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Research Article

# Protective role of curcumin in distant tissue damage (heart, kidney and lung) induced by liver ischemia-reperfusion in rats

## *Sıçanlarda karaciğer iskemisi-reperfüzyonunun neden olduğu uzak doku hasarında (kalp, böbrek ve akciğer) Kurkuminin koruyucu rolü*

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### Abstract

**Aim:** There are many different mechanisms in the pathogenesis of distant tissue injury, the generation of reactive oxygen species is the most frequently observed mechanism. Therefore, in this study, we investigated the protective role of curcumin on remote tissue (heart, kidney and lung) damage induced by experimentally induced liver ischemia reperfusion (I/R).

**Material and Methods:** A total, 24 Wistar-Albino rats were used. Three groups(n=8) consisted of Sham, I/R, and Curcumin. The I/R group was subjected to 45minutes of ischemia followed by 45minutes of reperfusion. Curcumin at a dose of 100mg/kg was given intraperitoneally to the treatment group. Rats were sacrificed after the experiment for biochemical examination. Reduced glutathione(GSH) and 8-isoprostagladin F2α (8-isoPGF2α) levels in liver, heart, kidney, and lung tissue samples were measured to determine remote tissue damage, oxidative stress damage, and protective effects of curcumin.

**Results:** GSH levels in liver, heart, kidney, and lung tissues were significantly higher, and 8-isoPGF2α levels were significantly lower in the curcumin group compared to the tissues of the sham and I/R groups ($p < 0.01$).

Conclusions: Intraperitoneal administration of curcumin after liver I/R induction may protect against I/R injury by regulating the functions of both local and distant tissues.

**Keywords:** ischemia, reperfusion, curcumin, liver

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## Öz

**Amaç:** : Uzak doku hasarının patogenezinde çok sayıda mekanizma rol oynamakla birlikte, reaktif oksijen türlerinin (ROT) oluşumu en sık gözlenen mekanizmalardan biridir. Bu çalışmada, deneysel olarak oluşturulan karaciğer iskemi-reperfüzyon (İ/R) hasarına bağlı gelişen uzak doku (kalp, böbrek ve akciğer) hasarı üzerine kurkuminin koruyucu etkisinin araştırılması amaçlanmıştır.

**Gereç ve Yöntemler:** Çalışmada toplam 24 adet Wistar-Albino sıçan kullanılmıştır. Hayvanlar her biri 8 sıçandan oluşan üç gruba ayrılmıştır: Sham, İ/R ve Kurkumin grupları. İ/R grubunda 45 dakika süreyle iskemi uygulanmasını takiben 45 dakika reperfüzyon gerçekleştirilmiştir. Tedavi grubuna intraperitoneal yolla 100 mg/kg dozunda kurkumin uygulanmıştır. Deney sonunda sıçanlar sakrifiye edilerek biyokimyasal analizler yapılmıştır. Karaciğer, kalp, böbrek ve akciğer doku örneklerinde uzak doku hasarı, oksidatif stres düzeyi ve kurkuminin koruyucu etkilerini değerlendirmek amacıyla indirgenmiş glutatyon (GSH) ve 8-izoprostaglandin F2α (8-isoPGF2α) düzeyleri ölçülmüştür.

**Bulgular:** Kurkumin grubunda karaciğer, kalp, böbrek ve akciğer dokularındaki GSH düzeylerinin, Sham ve İ/R gruplarına kıyasla anlamlı derecede yüksek olduğu; buna karşılık 8-isoPGF2α düzeylerinin anlamlı derecede düşük olduğu saptanmıştır ($p < 0,01$).

**Sonuç:** Karaciğer İ/R hasarı oluşturulduktan sonra intraperitoneal yolla uygulanan kurkuminin, hem lokal hem de uzak dokularda oksidatif stresin düzenlenmesi yoluyla iskemi-reperfüzyon hasarına karşı koruyucu etki gösterebileceği sonucuna varılmıştır.

