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Original Research Article

Curcumin improved liver and renal function in a systemic inflammation model induced by lipopolysaccharide in rats

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Abstract

Objective: Inflammation is reported to have some damaging effects on liver and renal tissues. The present investigation was done to assess the liver and renal function improving effects of curcumin (Cur) in a systemic inflammation model induced by lipopolysaccharide (LPS) in rats.

Materials and Methods: Thirty five rats (male) were assigned to five groups: Control, LPS injected group (1 mg/kg, intraperitoneal), and three Cur-treated groups (5-15 mg/kg, oral, 14 days) plus LPS. Serum biochemical indicators including alkaline phosphatase (ALKP), aspartate aminotransferase (AST), total protein, alanine aminotransferase (ALT), creatinine, and blood urea nitrogen (BUN) for liver and kidney function were measured. Oxidative stress markers and inflammation indicator (interleukin-6 (IL-6)) were also measured in the liver and renal tissues.

Results: An inflammation status was seen in the liver and kidney after LPS injection presented by increased levels of IL-6. It was also accompanied with increasing serum level of ALKP, AST, ALT, BUN, and creatinine and a decrease in total protein. Pre-treatment with Cur restored liver and kidney function markers. In addition, LPS injection was accompanied by enhancement of the level of malondialdehyde (MDA) and IL-6 in both liver and kidney tissues while decreased levels of total thiol, superoxide dismutase (SOD), and catalase. Administration of Cur before LPS attenuated the level of MDA and IL-6 while increasing total thiol content and SOD and catalase activities.

Conclusion: Curcumin confers hepatic and renal protective effects against LPS-mediated toxicity, likely attributable to its antioxidant and anti-inflammatory mechanisms.

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Introduction

A key component of the outer membrane in Gram-negative bacteria, lipopolysaccharide (LPS), functions as a potent endotoxin and serves as a major factor responsible for sepsis (Wang et al. 2011). Upon exposure to LPS, the immune system is strongly stimulated, resulting in the release of various cytokines and other inflammatory agents such as interleukins (IL) (IL-1, IL-6, IL-8, and IL-12), tumor necrosis factor-alpha (TNF-α), and nitric oxide (NO)(Bhatti et al. 1993; Hung et al. 2017). When released in an excessive and uncontrolled manner, these mediators can induce serious tissue injury, especially in vital organs like the liver and kidneys. Therefore, LPS is commonly employed in experimental models to reproduce sepsis-associated hepatic and renal dysfunctions (Xu et al. 2015).
In the context of LPS-induced renal damage, TNF-α and IL-6 are considered key mediators (Beheshti et al. 2018; Sadeghi et al. 2021). Moreover, overproduction of reactive oxygen species (ROS) in combination with NO, forms a "sepsis redox cycle" that accelerates renal cell damage and functional impairment (Khordad et al. 2021; Xu et al. 2014; Zhang et al. 2018).
In patients with sepsis, clinical evidence identifies inflammation-induced liver injury as a leading cause of death (Yao et al. 2017). According to recent studies, macrophage activity elevates proinflammatory cytokines like IL-6, which in turn, initiates a caspase cascade leading to hepatocyte death (Li et al. 2017; Zhao et al. 2015). This necrosis is deteriorated upon the secretion of ROS from activated macrophages and neutrophils and leads to liver failure (El Kamouni et al. 2017; Song et al. 2017; Yao et al. 2017). It also reported that a changes in liver function parameters, including aspartate aminotransferase and alanine aminotransferase (AST and ALT, respectively) are attributable to underlying inflammation (Beheshti et al. 2018). it is also suggested that mitochondrial damage during sepsis as a result of a reduction in the amount of superoxide dismutase (SOD) is the reason for cell necrosis and thus, organ failure (Beheshti et al. 2018; Ding et al. 2016).

Curcumin (Cur) is the main component in the roots of turmeric (*Curcuma longa*), a popular Asian spice (Abdullah et al. 2017; Shehzad et al. 2017). Due to its anti-inflammatory, anti-mutagenic, anti-oxidant, and anti-coagulant effects, it is widely used to treat different diseases including cardiovascular system disorders, depression, and Alzheimer's diseases, and diabetes (Abdullah et al. 2017; Lu et al. 2017; Shehzad et al. 2017). The anti-oxidant properties of Cur is attributed to its phenolic groups. It also has been mentioned that Cur could indirectly increase the activity of SOD (Samarghandian et al. 2017). Also, Cur is able to scavenge free-radicals (Zhong et al. 2016) which attenuates inflammation and oxidative stress in chronic disorders such as chronic kidney disease (Shehzad et al. 2017). Furthermore, Cur decreases macrophage infiltration in the kidneys (Lu et al. 2017). Cur was also reported to be protective in arsenic-induced hepatotoxicity and tetrachloride-induced hepatic fibrosis (Zhang et al. 2014). Therefore, because of its hepato-renal protective effects, it was decided to determine whether Cur could prevent from kidney and liver damage in LPS-injected rats.

