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Original Article

Protective effects of cilostazol against cisplatin-induced hepatorenal toxicity in male mice

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Abstract

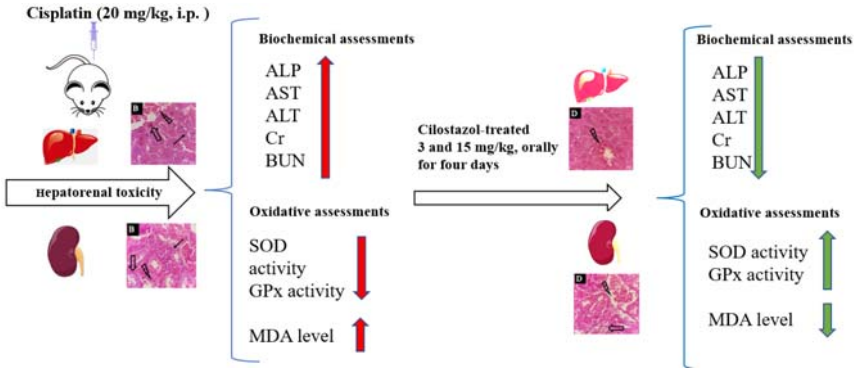
Background and purpose: Cisplatin (CPN) is a widely used and potent chemotherapy drug for cancer treatment. However, one of the major side effects of CPN is hepatorenal toxicity. Recently, cilostazol (CSZ), a type III phosphodiesterase inhibitor, has promising effects against liver and kidney toxicities. We assessed the effects of CSZ against CPN-induced hepatorenal toxicity (CIHR) in male mice.

Experimental approach: Twenty-four male mice were randomly assigned as follows: control group (no treatment), CPN group (treated with 20 mg/kg CPN on day one of the experiment), and CPN + CSZ 3 and 15 groups (treated with CPN on day one of the experiment plus CSZ (3 and 15 mg/kg) orally for four days). Biochemical, oxidative, and histological investigations were conducted to evaluate the effectiveness of CSZ in protecting the liver and kidneys from CPN-induced damage.

Findings/Results: The results showed that treatment with CSZ, especially at 15 mg/kg, significantly reduced the CPN-induced increase in serum concentrations of biochemical markers such as alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine. Furthermore, CSZ treatment at 15 mg/kg also restored the hepatorenal oxidative stress factors, including superoxide dismutase, malondialdehyde, and glutathione peroxidase. Histological examination revealed a significant improvement in groups receiving CSZ (15 mg/kg) compared to the CPN-treated group, alongside biochemical and oxidative results.

Conclusion and implications: The findings of this investigation point towards the potential of CSZ as a viable contender for subsequent exploration in the realm of devising efficacious therapeutic approaches for CIHR.

Keywords: Cilostazol; Cisplatin; Kidney; Liver; Oxidative stress.



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INTRODUCTION

Cisplatin (CPN) is a platinum-containing anticancer drug that forms cross-links in a single strand of DNA and between two strands (1). This mechanism inhibits DNA synthesis, leading to the death of tumor cells in all stages of the cell cycle (2). This drug has a strong anti-neoplastic effect on different kinds of cancers, such as esophageal and stomach cancers, as well as genitourinary tract cancers, especially testicular, ovarian, and bladder cancers (3). However, one of the main side effects of CPN is hepatorenal toxicity, which limits its use in treatment (4). The drug is primarily concentrated in the kidney, especially within the proximal tubule, which causes renal toxicity and symptoms such as kidney swelling, proteinuria, and an elevation of serum blood urea nitrogen (BUN) and creatinine (Cr) (5,6). Additionally, hepatotoxicity caused by CPN is marked by significantly increased serum levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (7). Several mechanisms contribute to CPN-induced hepatorenal toxicity, including tissue oxidative damage and the generation of reactive oxygen species (ROS), which are considered the most significant mechanisms (8). ROS, particularly hydroxyl radicals, can lead to lipid peroxidation, destruction of cell membranes, and oxidation of nucleic acids and proteins (6). One of the key preventive factors against CPN-induced oxidation damage is the enhancement of antioxidant enzyme activity, such as glutathione peroxidase (GPx) and superoxide dismutase (SOD) (9,10).