**Anahtar Kelimeler:** İskemi, reperfüzyon, kurkumin, karaciğer

## Introduction

Liver I/R injury occurs largely during hepatic resection or transplantation procedures [1,2]. Liver I/R injury can severely impair liver function after reperfusion, causing jaundice and even multiple organ failure [3,4]. Inflammatory responses and oxidative stress are the main factors contributing to liver I/R injury [3]. In addition, multiple factors such as anaerobic metabolism, mitochondrial damage, intracellular Ca2+ overload, cytokines and chemokines produced by Kupffer cells and neutrophils, and nitric oxide play a role in liver I/R injury [4].

Curcumin is a natural phenolic compound in the curcuminoid family. It exhibits pleiotropic activity and poor bioavailability [5]. It has been widely used in Ayurvedic medicine for centuries [6]. Curcumin prevents oxidative DNA damage and lipid peroxidation [LPO], and reduces arachidonic acid release through inhibition of lipoxygenase and cyclooxygenase [7].

GSH, a natural antioxidant that is found in high concentrations in all cells and epithelial surface fluid [7]. Its dual role as a nucleophile and reductant enables it to detoxify electrophilic or oxidizing species by converting them into more soluble substances, facilitating their excretion. Furthermore, GSH does not interact with more critical cellular components such as DNA or RNA, proteins, and lipids [8,9]. GSH is effective in the neutralization of ROS and inactivation of endogenous compounds such as prostaglandins and leukotrienes. [7].

LPO is an important pathological process caused by free radicals, involving the oxidation of polyunsaturated fatty acids in biological membranes. [10]. Isoprostanes are generated by non-enzymatic peroxidation of arachidonic acid and are eliminated via urinary excretion; they are also indicators of LPO [11]. It is noticed that the determination of isoprostane levels in various body fluids is the gold standard for quantifying oxidative stress [12]. 8-isoprostagladin F2α [8-isoPGF2α], a major isoprostane, is formed in various tissues. It can be found in esterified form, and can also be found in free form in various body fluids such as plasma, serum, and urine, which remains very stable in body fluids and tissues. Therefore, it is considered an ideal index of LPO and free radical oxidation in humans [10,12]. This study aims to evaluate the protective effects of curcumin on GSH and 8-isoPGF2α levels in distant organs following hepatic I/R injury in rats. Our findings may provide new insights into curcumin's systemic antioxidant potential in multi-organ protection.

## Material and Methods

Twenty-four adult Wistar albino male rats, weighing between 200-250 grams, were used in the study. Animals were divided into 3 groups as sham, I/R, and curcumin groups, and eight rats were used randomly in each group. All rats underwent surgical intervention under intramuscular ketamine (50 mg/kg) (Ketalar vial, Eczacıbaşı Turkey) anesthesia. All rats were

kept at a room temperature of 21 ± 1°C until the day of the experiment, under a 12-hour light and 12-hour dark period, fed with standard laboratory feed, and weighed before the experiment. All experimental procedures were carried out at the Kahramanmaras Sutcu Imam University Animal Laboratory following ethical guidelines approved by the Kahramanmaras Sutcu Imam University Experimental Animal Ethics Committee (Date: 30.01.2025, Decision number:02).

In this study, G*power analysis was used to determine the number of samples. With a predicted effect size of 0.7 for the difference between the groups (Sham, I/R and Curcumin groups), a confidence level of 95% (α =0.05), and with 80% power (β = 0.20), the minimum sample size per group was determined to be 8. Sham group (n = 8): Following ketamine anesthesia, rats underwent a midline incision. the hepatic artery and hepatic portal vein were clamped using a bulldog clamp for 45 minutes to induce ischemic injury. Subsequently, 1ml DMSO (dimethyl sulfoxide + olive oil) was administered intraperitoneally. After a 45-minute reperfusion period, tissue samples were collected. I/R group (n=8): Following ketamine anesthesia, a midline incision was performed on rats. To induce ischemia, the hepatic artery and hepatic portal vein were clamped using a bulldog clamp. 45 minutes of ischemia damage were created, then 45 minutes of reperfusion were applied, and tissue samples were taken. Curcumin group (n = 8): Following ketamine anesthesia, rats underwent a midline incision. The hepatic artery and hepatic portal vein were clamped using a bulldog clamp to induce ischemic injury. 45 minutes of ischemia damage was created, and 100 mg/kg of curcumin was administered intraperitoneally. After a 45-minute reperfusion period, tissue samples were collected. Curcumin was prepared by dissolving it in DMSO. Our study took seven days. Before the experiment, 1 mL of DMSO was administered intraperitoneally to rats in the sham group once a day for 7 days. 1 mL of curcumin (50 mg/kg/mL/day) was administered IP to rats in the curcumin groups once a day for seven days, while nothing was administered to rats in the control group.

