonly used treatments for acne and can be administered either topically or orally (4). Isotretinoin (ISOT) has been shown to be highly effective in patients with severe acne; approximately 85% of patients show improvement after 4 months of treatment, while improvement can be observed in about 30% of patients after the first month (5). Despite its high efficacy, the use of isotretinoin can be limited by its numerous side effects. Use of this drug can cause teratogenic effects, the possibility of developing depression, the progression of inflammatory bowel, liver, and kidney diseases, and toxic damage to these organs (2,6). Various herbal and pharmacological agents with antioxidant properties have been investigated to mitigate the adverse effects associated with ISOT, which is widely used in the treatment of severe acne. Turmeric, which is rich in antioxidant compounds, is an important phytotherapeutic plant known for its protective and therapeutic effects in various diseases, including cancer (7). Turmeric is known to contain many vitamins and minerals, such as vitamins C, K, and B, iron, phosphorus, and iodine. Its essential oil also contains numerous monoterpenes, sesquiterpenes, and active ingredients (α-turmerone, curcumin, arturmeron, α-phellandrene, and zingiberene) (8,9). In this context, the aim of this study was to investigate the protective effect of curcumin-rich turmeric extract against isotretinoin-induced kidney damage in rats, using oxidative stress parameters and routine biochemical parameters. The study aims to answer the question, "Can ISOT-induced side effects be eliminated with a natural herbal product?"

MATERIAL AND METHODS

Chemicals used in the study

The chemicals we used during our study were purchased from Sigma Chemical Co. Isotretinoin (Roaccutane® 20mg: gelatin capsule) ROCHE, curcumin-rich turmeric extract [Turmeric Root Extract® (400 mg CRTE: 30 Softgel)] SOLGAR company drugs were used.

Animals and experimental groups

In our study, 42 Wistar albino rats, each weighing 220-240 g, were bred at the Atatürk University Experimental Research and Application Center (ATADEM). All stages of our study were approved in accordance with ethical rules by the Atatürk University Animal Experiments Local Ethics Committee (AUHADYEK) with document number E-93722986-000-2200126065, dated April 22, 2022.

Experimental animals were fed pelleted feed and tap water

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at room temperature. For pretreatment, rats received 50, 100, and 200 mg/kg/day of CRTE dissolved in sunflower oil for 30 days, and 7.5 mg of ISOT dissolved in sunflower oil for the same period. For CRTE, pharmaceutical liquid capsules were opened, dissolved in sunflower oil and dosed as 50, 100, and 200 mg/kg. For ISOT, pharmaceutical soft gelatin capsules were opened, dissolved in sunflower oil, and dosed at 7.5 mg/kg. All these drugs were administrated orally to a necessary group for 30 days. To understand the protective effect of CRTE versus ISOT, CRTE drugs were administrated 10 min before ISOT. Experimental groups and diagram of experimental design are shown in detail (Figure 1).