Cilostazol (CSZ) is a selective phosphodiesterase type III inhibitor that prevents platelet aggregation and dilates peripheral blood vessels. It is commonly used to treat ischemic symptoms associated with peripheral vascular diseases, such as intermittent claudication (11). CSZ is generally well tolerated, with mild to moderate side effects, including headache, heart palpitations, and tachycardia (12). Research has indicated that CSZ has protective effects against liver and kidney toxicities via different mechanisms. For instance, it has been shown that CSZ reduces gentamicin-induced kidney damage by decreasing apoptotic markers and malondialdehyde (MDA) and increasing antioxidative markers such as SOD and GPx (13). In another study, simultaneous usage of CSZ and rosuvastatin reduces inflammatory markers and improves kidney damage caused by a high-fat diet (14). Additionally, a study by Chian *et al*. showed that CSZ improved diabetic nephropathy by reducing free radical production and inflammatory markers (15). Furthermore, CSZ has beneficial effects against thioacetamide-induced hepatotoxicity by regulating inflammatory cytokines and apoptotic markers (13). Moreover, it has been demonstrated that administering CSZ to animals with cholestatic liver injury induced by common bile duct ligation, improved hepatic functions and lowered fibrosis (16).

Considering the antioxidant properties of CSZ and the impact of free radicals in CPN-induced hepatorenal toxicity (CIHR), we assessed the effect of CSZ on CIHR in male mice by analyzing the biochemical, oxidant, and histological indices.

MATERIALS AND METHODS

Animals and experimental design

Twenty-four male albino mice (30 ± 2 g) were prepared by the animal house of Rafsanjan University of Medical Sciences and maintained under standard conditions (21 ± 1 °C, 12/12-h dark/light cycle) in polycarbonate cages (3 per cage) with free access to water and food.

The mice were assigned to four groups (n = 6) including control group: normal mice with no treatment; CPN group: treated with CPN (20 mg/kg, i.p. injection) on day one of the experiment (17); CPN + CSZ 3 group: treated with CPN (20 mg/kg, i.p. injection) on day one of the experiment and CSZ (3 mg/kg, orally) for four days; CPN + CSZ 15 group: treated with CPN (20 mg/kg, i.p. injection) on day one of the experiment and CSZ (15 mg/kg, orally) for four days.

Ethical considerations

Approval for the present research was granted by the Ethics Committee of Kerman University of Medical Sciences (Ethic No.

IR.KMU.REC.1400.502). All experiments adhered to the guidelines of the ethics committee of Kerman University of Medical Sciences and the European Communities Council Directive 86/609/EEC of 24 November 1986.

Sample collection

Twenty-four hours after the final administration of drugs, the mice were anesthetized, and blood specimens were collected from the orbital sinus and underwent centrifugation (3000 rpm, 15 min) to isolate the serum, which was then stored at -20 °C for measuring biochemical parameters of the kidney and liver. The mice were subsequently euthanized by rapid decapitation, and then the liver and kidneys were harvested. The liver was divided into two parts. One kidney and one part of the liver were homogenized at a ratio of 1:10 (weight to volume) in ice-cold Tris-HCl buffer (100 mM, pH 7.4). The homogenate was then centrifuged at 6000 rpm for 20 min, and the supernatant was collected and stored at -80 °C to assess oxidative parameters in liver and kidney tissues. The other kidney and the remaining part of the liver were preserved in 10% formalin for histopathological analysis (18).

Biochemical and oxidative assessments

The ALP, AST, ALT, BUN, and Cr serum concentrations were evaluated by an automated biochemical analyzer (MINDRAY, China) (19), whereas hepatic and renal activities of SOD and GPx, as well as MDA concentrations were assessed by commercially available kits (ZellBio, Germany) according to the manufacturer's instructions using an automatic microplate reader (BioTek, USA).

Histological assessments

For histological analysis, the fixed livers and kidneys underwent dehydration with sequential ethanol solutions and were embedded in paraffin; 5-µm thick sections were cut; the sections were subjected to staining with hematoxylin and eosin (H&E) and examined under a light microscope (Nikon Labophot, Japan) (14). A pathologist blindly evaluated all slides for histological abnormalities of the liver and kidney. The inflammation, pyknosis, and congestion were assessed in liver samples. The inflammation, tubular necrosis, and congestion were assessed in kidney samples. The severity of each parameter was graded using a semi-quantitative method into four categories: normal (scored as 1), mild (scored as 2), moderate (scored as 3), and severe (scored as 4). Finally, the average score for each slide was recorded (20).