Materials and Methods

Animals

This experimental study utilized thirty-five male rats (Wistar) obtained from the Central Animal House at School of Medicine, Mashhad University of Medical Sciences (weight: 250 ± 10 g). During the course of the experiment, the animals were housed under standard laboratory

conditions with a 12-hr light/dark cycle and a controlled temperature of 23 ± 2°C.

The obtained rats were randomly categorized into five following groups:

(1) Control group: Rats in this group were injected with 1 ml/kg of saline intraperitoneally (ip) instead of LPS and were also administered saline plus dimethyl sulfoxide (DMSO) orally instead of Cur

(2) LPS group: These rats were daily given LPS (1 mg/kg, dissolved in saline) (intraperitoneally,14 days) (Mokhtari-Zaer et al. 2020) and DMSO plus saline instead of Cur.

(3-5) Cur plus LPS groups including LPS - Cur 5 mg, LPS - Cur 10 mg, and LPS - Cur 15 mg groups: Rats were treated with Cur at a dose of 5,10 or 15 mg/kg (oral gavage, daily, 14 days) in addition to 1 mg/kg LPS (Ahmadabady et al. 2021).

Cur was purchased from Sigma-Aldrich (USA) and the Cur treatments were administered daily for two weeks (30min before LPS). LPS injections were performed at 8:00 a.m. each day. At the end of the treatment period, the rats were anesthetized deeply using urethane. The liver and kidney tissues were excised immediately and kept at -80 °C for further biochemical analyses.

The collected tissues were used to determine IL-6 level as an inflammation marker and to assess biomarkers of oxidative stress such as malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD) and total thiols. Blood samples were collected to evaluate serum total protein levels and enzymatic indices of liver function including alkaline phosphatase (ALKP), AST, and ALT as well as renal function parameters such as blood urea nitrogen (BUN) and creatinine.

The Animal Care and Use Committee at Mashhad University of Mashhad Sciences approved this experimental protocol (IR.MUMS.MEDICAL.REC.1399.162).

Biochemical measurements

Liver and renal tissue oxidative damage indicators

The used methods for measuring MDA, thiol, SOD, and CAT have been provided in previous studies (Eftekhar et al. 2019).

Liver function criteria

The serum levels of ALKP, AST, and ALT were assessed using commercial kits in a medical laboratory and by following the company's protocol.

Renal function

Serum amounts of BUN and creatinine were measured using commercial kits in a medical laboratory by following the company's protocol.

Measurement of IL-6

To quantify IL-6 levels in kidney and liver tissues, specific ELISA kit from ebioscience Company, San Diego, CA, USA, was utilized, and the methods provided in the kit was followed. The absorbance readings of the samples obtained with a microplate reader (Biotek, USA) were compared against a pre-established standard curve for the same assay, allowing for the calculation of IL-6 concentration.

Statistical analysis

Data are shown as mean ± SEM. Differences were assessed by one-way ANOVA with Tukey’s post hoc test (SPSS, v26.0), where $p< 0.05$ indicated statistical significance.

Results

Kidney tissues oxidative damage criteria

Oxidative damage parameters in kidney tissue are presented in Figure 1. A significant increase in renal MDA concentration was observed in the LPS group and in the groups receiving the two lower doses of Cur (5 and 10 mg/kg) relative to the control group ($p<0.001$). Treatment with the highest dose of Cur (15 mg/kg) effectively reduced the LPS-induced elevation in lipid peroxidation, showing significant differences ($p<0.01$-

p<0.001) compared to both the LPS group and the groups treated with 5 or 10 mg/kg. In contrast, the 5 and 10 mg/kg doses of Cur were ineffective (Figure 1A).

LPS and LPS-Cur 5 mg groups showed a significant reduction in the CAT activity in the kidney tissues (p<0.001). It was also showed that 10 and 15 mg/kg doses of Cur improved the CAT activity (p<0.05 and p<0.001, respectively). In addition, treatment by 15 mg/kg of Cur increased CAT activity compared to the LPS-Cur 5 mg and LPS-Cur 10 mg groups (p<0.001; Figure 1B).

A significant reduction was also seen in SOD activity in the LPS, LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups (all p<0.001). Pretreatment by 15 mg/kg dosage improved SOD activity compared to LPS and the lowest dose of Cur (p<0.01) while the other doses were ineffective (Figure 1C).

Total thiol contents were lower in the kidney of all LPS (p<0.001), LPS-Cur 5 mg (p<0.001), LPS-Cur 10 mg (p<0.001), and LPS-Cur 15 mg (p<0.05) groups than the control level. In contrast to 5 mg/kg dosage, administration of Cur at 10 (p<0.01) and 15 mg/kg (p<0.001) doses significantly improved total thiols compared to LPS and LPS-Cur 5 mg (p<0.05 compared to the medium dose of Cur and p<0.001 compared to the highest dose) (Figure 1D).