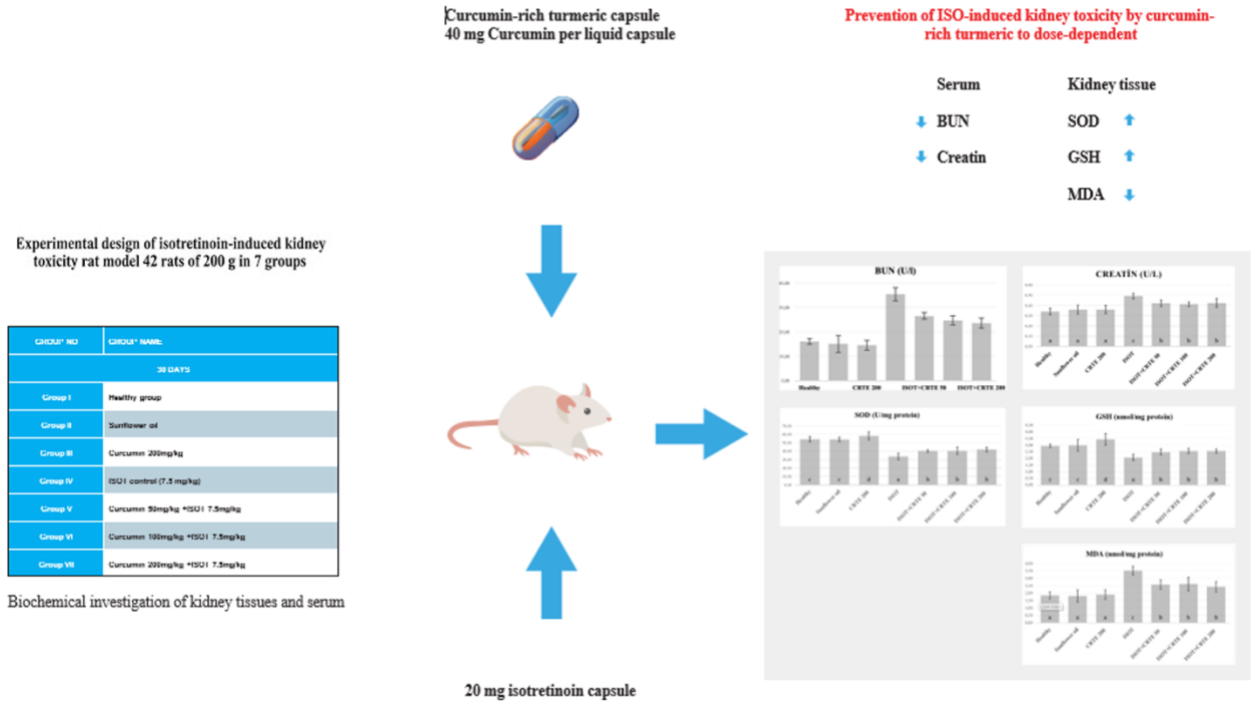


Figure 1. Experimental groups and diagram of experimental design.

At the end of the 30th day, intracardiac blood and kidney tissue were collected from these animals anesthetized with Ketamine and Xylazine (80:20). The collected blood samples were centrifuged at 3000 rpm for 10 min, and serums were obtained and stored at −80 °C until the measurement of biochemical analysis. Kidney tissue was washed with physiological saline and stored at −80 °C for biochemical analysis.

Biochemical parameters

CRT and BUN Determination

CRT and BUN analyses were performed at the Biochemistry Laboratory of Atatürk University Research Hospital.

Oxidative stress parameter analyses in kidney tissues

After the kidney tissue of the rats was collected, it was stored in the refrigerator at −80 °C for biochemical processes. Kidney issues from each rat were ground with liquid nitrogen using the TissueLyser grinding set (Qiagen, Hilden, Germany). Subsequently, 100 mg of ground kidney tissue was homogenized in 1 ml of PBS using an Eppendorf tube at 30 Hz for 2 minutes and then centrifuged. Superoxide dismutase activity (SOD) (10), glutathione (GSH) levels (11), malondialdehyde (MDA) levels (12), protein levels (13) were measured according to the related references. SOD, GSH, and MDA measurements in the upper phase of homogenized and centrifuged samples were measured three times in a Biotek Epoch reader at room temperature in accordance with the literature. The mean absorbance of the samples and standards was then determined. The standard curve was drawn from the absorbance of the standards. Analysis results of GSH, SOD, and MDA levels in tissues were shown as nmol/mg protein, U/mg protein, and nmol/mg protein, respectively. Results obtained according to the standard curve are given as mean ± standard deviation (SD) per mg protein.

Statistical analysis

The study's data were subjected to analysis of variance (ANOVA) at the significance level of p=0.05 using the IBM Statistical 19.0 program. Differences between groups were acquired using the One-way ANOVA post hoct test from Duncan multiple comparison test which allows inter-comparison of all groups. Results are presented as means, and values within the same column sharing the same letter are not significantly different according to Duncan's multiple range test ($p<0.05$). All conclusions are expressed as means ± SD for the rat in every group.