Statistical analysis

Statistical analyses were conducted using the GraphPad Prism program 6.01. The results were presented as mean ± standard error of the mean (SEM). The data's normality was assessed using the Kolmogorov-Smirnov test. Differences among the groups were analyzed by the one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Non-parametric variables were assessed by the Kruskal-Wallis test followed by Dunn's post-hoc test. $P < 0.05$ was considered statistically significant.

RESULTS

Effects of CSZ on serum levels of biochemical markers against CIHR in mice

ALP, AST, and ALT levels, as hepatic functional tests, were higher in the serum of the CPN group than in the control group (Fig. 1A-C). CSZ treatment (3 mg/kg) significantly decreased the ALP and ALT levels in the serum of the animals exposed to CPN. Similarly, CSZ administration (15 mg/kg) lowered all serum levels of biochemical markers in comparison with the CPN group.

Cr and BUN levels, as renal functional tests, were higher in the serum of the CPN group than in the control group (Fig. 1D and E). CSZ treatment (3 mg/kg) significantly decreased the Cr level in the serum of the animals exposed to CPN. Similarly, CSZ administration (15 mg/kg) lowered both Cr and BUN levels in comparison with the CPN group.

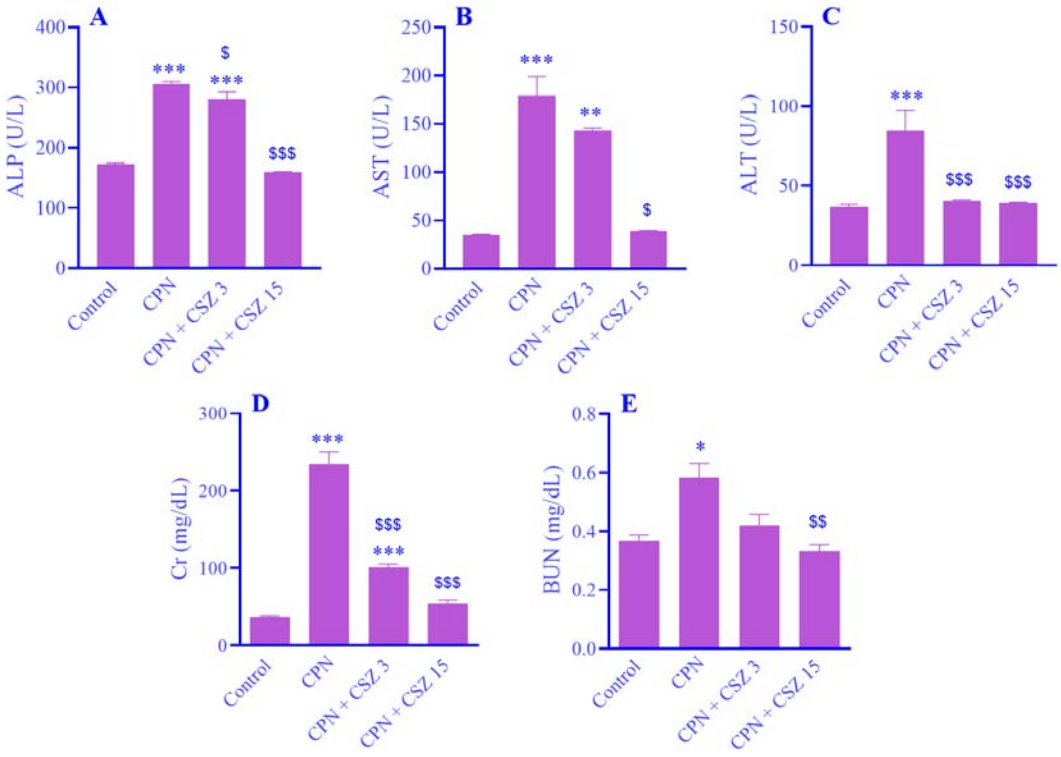

Fig 1. Effects of CSZ (3 and 15 mg/kg/day; orally administered for four days) on (A) ALP, (B) AST, (C) ALT, (D) Cr, and (E) BUN levels in serum of CPN-exposed mice. Data are expressed as mean ± SEM (n = 6). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ indicate significant differences compared to the control group; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, and $^{\$\$\$}P < 0.001$ versus the CPN group. CSZ, Cilostazol; CPN, cisplatin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; BUN, blood urea nitrogen.