**Collection of Samples**

After 12 hours of fasting, rats were anesthetized intramuscularly. After shaving the abdominal skin of the rats, they were cleaned with povidone-iodine solution, and a midline incision was used to open the rats, and the hepatic portal vein and hepatic artery leading to the liver were closed with a bulldog clamp. Then, 45 minutes of ischemia and then 45 minutes of reperfusion were applied, and tissue samples were taken. All rats were sacrificed after the procedure. The tissue samples taken were stored at –80 C° until the time of the experiment for biochemical analyses.

**Biochemical Analyses**

The tissue samples separated for biochemical studies were left to thaw at +4 ˚C on the day of the study. Before the analysis, the tissues were weighed and homogenized with 1.15% KCl at a ratio of 1/5 (weight/volume) (ultra turrax, 60 sec at 13500 rpm). The supernatants were separated by centrifuging at +4˚C at 14000 rpm for 30 min. GSH and protein were measured by the spectrophotometric method (UV 1000 Spectrophotometer), 8-isoPGF2α levels were measured by ELISA reader (ChemWell 2910 Automated EIA ELISA BioChemistry Analyzer).

GSH levels in tissues were measured spectrophotometrically using the Beutler method [13]. Results were given as µmol/g tissue.

8-iso-PGF2α (Mybiosource, USA) levels in tissues were analyzed with an ELISA reader based on the content of the commercial kit. Results were given as ng/mL.

Protein analyses were performed using the method of Lowry et al. [14].

## Statistical Analyses

The SPSS 21.0 program was used for statistical analyses. Results were given as mean±standard deviation (mean ± std. deviation). Pairwise comparisons between two independent groups were conducted using the Mann-Whitney U test, while the Kruskal-Wallis test was employed for three-group comparisons. Statistical significance level was accepted as $p < 0.05$.

## Results

In the present study, increased GSH level and decreased 8-iso-PGF2α level were found in the liver, heart, kidney, and lung tissues of the curcumin group compared to the tissues of the sham and I/R groups ($p < 0.01$). In the curcumin group, the liver tissue exhibited the highest GSH levels, while the kidney tissue showed the lowest ($p<0.01$). In the I/R group, the highest 8-iso PGF2α level was found in the liver, while the lowest was observed in the heart ($p<0.01$). In the sham group, the heart tissue demonstrated the highest GSH level, while the lowest was observed in the liver($p < 0.01$). These results are summarized in table 1.

**Table 1 .** GSH and 8-iso PGF2α levels of the groups (mean±std. deviation)

| | | Sham (n=8) | I/R (n=8) | Curcumin (n=8) | p1 |
|---|---|---|---|---|---|
| Liver | GSH (µmol/g) | 3.97±0.84 | 4.15±1.23 | 17.88±2.37[ab] | < 0.001 |
| | 8-iso PGF$^{2\alpha}$ (ng/mL) | 65.22±15.18 | 78.37±14.5 | 21.51±7.97[ab] | < 0.001 |
| Heart | GSH (µmol/g) | 8.12±1.83 | 8.3±2.22 | 11.88±2.39[ab] | 0.009 |
| | 8-iso PGF$^{2\alpha}$ (ng/mL) | 35.23±6.76 | 35.75±7.56 | 16.07±3.81[ab] | < 0.001 |
| Kidney | GSH (µmol/g) | 5.13±1.52 | 5.13±2.46 | 10.37±2.79[ab] | 0.001 |
| | 8-iso PGF$^{2\alpha}$ (ng/mL) | 45.74±8.09 | 46.12±12.52 | 29.49±6.27[ab] | 0.004 |
| Lung | GSH (µmol/g) | 4.97±1.22 | 5.99±1.98 | 11.44±2.12[ab] | 0.001 |
| | 8-iso PGF$^{2\alpha}$ (ng/mL) | 46.69±9.23 | 49.19±9.65 | 21.48±6.97[ab] | 0.001 |