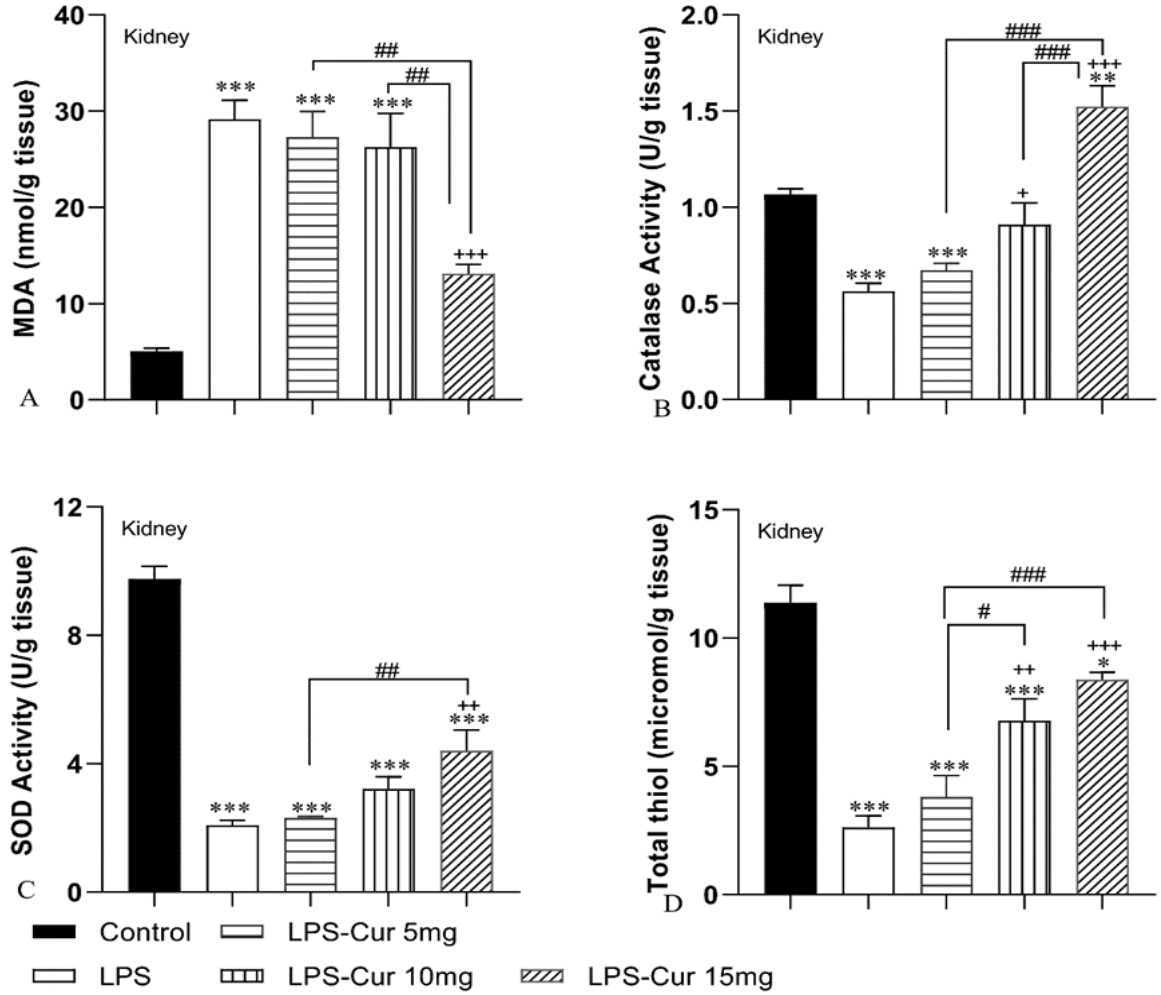

Figure 1. Kidney tissue MDA (A), Catalase (B), SOD (C), and thiol (D) levels. Data are presented as mean ± standard error of the mean (n=7). The rats in control group received saline while in LPS group 1 mg/kg of LPS was injected. In LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups, the rats received 5, 10, and 15 mg/kg of Curcumin (Cur), respectively, before LPS. *p<0.05, **p<0.01, and ***p<0.001, vs. control group, $^{+}$p<0.05, $^{++}$p<0.01, and $^{+++}$p<0.001 vs. LPS group. $^{\#}$p<0.05, $^{\#\#}$p<0.01, and $^{\#\#\#}$p<0.001 vs. other doses of curcumin.