Effects of CSZ on SOD, GPx, and MDA activities or levels of the hepatic and renal tissue against CIHR in mice

SOD activities as a free radical scavenger enzyme were lower in the CPN group's hepatic and renal tissues than in the control group (Fig. 2A and D). CSZ treatment at 3 mg/kg notably increased the SOD activity only in the renal tissue of the animals exposed to CPN. Likewise, CSZ administration (15 mg/kg) enhanced SOD activities in both hepatic and renal tissues compared with the CPN group.

GPx activities as an antioxidant enzyme were lower in the CPN group's hepatic and renal tissues than in the control group (Fig. 2B and E). CSZ treatment (3 mg/kg) notably increased the GPx activity in only the hepatic tissue of the animals exposed to CPN. Likewise, CSZ administration (15 mg/kg) enhanced GPx activities in both hepatic and renal tissues compared with the CPN group.

The free radical damage was measured by lipid peroxidation as indicated by MDA level. As shown in Fig. 2C and F, the MDA levels were higher in the CPN group's hepatic and renal tissues than in the control group. CSZ administration (15 mg/kg) decreased the MDA levels in both hepatic and renal tissues compared to the CPN group.

Effects of CSZ on histological parameters of the renal tissue against CIHR in mice

The typical liver architecture was observed in the histological examinations of the control group, as depicted in Fig. 3A and Table 1. In contrast, the CPN group exhibited significant congestion, infiltration of leukocytes, and necrosis of hepatocytes, as shown in Fig. 3B and Table 1. CSZ treatment (3 mg/kg) had no significant effect on the mentioned indices of liver (Fig. 3D and Table 1). Moreover, administration of CSZ (15 mg/kg) ameliorated these abnormalities and played a notable protective role in mitigating the aforementioned pathological changes, as illustrated in Fig. 3D and Table 1.