[p1] Kruskal Wallis test and Mann- Whitney U tests were used to compare the groups,
[a]Compared with Sham group, [b]Compared with I/R group

## Discussion

In this first experimental study, it was shown that curcumin can reduce the damage in distant organ systems due to liver I/R. These results may be a treatment modality for the recovery of kidney, lung, and heart tissues adversely affected by I/R.

Liver I/R injury is an important complication that causes functional or dysfunctional failure in the liver during liver surgery and liver transplantation [5,6,15]. Reducing the negative effects of I/R injury is important as it can increase transplantation success in patients. It is stated that different mechanisms, including inflammation, oxidative/nitrosative stress, liver Kupffer cell activation, and mitochondrial dysfunction, contribute to the pathophysiology of hepatic I/R injury [15]. Intense hepatocyte damage occurs with the production of ROS as a result of the blockage and restoration of blood flow during I/R [5,15]. Although there are many studies designed to prevent damage in liver I/R injury, no fully suitable solution has been found to protect organs from harmful effects [5].

I/R injury causes an inflammatory response and the production of ROS, affecting organs distant from I/R sites [15-17]. Curcumin, known as Indian spice turmeric, is a yellow polyphenolic compound obtained from Curcuma longa that is known to suppress I/R-related pathways and consequently reduce liver I/R damage [6,7,15]. It was shown that curcumin has protective effects on many organs, including pulmonoprotective, cardioprotective, and renoprotective effects [15,18,19].

The liver plays a pivotal role in maintaining the GSH homeostasis between organs by releasing the majority of the synthesized GSH into bile and plasma. A change in GSH synthesis in the liver or its delivery to other organs exerts an effect on systemic GSH homeostasis [8,9,20,21]. γ-glutamyl transpeptidase [GGT], the key enzyme involved in GSH degradation, is found on the outer surface of epithelial cells in the renal tubules, brain capillaries, and biliary epithelium [9]. Serteser et al. showed that hepatic changes after renal I/R injury in mice, GSH levels decreased as the ischemia period increased [16]. In a study by Stein et al., hepatic I/R caused a decrease in hepatic GSH but no increase in liver LPO products. Based on these findings, it has been noticed that hepatic endogenous GSH is crucial in protecting against oxygen radical damage after short-term total hepatic ischemia and that oxygen radical damage will occur after depletion of these endogenous GSH stores [23].

Hepatic stellate cells are the key cellular element involved in the development of hepatic fibrosis [20]. Zheng et al. reported that curcumin reduced oxidative stress in passaged hepatic stellate cells by scavenging ROS and reducing LPO, depending on the dose and time [20]. In our study, liver GSH levels were statistically significantly increased in the curcumin group compared to the sham and I/R groups.

Myocardial I/R injury represents a leading cause of cardiac mortality [24]. The most dangerous perioperative myocardial infarction is the one that occurs following non-cardiac surgeries such as liver transplantation [25]. In the case of I/R, the imbalance between the production of ROS and the availability of endogenous antioxidants is a significant factor in the development of myocardial damage [26]. The curcumin's impact on myocardial I/R damage was investigated in the study by Kim et al. noticed that curcumin had anti-inflammatory activity and apoptosis inhibition in cardiomyocytes [24].