Kidney function criteria

The result of kidney function criteria is shown in Figure 2. LPS treatment significantly elevated BUN concentration in the rats ($p<0.001$). Treatment by 10 and 15 mg/kg of Cur was significantly effective in reducing the serum BUN level ($p<0.01$ for both), however, 5 mg/kg dosage was ineffective. No significant difference was seen between the two higher doses in reducing serum BUN level. Upon administration of LPS, a significant increase was seen in the serum level of creatinine ($p<0.01$). All the three dosages were effective in reducing the level of creatinine ($p<0.05$ for 5 mg/kg, $p<0.001$, for both 10 and 15 mg/kg). However, no significant difference was revealed between the three dosages. The results are shown in Figure 2B.

Liver tissues oxidative damage criteria

As the result shows, in LPS, LPS-Cur 5 mg, and LPS-Cur 10 mg groups, MDA concentration was significantly greater than that of the control animals ($p<0.001$). Pretreatment with 10 and 15 mg/kg Cur was effective to reduce the liver concentration of MDA compared to LPS ($p<0.01$ for 10 mg/kg dose and $p<0.001$ for 15 mg/kg dose) and LPS-Cur 5 mg group ($p<0.01$ for 10 mg/kg dose and $p<0.001$ for 15 mg/kg dose), however, 5 mg/kg dosage was not effective. No significant difference was seen between the two higher doses (Figure 3A).

The activity of CAT was significantly lowered due to LPS administration in comparison to the control level ($p<0.001$). CAT activity had also a lower level in LPS-Cur 5 mg and LPS-Cur 10 mg groups than the control level ($p<0.001$ for both 5 and 10 mg/kg doses). The two higher dosages were able to improve the CAT activity ($p<0.05$ for 10 mg/kg and $p<0.001$ for 15 mg/kg), while 5 mg/kg dosage was ineffective. No significant difference was revealed between the 5 mg/kg and the 10 mg/kg dosages. In addition, treatment by 15 mg/kg of Cur increased CAT activity compared to LPS-Cur 5 mg and LPS-Cur 10 mg groups ($p<0.001$ for both; Figure 3B).

A significant decrease was seen in the SOD activity level in the LPS-administered group compared to the control level ($p<0.05$). Treatment by 10 and 15 mg/kg prior to LPS administration was effective in improving the SOD activity compared to LPS ($p<0.001$ for 10 mg/kg dose and <0.01 for 15 mg/kg dose) and LPS-Cur 5 mg groups ($p<0.001$ for 10 mg/kg dose and $p<0.01$ for 15 mg/kg dose) while the lowest dosage was ineffective. No significant difference was revealed between the effectiveness of the two higher dosages (Figure 3C).

LPS administration caused a significant reduction in the thiol concentration in all LPS ($p<0.001$), LPS-Cur 5 mg ($p<0.001$), LPS-Cur 10 mg ($P<0.001$), and LPS-Cur 15 mg ($P<0.001$) groups compared to control level. The two higher dosages improved the thiol concentration ($p<0.05$ for both); however, the 5 mg/kg dosage was ineffective. The effectiveness of the two effective dosages did not differ significantly (Figure 3D).

Serum levels of Liver enzymes and total protein

The level of ALKP in the serums was significantly higher in LPS ($p<0.001$) and LPS-Cur 5 mg ($p<0.05$) groups than the control level. All three dosages of Cur were effective in reducing the ALKP level ($p<0.01$ for 5 mg/kg, $p<0.001$ for 10 mg/kg, and $p<0.001$ for 15 mg/kg). ALKP in LPS-Cur 15 mg had a lower level than that in LPS-Cur 5 mg group ($p<0.05$) (Figure 4A).

AST level was higher in LPS ($p<0.001$) and LPS-Cur 5 mg ($p<0.01$) groups than the control level. All three dosages attenuated the AST level dose dependently ($p<0.001$ for all) and AST in the LPS-Cur 15 mg showed a lower level than that in the LPS-Cur 5 mg group ($p<0.01$) (Figure 4B).

Total protein concentration showed a significant reduction as a result of LPS administration compared to the control level ($p<0.05$). While 5 mg/kg dosage did

not have a protective effect, the two higher dosages were effective ($p<0.01$ for both; Figure 4C).

Compared with the control level, the rats in the LPS ($p<0.001$) and LPS-Cur 5 mg ($p<0.001$) groups had a significantly higher level of ALT. While pretreatment with 10 and 15 mg/kg dosages decreased ALT concentration compared to LPS and LPS-Cur 5 mg groups ($p<0.001$ for both), 5 mg/kg dosage was ineffective. No significant difference was revealed between the 10 and 15 mg/kg dosages (Figure 4D).