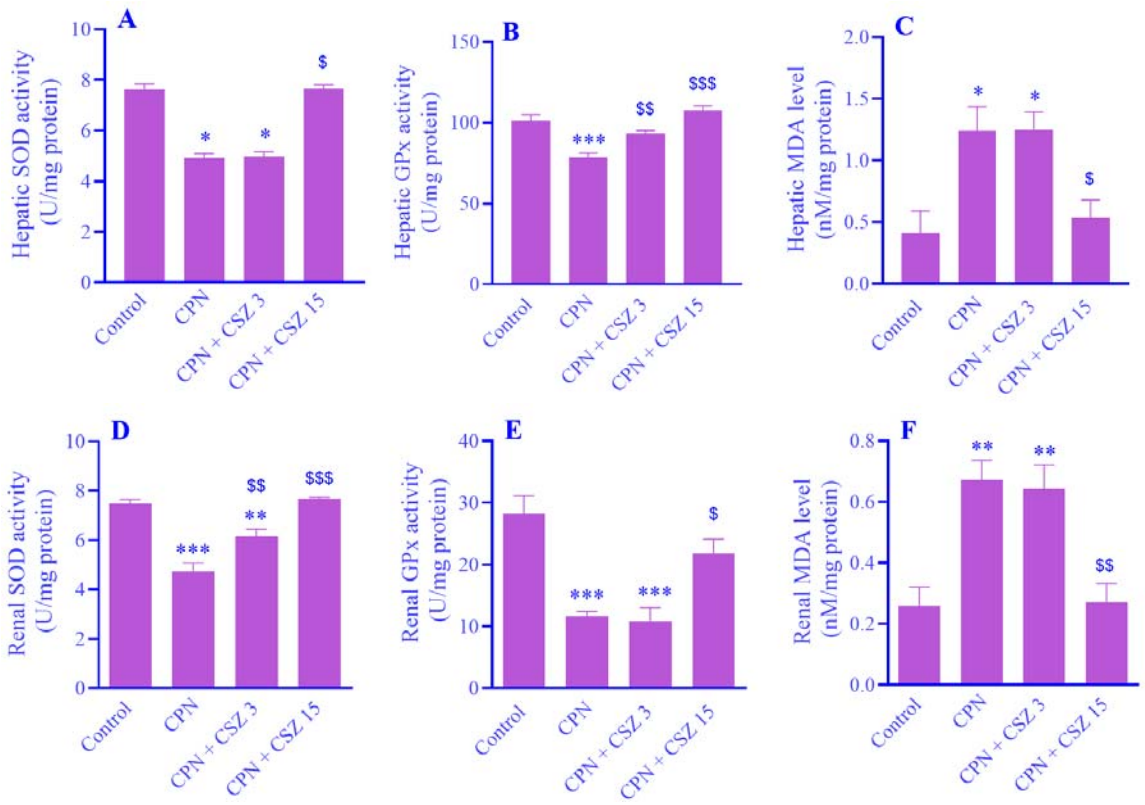

Fig 2. Effects of CSZ (3 and 15 mg/kg/day; orally administered for four days) on hepatic (A) SOD activity, (B) GPx activity, (C) MDA level, renal (D) SOD activity, (E) GPx activity, and (F) MDA level in CPN-exposed mice. Data are expressed as mean ± SEM (n = 6). **P* < 0.05, ***P* < 0.01, and ****P* < 0.001 indicate significant differences compared to the control group; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, and $^{\$\$\$}P < 0.001$ versus the CPN group. CSZ, Cilostazol; CPN, cisplatin; SOD, superoxide dismutase; GPx, glutathione peroxidase; MDA, malondialdehyde.

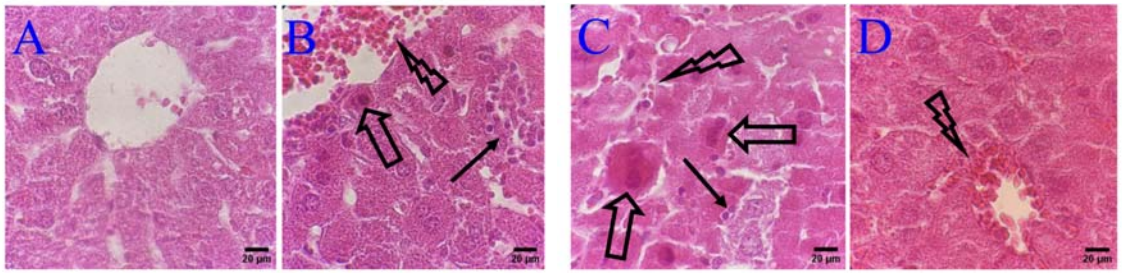

Fig. 3. The effects of CSZ (3 and 15 mg/kg/day; orally administered for four days) on histological changes in CPN-exposed mice's hepatic tissue (H&E staining; magnification: 400 ×). (A) Control group, (B) CPN group, (C) CPN + CSZ 3 group, and (D) CPN + CSZ 15 group. The black arrow indicates inflammation; the lightning bolt indicates congestion; and the hollow arrow indicates pyknosis. CSZ, Cilostazol; CPN, cisplatin.

Normal kidney structure was seen in the histological studies of the control group (Fig. 4A; Table 1). The CPN group showed severe congestion, leukocyte infiltration, and tubular necrosis (Fig. 4B; Table 1). CSZ treatment (3 mg/kg) has no significant effect on mentioned indices of kidney (Fig. 4D and Table 1). Furthermore, CSZ treatment (15 mg/kg) alleviated these lesions and had a remarkable protective role on the above-mentioned pathological lesions (Fig. 4D; Table 1).

Table 1. Effects of CSZ (3 and 15 mg/kg/day; orally administered for four days) on pathological indices of CPN-exposed mice. Data are expressed as mean ± SEM (n = 6). *P < 0.05, **P < 0.01, and ***P < 0.001 indicate significant differences compared to the control group; $^{\$}P$ < 0.05 and $^{\$\$}P$ < 0.01 versus the CPN group.