RESULTS

Superoxide dismutase activity (SOD)

Data describing the amounts of SOD determined from kidney tissues of the sunflower oil, CRTE 200, ISOT, ISOT+CRTE, and healthy control groups are presented in Figure 2. SOD levels decreased significantly in the ISOT group compared to the healthy group ($p<0.05$). SOD levels

increased significantly in the ISOT and ISOT+CRTE groups ($p<0.05$). When we compared the ISOT+CRTE50, ISOT+CRTE100, ISOT+CRTE200 groups among themselves, no significant difference was found in SOD levels ($p>0.05$). When the CRTE200 group, sunflower oil group and healthy group were compared with each other, although no significant difference was observed between the healthy group and the sunflower group ($p>0.05$), a significant increase was observed in SOD levels in the CRTE200 group ($p<0.05$).

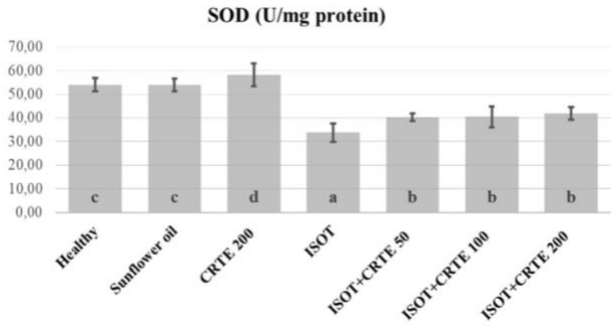


Figure 2. The efficiency of the SOD enzyme ISOT-induced kidney in rats model of rats.

GSH levels

A statistical decrease in GSH activity was determined after chronic ISOT administration of 7.5 mg/kg compared to the healthy control group ($p<0.05$) (Figure 3).

When the ISOT group was compared with the healthy group, GSH levels decreased significantly ($p<0.05$). When we compared the ISOT group and the ISOT+CRTE groups, a significant increase in GSH levels was observed ($p<0.05$). When we compared the ISOT+CRTE50, ISOT+CRTE100, ISOT+CRTE200 groups among themselves, no significant difference was observed in GSH levels ($p>0.05$). When the CRTE200 group, sunflower group, and healthy group were compared with each other, no significant difference was observed between the healthy group and the sunflower group ($p>0.05$), while a significant increase in GSH levels was observed in the CRTE200 group ($p<0.05$).

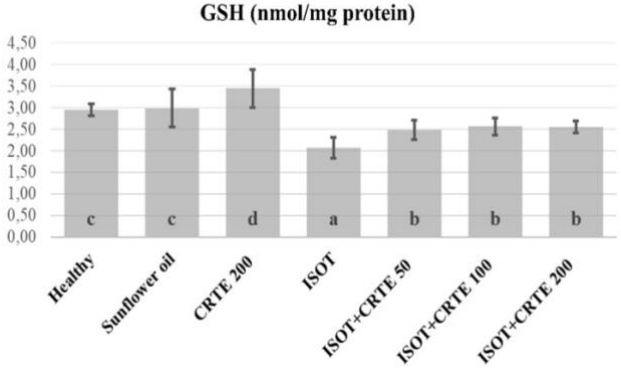


Figure 3. The efficiency of the GSH levels ISOT-induced kidney in rats model of rats.

MDA levels

When the ISOT group was compared with the healthy group, MDA levels increased significantly ($p < 0.05$). When we compared the ISOT group and the ISOT+CRTE groups, MDA levels decreased significantly in the ISOT+CRTE group ($p<0.05$) (Figure 4). When we compared the ISOT+CRTE50, ISOT+CRTE100, and ISOT+CRTE200 groups with each other, no significant difference was found in MDA levels ($p>0.05$). When the CRTE200 group, the sunflower group, and the healthy group were compared with each other, no significant difference was found in MDA levels ($p>0.05$).

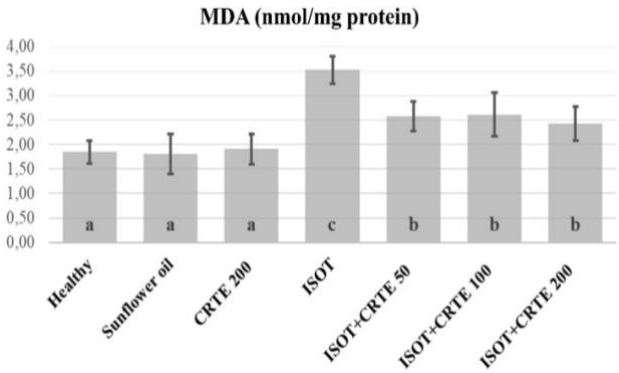


Figure 4. The efficiency of the MDA levels ISOT-induced serum in rats model of rats.