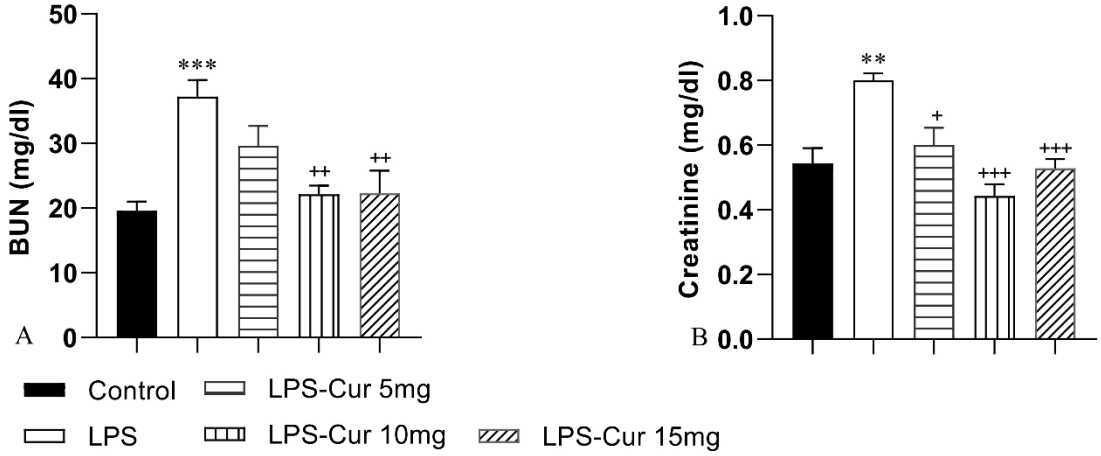

Figure 2. Kidney function tests including BUN (A), and Creatinine (B) levels. Data are presented as mean ± standard error of the mean (n=7). The rats in control group received saline while in LPS group 1 mg/kg of LPS was injected. In LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups, the rats received 5, 10, and 15 mg/kg of curcumin (Cur), respectively, before LPS. **p<0.01 and ***p<0.001, vs. control group, $^{+}$p<0.05, $^{++}$p<0.01, and $^{+++}$p<0.001 vs. LPS group.

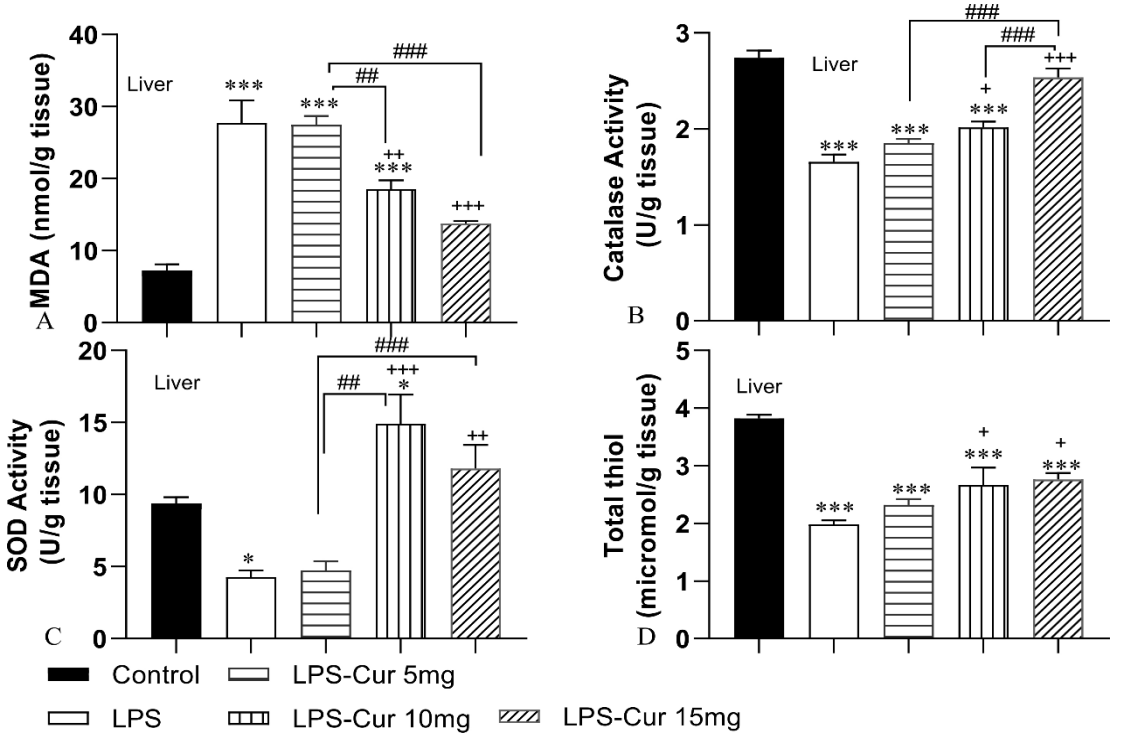

Figure 3. Liver tissue MDA (A), catalase (B), SOD (C), and thiol (D) levels. Data are presented as mean ± standard error of the mean (n=7). The rats in control group received saline while in LPS group 1 mg/kg of LPS was injected. In LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups, the rats received 5, 10, and 15 mg/kg of curcumin (Cur), respectively, before LPS. *p<0.05 and ***p<0.001, vs. control group, $^{+}$p<0.05, $^{++}$p<0.01, and $^{+++}$p<0.001 vs. LPS group. $^{\#\#}$p<0.01, and $^{\#\#\#}$p<0.001 vs. other doses of curcumin.