Pathological indices	Groups			
	Control	CPN	CPN + CSZ 3	CPN + CSZ 15
Renal inflammation	1.00 ± 0.00	3.66 ± 0.21***	3.00 ± 0.25*	1.50 ± 0.22$
Renal tubular necrosis	1.00 ± 0.00	3.50 ± 0.22***	2.50 ± 0.22*	1.33 ± 0.21$$
Renal congestion	1.00 ± 0.00	3.83 ± 0.16***	2.66 ± 0.21	1.50 ± 0.22$$
Hepatic inflammation	1.00 ± 0.00	3.83 ± 0.16**	3.33 ± 0.21*	1.16 ± 0.16$$
Hepatic pyknosis	1.00 ± 0.00	3.33 ± 0.21***	2.16 ± 0.16	1.16 ± 0.16$$
Hepatic congestion	1.00 ± 0.00	3.50 ± 0.22***	2.33 ± 0.21	1.33 ± 0.21$$

CSZ, Cilostazol; CPN, cisplatin.

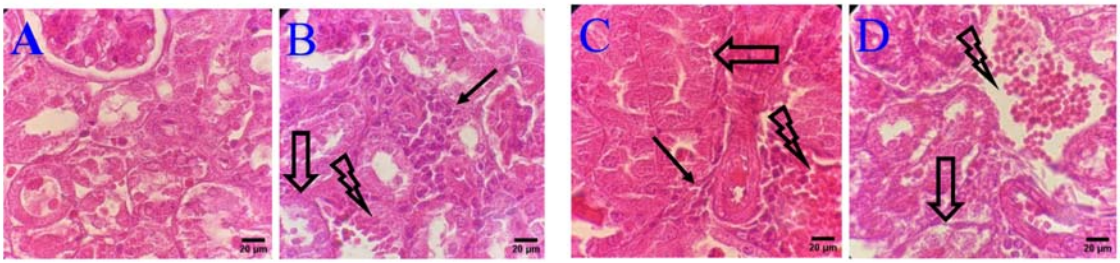

Fig. 4. The effects of CSZ (3 and 15 mg/kg/day; orally administered for four days) on histological changes in CPN-exposed mice's renal tissue (H & E staining; 400x). ((H&E staining; magnification: 400 ×). (A) Control group, (B) CPN group, (C) CPN + CSZ 3 group, and (D) CPN + CSZ 15 group. The black arrow indicates inflammation; the lightning bolt indicates congestion; and the hollow arrow indicates tubular necrosis. CSZ, Cilostazol; CPN, cisplatin.

DISCUSSION

This investigation examined the effect of CSZ on CIHR in male mice. We found that CPN administration (20 mg/kg, i.p.) caused significant damage to the liver and kidney, as indicated by elevated levels of ALP, AST, ALT, BUN, and Cr. Additionally, CPN treatment increased MDA content, along with a reduction in GPx and SOD activities in the liver and kidney tissues. These biochemical changes were associated with pathological lesions in both the hepatic and renal tissues. However, oral administration of CSZ for four consecutive days, particularly at 15 mg/kg/day, significantly mitigated the harmful effects of CPN on the liver and kidneys.

Serum concentrations of ALP, AST, ALT, BUN, and Cr are commonly used as diagnostic markers to evaluate liver and kidney function (10,18). There is substantial evidence connecting the increased production of ROS in liver and kidney tissues to elevated levels of these biochemical markers following the administration of CPN (7,19). While CPN offers valuable antitumor effects, its significant hepatorenal toxicity manifests as increased serum ALP, AST, ALT, BUN, and Cr levels, a finding corroborated by prior studies (21-23). In our research, i.p. injection of CPN similarly elevated specific biochemical markers, which is consistent with existing literature (7,17,24). We further demonstrated that CSZ administration (15 mg/kg/day) significantly reduced these elevated parameters in mice treated with CPN. This protective effect is in line with previous studies that highlight the benefits of antioxidants, such as myrtenol, ellagic acid, calcium dobesilate, and isoliquiritigenin, in alleviating oxidative stress and normalizing levels of ALP, AST, ALT, BUN, and Cr in models of CIHR (21,25-27). CSZ's antioxidant properties are well-documented, including its ability to suppress superoxide generation and scavenge hydroxyl radicals (28). Our findings reinforce that CSZ exerts potent antioxidative effects by directly inhibiting ROS production (13). Previous research supports CSZ's protective role in various toxicity models. For example, CSZ administered (10 mg/kg/day) for eight days significantly reduced Cr and urea levels in gentamicin-induced nephrotoxicity due to its strong antioxidative properties (13), while its nephroprotective effects