Data showing the BUN and CRT levels determined in the blood serum of the sunflower oil, CRTE200, ISOT, ISOT+CRTE, and healthy control groups are presented in Figures 5,6.

When the ISOT group was compared with the healthy group, BUN levels increased statistically significantly ($p<0.05$). When we compared the ISOT group and the ISOT+CRTE groups, BUN levels decreased statistically significantly in the ISOT+CRTE groups ($p<0.05$). When we compared the ISOT+CRTE50, ISOT+CRTE100, and ISOT+CRTE200 groups among themselves, no statistically significant difference was observed in BUN levels ($p>0.05$). When the CRTE200 group, sunflower oil group, and healthy group were compared with each other, no statistically significant difference in BUN levels was observed($p>0.05$).

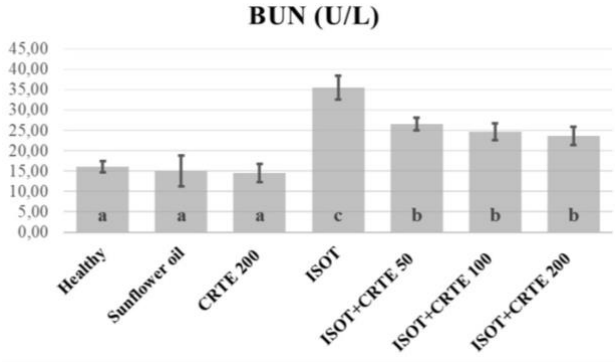


Figure 5. The efficiency of the BUN levels ISOT-induced serum in rats model of rats

The data describing the CRTE levels determined in the blood serum of the sunflower oil, CRTE 200, ISOT, ISOT+CRTE, and healthy control groups are presented in Table 4.1. When the ISOT group was compared with the healthy group, CRT levels increased significantly in the

ISOT group ($p<0.05$). When the ISOT group and ISOT+CRTE groups were compared, CRT levels decreased significantly in the ISOT+CRTE groups ($p<0.05$). No significant difference was observed in the CRTE200 group and the sunflower oil group ($p>0.05$). When the CRTE200 group, the sunflower oil group, and the healthy group were compared with each other, no significant difference was observed in CRT levels ($p>0.05$).

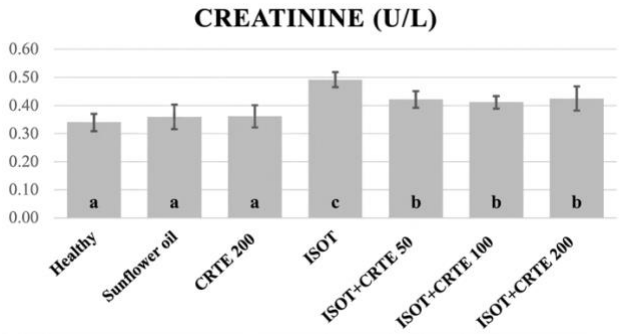


Figure 6. The efficiency of the CRT levels ISOT-induced serum in rats model of rats.

DISCUSSION

Retinoids are among the most effective drugs for inducing complete or long-term remission of severe acne vulgaris, but side effects associated with their use raise concerns about the potential impact of these drugs on internal organ functions such as the kidneys. Systemic oral isotretinoin use has been associated with renal dysfunction. These include acute interstitial nephritis, nephrotic syndrome, CRT, and abnormal BUN levels (14). Suspicion of acute kidney injury due to isotretinoin is seen in many patients. In patients receiving chronic medication, kidney function tests should be monitored in addition to liver function tests (15).