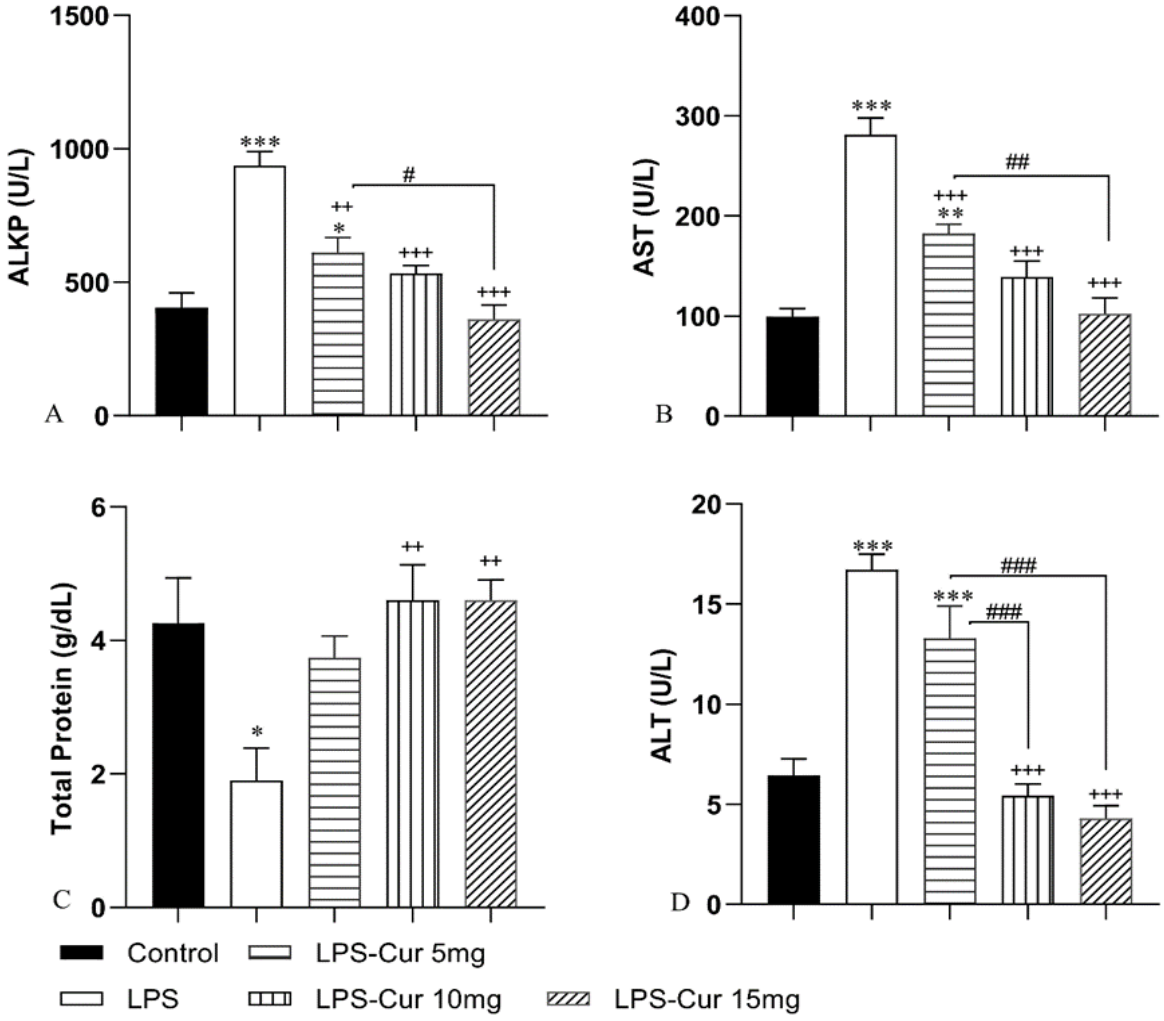

Figure 4. Liver function tests ALKP (A), AST (B), Total protein (C), and ALT (D) levels. Data are presented as mean ± standard error of the mean (n=7). The rats in control group received saline while in LPS group 1 mg/kg of LPS was injected. In LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups, the rats received 5, 10, and 15 mg/kg of curcumin (Cur), respectively, before LPS. *p<0.05, **p<0.01, and ***p<0.001, vs. control group, $^{++}$p<0.01 and $^{+++}$p<0.001 vs. LPS group, $^{\#}$p<0.05, $^{\#\#}$p<0.01, and $^{\#\#\#}$p<0.001 vs. other doses of curcumin.