against amikacin-induced renal injury stem from its anti-inflammatory, antioxidant, and anti-apoptotic properties (29). In a model of liver injury, administration of CSZ improved the levels of AST and ALT after exposure to thioacetamide. This improvement is attributed to enhanced redox status, as indicated by increased levels of reduced glutathione and decreased levels of MDA (30). Similarly, oral administration of CSZ reduced elevations in ALT and AST levels in cases of liver ischemia/reperfusion injury, likely due to its anti-inflammatory effects (31). Collectively, these findings suggest that the protective effects of CSZ on the liver and kidneys result from its ability to reduce oxidative stress and enhance the activity and levels of antioxidant enzymes (29,32). By alleviating the oxidative damage caused by chemotherapeutic agents like CPN, CSZ emerges as a promising therapeutic adjunct for mitigating chemotherapy-related liver and kidney damage.

Excessive ROS production in the liver and kidney has been established as a key contributor to CIHR (33,34). This oxidative stress is characterized by elevated MDA levels and decreased activity and/or levels of antioxidant enzymes like SOD, GPx, and catalase in liver and kidney tissues (24,27). Consequently, oxidative stress can lead to hepatorenal abnormalities and impaired function (27,35,36). In our study, CPN administration significantly increased MDA levels in liver and kidney tissues while markedly decreasing SOD and GPx activities. Moreover, CSZ treatment, especially at 15 mg/kg/day in mice treated with CPN, notably decreased the MDA level as well as increased the mentioned antioxidative indicators. These findings align with prior studies demonstrating CSZ's antioxidant properties across various experimental models of tissue injury (28,32). For instance, Hafez *et al*. assessed the effects of CSZ on thioacetamide-related nephrotoxicity. They showed that CTZ lowers serum Cr and urea levels and restores the MDA level and SOD activity (32). Similarly, CSZ has been shown to reduce cyclosporine-induced nephrotoxicity by increasing catalase and SOD activities and decreasing MDA levels (37). Additional evidence supports CSZ's role in alleviating diabetic nephropathy in rats through regulation of oxidative stress (38) and reducing ROS production in ethanol-induced hepatitis (39). Collectively, these studies suggest that CSZ ameliorates hepatorenal toxicity in CPN-treated animals, at least in part, by attenuating oxidative stress in these tissues.

It is well established that CPN induces over-production of ROS in liver and kidney tissues, which is associated with renal and hepatic pathological lesions (20). Pathological changes caused by oxidative stress can lead to functional abnormalities in the liver and kidney (26). Consistent with previous reports, we found that CPN induces pathological lesions in the liver and kidney, such as inflammation, necrosis, and congestion (9,40,41). Additionally, we verified the effectiveness of CSZ (especially at 15 mg/kg/day) on the improvement of pathological lesions by histological studies of these tissues. El Awdan *et al*. demonstrated that CSZ reduced pathological lesions, such as centrilobular necrosis of hepatocytes, and leukocyte infiltration in liver damage induced by thioacetamide (30). Moreover, CSZ attenuated tubular necrosis and interstitial cellular infiltrations in the renal tissue of animals treated with gentamicin by beneficial effects on the antioxidant defense system (13).

CONCLUSIONS

In summary, our findings demonstrated the protective properties of CSZ against CIHR. This protection may be attributed to reduced MDA levels and increased SOD and GPx activities in liver and kidney tissues. However, further research is needed to elucidate the precise underlying mechanism(s) mediating these effects on hepatic and renal functions.

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Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

I. Fatemi and E. Hakimizadeh conceived and designed the experiments; J. Hassanshahi and M. Amirteimoury performed the experiments; F. Khajehasani analyzed the data; I. Fatemi contributed to providing the reagents, materials,

and analysis tools; A. Kaeidi wrote the paper. All authors have read and approved the finalized article. Each author has fulfilled the authorship criteria and affirmed that this article represents honest and original work.

AI declaration

During the preparation of this work, the author(s) used Grammarly to improve readability and language. After using this tool, the author(s) reviewed and edited the content and take full responsibility for the content of the publication.

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