It is extremely important to pay attention to the dosing and side effects of ISOT when using this drug. Our study investigated the duration of ISOT use and the incidence of renal side effects. A study including five case reports identified that systemic oral isotretinoin at usual doses (2 or 5 mg/kg/day) or high doses (10, 20, 25, or 40 mg/kg/day) within 1 to 4 months of treatment may be associated with various renal dysfunctions (14). Pavese et al. (16) also observed severe renal failure in a 34-year-old man who received isotretinoin (40 mg/day) for more than two months due to severe acne. The authors reported a significant increase in serum CRT (from 81 to 259 µmol/L), proteinuria, microscopic hematuria, and a moderate inflammatory syndrome accompanying these values. (16,17) All laboratory abnormalities normalized within seven days after discontinuation of ISOT, consistent with its half-life, suggesting that ISOT was responsible for the observed renal dysfunction. Armaly et al. (15) reported a case of acute kidney injury in a previously healthy 17-year-old female who developed acute kidney injury during two months of acne treatment with ISOT (unknown dose). All laboratory abnormalities began to normalize within a few days after discontinuation of ISOT (15). Van Oers et al. (18) reported a case of isotretinoin (40 mg/day)-induced nephrotic syndrome in a 19-year-old male treated for severe acne vulgaris.

Due to its antioxidant and anti-inflammatory properties, curcumin's ability to treat ISOT-induced renal toxicity and oxidative stress prompted us to conduct this study (19). Several hypotheses explain the anti-inflammatory effect of curcumin by downregulating transcription factors such as cyclooxygenase-2 (COX-2), signal transducer and activator of transcription 3 (STAT3), and IκB kinase β (nuclear inhibitor of IKKβ). Curcumin can reduce cytokine synthesis, improve nitric oxide (NO) bioavailability, and scavenge reactive oxygen species (ROS) that promote inflammation. Curcumin exerts both direct and indirect antioxidant effects by scavenging both cytosolic and mitochondrial ROS and inducing the expression of the nuclear factor erythroid 2-related factor-2 (20). Aparicio-Trejo et al. (21) proved in their studies that curcumin prophylactic treatment reduces blood urea nitrogen, plasma CRT and renal vascular resistance, and increases glomerular filtration rate (GFR) and renal blood flow.

In our study, SOD, GSH and MDA levels were analyzed in the kidneys after in vivo kidney toxicity in order to see the level of free radical-induced damage caused by ISOT, especially in the kidney, and to evaluate the effect of CRTE against the formed radicals. In a study by Ramazan et al. (22), who created a nephrotoxicity model by administering cisplatin to rats and giving curcumin as treatment, the SOD levels of the rats were examined, and a significant difference was observed in the curcumin group ($p <0.05$).

In our study, we also determined a statistically significant decrease in SOD levels after 30 days of oral ISOT administration of 7.5 mg/kg/day ($p< 0.05$). When we compared the sunflower group and the healthy control group, we observed no statistically significant change. We determined that the decreased SOD level in the ISOT group in our study caused a statistically significant increase in SOD levels in all ISOT+curcumin combined groups, independent of dose.

We believe that the antioxidant molecules contained in CRTE exert a modulatory effect on the SOD enzyme, whose activity is reduced by ISOT. This modulatory effect suggests that CRTE has a strong protective effect.

The ratio of reduced to oxidized glutathione (GSH:GSSG) serves as an important indicator of the cell's antioxidant capacity. Badreldin et al. (23) investigated the effects of curcumin (diferuloylmethane, a phenolic pigment of turmeric) on kidney structure and function in rats exposed to adenine-induced GSH. They administered curcumin as a pretreatment and reported that GSH levels increased due to the antioxidant properties of this plant. We determined that the decreased GSH levels in the ISOT group in our study resulted in a statistically significant increase in GSH levels in all ISOT+curcumin combined groups, independent of dose. We believe that curcumin's richness in antioxidants is responsible for this protective effect on GSH levels.