Kidney tissues inflammation criteria

Compared to controls, IL-6 concentration was markedly increased in the LPS (p<0.001), LPS-Cur 5 mg (p<0.001), and LPS-Cur 10 mg (p<0.01) groups. Pretreatment with 10 mg/kg (p<0.001) or 15 mg/kg (p<0.001) of Cur, but not 5 mg/kg (p>0.05), effectively reduced liver IL-6. Both higher doses also resulted in significantly lower IL-6 than the 5 mg/kg dose (p<0.001; Figure 5). A dose-dependent effect was further evident in the kidney, where IL-6 in the 15 mg/kg group was lower than that in the 10 mg/kg group (p<0.05).

Liver tissues inflammation criteria

IL-6 concentration was seen to be higher than the control level in the liver tissue of LPS (p<0.001), LPS-Cur 5 mg (p<0.001), and LPS-Cur 10 mg (p<0.01) groups. Pretreatment with 5 mg/kg (p<0.05), 10 mg/kg (p<0.001) and 15 mg/kg (p<0.001) of Cur was effective in reducing the liver concentration of IL-6. IL-6 was lower in LPS-Cur 10 mg (p<0.05) and LPS-Cur 15 mg (p<0.001) groups than in the LPS-Cur 5 mg group (Figure 6).

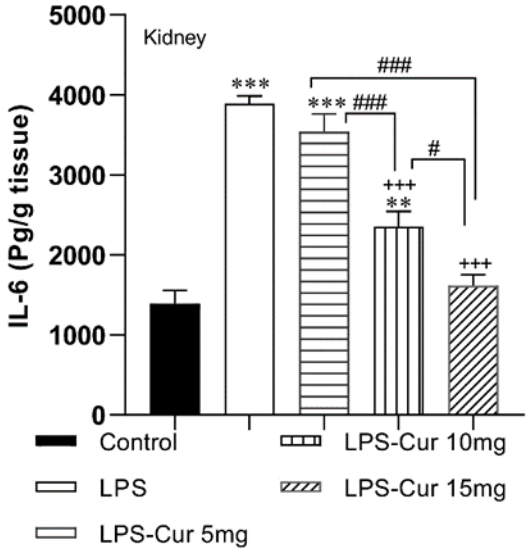

Figure 5. Kidney tissue IL-6 levels. Data are presented as mean ± standard error of the mean (n=7). The rats in control group received saline while in LPS group 1 mg/kg of LPS was injected. In LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups, the rats received 5, 10, and 15 mg/kg of curcumin (Cur), respectively, before LPS. **p<0.01 and ***p<0.001, vs. control group, $^{+++}$p<0.001 vs. LPS group, $^{\#}$p<0.05 and $^{\#\#\#}$p<0.001 vs. other doses of curcumin

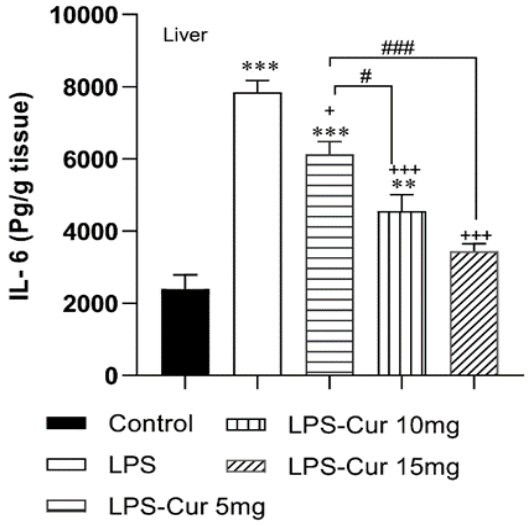

Figure 6. Liver tissue IL-6 levels. Data are presented as mean ± standard error of the mean (n=7). The rats in control group received saline while in LPS group 1 mg/kg of LPS was injected. In LPS-Cur 5 mg, LPS-Cur 10 mg, and LPS-Cur 15 mg groups, the rats received 5, 10, and 15 mg/kg of curcumin (Cur), respectively, before LPS. **p<0.01 and ***p<0.001, vs. control group, $^{+}$p<0.05 and $^{+++}$p<0.001 vs. LPS group, $^{\#}$p<0.05 and $^{\#\#\#}$p<0.001 vs. other doses of curcumin.