ROS are produced during reperfusion and are considered a key factor in the development of myocardial reperfusion injury. Although the myocardium is equipped with antioxidants that protect against ROS injury, it is stated that these antioxidants are depleted due to the initial ischemic damage. GSH is

a vital antioxidant in the heart [22]. Ferrari et al. showed that the reduction of myocardial GSH, together with other antioxidants during ischemia, contributes significantly to the development of myocardial reperfusion damage[27]. In the study conducted by Amar et al., it was reported that elevated myocardial GSH levels were associated with a decrease in myocardial infarct size and accelerated recovery of contractile function in ischemic myocardium [22]. Nazam Ansari et al. reported that tissue GSH levels increased when curcumin [200 mg/kg] treatment was given to rats treated with isoproterenol for 20 days [28]. In our study, we found that an increase in heart tissue GSH levels was detected in the curcumin-treated group relative to the sham or I/R groups.

Renal I/R injury is a common clinical condition associated with renal dysfunction and tissue damage [19]. The kidney, as a highly perfused organ, is particularly sensitive to I/R [18]. Renal I/R injury is the main cause of acute kidney injury after partial nephrectomy and kidney transplantation, which is closely associated with morbidity and mortality [29,30]. It also contributes to acute kidney injury, a clinically common and heterogeneous disorder with high mortality rates among hospitalized patients, and may increase the risk of progression to end-stage renal disease [19]. Current studies on the treatment and prevention of renal I/R injury mainly focus on antioxidants and antiapoptotic drugs. Yang et al. found that curcumin was shown to significantly reduced renal apoptosis and improved renal function in I/R injured rats [19]. Cui et al. noticed that I/R caused a decrease in serum GSH levels, while curcumin pretreatment significantly increased GSH levels. GSH levels in the renal I/R injury group were significantly lower than in the sham group. GSH expression levels in the curcumin group were significantly higher than in the renal I/R injury group exhibiting a dose-dependent relationship [29]. Erturk et al. determined that GSH levels in rat kidney tissue in groups treated with curcumin increased significantly compared to the I/R group, but no statistically significant difference was found between the groups treated with different doses of curcumin [30]. In our study, a significant increase in kidney tissue GSH levels was determined in the curcumin-treated group relative to the sham and I/R groups. It has been stated that the pathophysiological pathway of lung injury associated with hepatic hot I/R injury followed by prolonged liver resection or acute hypotension is characterized by a substantial generation of ROS. This ROS production results from the disruption of the redox status in hepatocytes and sinusoidal endothelial cells, as well as the activation of Kupffer cells, which trigger the release of proinflammatory cytokines and chemokines [31]. GSH is in the micromolar range in plasma; however, in some extracellular spaces, such as the lung lining fluid, a thin layer of fluid covering the air spaces where gas exchange occurs, there is a high concentration of GSH secreted by epithelial cells [21]. During I/R injury, proinflammatory mediators are released and the integrity of the lung endothelium is disrupted [5]. Oğuz et al. observed that curcumin did not significantly reduce the effects of hepatic I/R injury on distant organs including the liver, kidneys, and lungs[5]. Wu et al. reported that curcumin attenuated hepatic I/R-induced combined restrictive and obstructive lung disease [31]. Zou bo et al. showed that it was observed that pulmonary damage caused by limb I/R injury in rats was reduced after curcumin treatment [17]. Sun et al. demostrated that curcumin reduced I/R-induced acute lung injury in rats [32]. This is probably due to curcumin's amelioration of oxidative stress and inhibition of nuclear factor-κB mediated inflammatory cytokine expression.

GSH exerts a key protective function against oxidative stress by directly scavenging ROS or acting as a cofactor for antioxidant enzymes [33]. Sommer et al. noticed, pulmonary I/R significantly reduced mitochondrial viability. GSH preconditioning improved mitochondrial viability [34]. Marczylo et al. observed, the amount of curcumin after oral administration was measured in the intestine, liver, heart, and kidney tissues, from high to low levels [35]. Bringhentti et al. found that intestinal I/R led to a decrease in GSH levels in the lungs and kidneys. Curcumin prevented all changes in the liver. Curcumin did not prevent GSH changes in the kidneys. Due to its systemic distribution, curcumin exerted protective effects mainly in the lungs and liver, with comparatively weaker effects observed in the kidneys. This situation has been attributed to the changes in curcumin's tissue distribution across different organs [33]. In our study, a significant increase in lung tissue GSH levels was observed in the curcumin-treated group compared to the sham and I/R groups.