MDA is formed as a product of both lipid peroxidation and the cyclooxygenase reaction in prostaglandin metabolism. Farombi et al. (24) administered curcumin as a treatment for gentamicin-induced kidney damage and observed a decrease in MDA levels. In addition to these studies, Soetikno et al. (25) observed elevated MDA and decreased SOD and GSH levels in rats with kidney damage. They demonstrated that MDA, SOD, and GSH levels returned to normal after treatment with curcumin. We determined that the increased MDA levels in the ISOT group in our study

resulted in a statistically significant decrease in MDA levels in all ISOT+curcumin combined groups, independent of dose. We believe that the decrease in MDA is due to the antioxidant molecules contained in CRTE.

Serum CRT concentration is commonly interpreted as a measure of GFR and is used as an index of renal function in clinical practice. However, glomerular filtration of CRT is only one variable that determines serum CRT concentration. Accurate interpretation of serum CRT concentration requires careful consideration of physiology, metabolism, and the patient's age and gender. CRT levels fluctuate in important clinical conditions such as aging, pregnancy, diabetes, drug administration, and acute and chronic renal failure (26). BUN is a screening test for renal function. It is primarily known as a blood test frequently used in conditions such as renal toxicity and renal failure (27). Tirkey et al. (28) demonstrated that curcumin suspended at low concentrations of 5, 10, and 15 mg/kg/day for 21 days reduced elevated BUN and serum CRT in cyclosporine-induced acute renal failure. Tikoo et al. (29) found that treatment of diabetic rats with 50 mg/kg/day curcumin for 6 weeks normalized BUN and serum CRT, along with preventing variables associated with the development of diabetic nephropathy. Wang et al. (30) administered curcumin to protect the kidney from ischemia-reperfusion injury and observed that BUN and serum CRT levels returned to normal. In our study, we determined that the increase in serum CRT and BUN levels following ISOT administration to rats was statistically reduced in all ISOT+curcumin combined groups, independent of dose. We believe that the protective effect of CRTE stems from the chemical compounds, vitamins, antioxidants, and anti-inflammatory substances it contains. In our study, we believe that CRTE normalized BUN and serum CRT levels, increased SOD and GSH levels, and reduced MDA levels, thus demonstrating a protective effect against ISOT-induced kidney damage.

CONCLUSION

Our research emphasized that CRTE normalizes renal function tests in ISOT-induced kidney damage and exerts a strong antioxidant effect by inhibiting the formation of free radicals resulting from oxidative stress. Curcumin-rich turmeric extract was found to normalize BUN, CRTE, SOD, GSH, and MDA levels in ISOT-induced kidney damage. Curcumin treatment against ISOT-induced kidney toxicity has been shown to contribute to the prevention of kidney cell damage by scavenging free radicals and increasing antioxidant activity.

The anti-inflammatory effects of curcumin are believed to be a result of inhibiting proinflammatory signals such as prostaglandins, leukotrienes, and COX-2. Additionally, curcumin has been shown to suppress several proinflammatory cytokines, including tumor necrosis factor-α, IL-1, IL-8, and nitric oxide synthase (31). CRTE may be recommended as a treatment to reduce the renal side effects of ISOT-induced kidney damage in acne patients. We expect our study results to shed light on this topic for the future. This study demonstrates, for the first time, the protective effect of curcumin in a model of ISOT-induced kidney injury.

DECLARATIONS

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Author Contributions: Conceptualization, Y.B.; Methodology, O.A. and Y.B.; Validation, Y.B.; Formal Analysis, O.A., E.E.Y., E.K. and Y.B.; Investigation, O.A., Y.B., E.K. and E.E.Y.; Resources, O.A., Y.B..; Data Curation, O.A. and Y.B.; Writing–Original Draft, O.A., Y.B. and E.K.; Writing–Review & Editing, O.A and E.K.; Supervision, Y.B.; Project administration, O.A., E.E.Y. and Y.B.. All authors have read and approved the final version of the manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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Ethical Approval: All stages of our study were approved in accordance with ethical rules by the Atatürk University Animal Experiments Local Ethics Committee (AUHADYEK) with document number E-93722986-000-2200126065, dated April 22, 2022.

Plagiarism Statement: This article has been evaluated for plagiarism, and no instances of plagiarism were detected.

Use of Artificial Intelligence (AI) Tools: The author/authors declare that no AI tools were used in the creation of this article.

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