Discussion

The current investigation was conducted to explore the protective influence of Cur on hepatic and kidney functions under inflammatory conditions induced by LPS. Several biochemical indicators, including MDA, CAT and SOD activities and total thiol content were analyzed as markers of oxidative stress within the liver and kidney tissues. Since LPS is commonly recognized as a reliable agent for inducing systemic inflammation in experimental models (Doi et al. 2009; Vos et al. 1997), it was anticipated to provoke strong oxidative and inflammatory responses. In line with this expectation, a remarkable elevation of IL-6 levels was observed in both organs following LPS exposure, confirming previous findings that emphasized IL-6 as a critical cytokine mediating organ injury triggered by LPS (Luig et al. 2015). Additionally, increases in MDA levels and alterations in SOD activity were recorded, serving as indirect indicators of oxidative and inflammatory tissue damage (Kim and Ha 2010; Visner et al. 1990).

Our findings demonstrated that administration of LPS significantly enhanced IL-6 concentrations in both hepatic and renal tissues. These changes are in line with previous reports by Chunzhi et al. (2016) and Gong et al. (2017), which highlighted the crucial role of IL-6 in tissue dysfunction. The increased cytokine levels were associated with deteriorated organ function, evidenced by elevated biochemical parameters such as ALKP, AST, ALT, BUN, and creatinine (Chunzhi et al. 2016; Gong et al. 2017). These results reinforce earlier investigations showing that LPS-mediated inflammation leads to liver and kidney dysfunction (Hsu et al. 2006; Olinga et al. 2001; Xu et al. 2014).

The high death ratio due to liver and kidney dysfunctions asserts the importance of developing an appropriate cure with minimal side effects. Plants and the seeds of

the plants have lately been in the center of attention as a way of treating kidney and liver diseases (Musabayane 2012; Sachin and Ajay 2011). Cur is a compound derived from herbal remedy turmeric, a yellow color spice. Cur has been known for its anti-inflammatory, anti-cancer and antioxidant effects (Anand et al. 2007; Sharma et al. 2005).

Studies have shown a decrease in oxidative damage in kidney and liver tissue as a result of Cur administration (Iqbal et al. 2009; Sankar et al. 2016). Some other studies attributed other beneficial effects on liver and kidney function to Cur (Jang et al. 2008; Kowluru et al. 2007). Results of this study showed that Cur have anti-inflammatory effects in liver and kidney tissues. It was shown that Cur decreased IL-6 in both kidney and liver tissues of LPS-treated rats. Pre- and post-treatment with Cur decreased IL-6 in nephrotoxicity induced by cisplatin (Kumar et al. 2017). Also, cadmium increases and Cur decreases IL-6 in the liver (Bayindir et al. 2016). In the current examination, the rats treated with Cur prior to LPS administration had a lower amount of MDA as a marker of oxidative tissue damage in the Cur-treated rats than in LPS-administered group. SOD and CAT activity and total thiol concentration was higher in the Cur-treated rats than in LPS-administered group. These results confirms that Cur can be used as a treatment to inflammation-induced kidney injury (Chen et al. 2007). SOD and CAT activity were used to evaluate the level of oxidative stress. Several studies have denoted the role of SOD in protecting cells against oxidative stress (Rukkumani et al. 2004). The role of Cur in protecting renal cells through scavenging the ROS has been well established. It has also been reported that Cur has been effective in ameliorating renal oxidative stress induced by ferric nitrilotriacetic in mice (Memis et al. 2008). In the present study, there was a reduction in the activity of the two enzymes because of LPS administration and there was an improvement in their activity as a result of Cur treatment. These results match with previous studies (Trujillo et al. 2013).

In the case of kidney function improvement; we also observed that Cur-treated rats had a lower amount of both BUN and creatinine. Other studies have shown the same result (Farombi and Ekor 2006). Furthermore, Cur caused a reduction in the level of ALKP, AST, ALT and total protein. These data are consistent with previous studies (El-Sheikh and HNA 2011; Gupta and Dixit 2011). Cur has also been able to reverse hepatic damage caused by CCl4 cirrhosis to some extent (Fu et al. 2008).

In this study, we examined three different doses of Cur based on previous studies. As the results show, their effectiveness has increased with increasing doses. It was shown that 15 mg/kg dose was significantly more effective than 5 mg/kg dose. Accordingly, it is suggested to investigate this dose in future studies.

The present study has certain limitations. First, histology and pathology studies were not conducted. Second, inflammatory parameters were assessed in tissue samples but not in the serum. These aspects are suggested to be investigated in future work.

The protective effects of Cur on LPS-induced kidney and liver damage was investigated in the present study. Cur decreased LPS-induced inflammation and oxidative stress parameters and it conversed renal and liver function.

Acknowledgment

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Conflicts of interest

The authors declare no conflict of interest.

Ethical Considerations

The research was validated by ethical committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.162)

Code of Ethics
IR.MUMS.MEDICAL.REC.1399.162

Authors' Contributions
FB and MH planned the experiments. VM wrote the initial version of the manuscript, RS and MMB carried out the experiments, FB carried out the biochemical tests, MH analyzed the data, FB and MH finalized the manuscript

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