Increased ROS levels cause abnormal oxidation of arachidonic acid found in phospholipid membranes, leading to the formation of 8-iso-PGF2α [11,21,36-38]. This marker demonstrates stability in both urine and blood samples, allows for reliable quantification in detection, and increases with oxidative stress [36,38]. Szymanska et al. found that 8-iso-PGF2α in urine was higher in bladder cancer patients compared to the control group [39]. Also, plasma 8-iso-PGF2α concentrations are increased in patients with acute myocardial infarction [40].

Xue et al. stated that the increased expression of 8-iso-PGF2α in the control group compared to the sham group indicates that myocardial infarction conditions create oxidative stress [41]. Lim et al. showed that plasma 8-iso-PGF2α levels were found to be significantly higher in end-stage renal disease patients receiving hemodialysis and continuous ambulatory peritoneal dialysis than in age-matched controls [42]. Cort et al. reported that curcumin inhibited oxidative stress in human testicular cancer cells by significantly reducing 8-iso-PGF2α content and increasing GSH levels [43]. Similarly, curcumin was reported to cause a decrease in 8-iso-PGF2α levels in breast cancer cells following exposure to radiation [44].

In our study, GSH significantly increased in liver, heart, kidney and lung tissues in the curcumin group compared to the sham and I/R groups, while 8-iso-PGF2α significantly decreased. In these four tissues, the highest GSH levels were observed in the liver tissue and the lowest GSH levels were observed in the kidney tissue. This was attributed to the central role of the liver in GSH synthesis and homeostasis and the presence of GGT, the enzyme responsible for GSH degradation, in the kidney tubules. The increase in 8-iso-PGF2α levels in the kidney tissue compared to other tissues suggests that the antioxidant effect on 8-iso-PGF2α levels may have decreased due to the destruction of GSH. In addition, Marczylo et al. and Zheng et al. showed that curcumin tends to accumulate more in the liver[20,35]. In our study, we can say that curcumin activates GSH synthesis, and curcumin supports higher GSH levels in the liver compared to other tissues. Similarly, the tendency of curcumin to accumulate less in the kidneys compared to other tissues may have affected the decrease in antioxidant effect and the increase in 8-iso-PGF2α levels. In our study, the increase in GSH levels and the decrease in 8-iso-PGF2α levels in all tissues were due to the protective effect on the liver and distant tissue damage after hepatic I/R damage. Preventing or minimizing liver I/R damage during liver surgery will be effective in preventing damage to distant tissues. An effective prevention or treatment method has not yet been found for this. We think that different mechanisms should be investigated to determine the effect of curcumin in hepatic I/R treatment.

In conclusion, based on the biochemical data obtained, it can be stated that curcumin plays an effective antioxidant role in distant tissues in hepatic I/R damage. Notably, our study is, to the best of our knowledge, the first to demonstrate changes in the levels of 8-iso-$PGF_2\alpha$, a relatively novel and increasingly recognized biomarker of lipid peroxidation within this experimental model. However, detailed studies are needed in the future regarding the mechanism of this effect and the relationship between GSH and 8-iso PGF2α.

## Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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## Ethics approval

The study was approved by the ethics committee of the Kahramanmaras Sutcu Imam University Experimental Animal Ethics Committee (Date: 30.01.2025, Decision number: 02)

## Authors' contribution

C¬¬onceptualization: UO, IY, EBK; Design: UO,EBK; Supervision; UO, EBK, Materials; UO, IY; Data Collection and/or Processing; UO EBK,FG, Analysis-Interpretation; EBK, IY, Literature review FG, Writing: UO, EBK, FG; Critical review: EBK, FG.

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