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Research article

Renoprotective effects of zinc sulfate against transient liver ischemia/reperfusion injury in rats

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ABSTRACT

Objectives: Liver ischemia/reperfusion damage frequently occurs in setting of hepatic resection and liver transplantation. It leads to disturbance in remote organs such as heart, lung and kidneys. This study explored the consequences of hepatic ischemia/reperfusion on the oxidative stress parameters, biochemical factors, and histopathological alterations in the kidney's rats, as well as evaluated the role of zinc sulfate on above-mentioned parameters.

Materials and methods: Twenty-eight male Wistar rats were accidently assigned into four groups (n = 7). They were Sham, ischemia/reperfusion, zinc sulfate pretreatment, and zinc sulfate pretreatment + ischemia/reperfusion groups. Sham group: obtained normal saline (2 ml/day, seven consecutive days), intraperitoneally, zinc sulfate pretreatment group: obtained zinc sulfate (5 mg/kg, seven consecutive days, intraperitoneally). Ischemia/reperfusion group: obtained normal saline as mentioned previous, then rats experienced the partial ischemia (%70) for 45 min followed by 60 min reperfusion. Zinc sulfate pretreatment group: obtained zinc sulfate as mentioned previous, then rats experience the partial ischemia/reperfusion as presented earlier. At the end of investigation, blood was withdrawn, liver and renal tissues were removed. Then, biochemical and oxidative stress parameters, and histological changes were evaluated in the mentioned tissues.

Results: The findings of this experiment indicated that zinc sulfate markedly reduced the serum levels of liver and kidney function tests in relative to ischemia/reperfusion group. Also, antioxidant enzymes activity, ferric reducing antioxidant power, and nitric oxide significantly increased, while malondialdehyde level declined in the renal tissue of zinc sulfate + ischemia/reperfusion group compared to ischemia/reperfusion rats. Furthermore, zinc sulfate alleviated the liver and kidneys histopathological alterations following ischemia/reperfusion.

Conclusion: Zinc sulfate ameliorated liver and kidney function, and improved oxidant-antioxidant balance in favor of antioxidants. It is suggested that zinc sulfate may be beneficial effects on hepato-renal injury after ischemia/reperfusion.

Abbreviations: IR, Ischemia/reperfusion; ALF, Acute liver failure; HRS, Hepatorenal syndrome; AKI, Acute kidney injury; ROS, Reactive oxygen species; ATP, Adenosine triphosphate; MDA, Malondialdehyde; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; H2O2, Hydrogen peroxide; NOS, Nitric oxide synthase; eNOS, Endothelial NOS; iNOS, Inducible NOS; nNOS, Neuron NOS; GFR, Glomerular filtration rate; Zn, Zinc; MT, Metallothionein; BUN, Bood urea nitrogen; Cr, Creatinine; N/S, Normal saline.

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1. Introduction

Liver ischemia/reperfusion (IR) damage commonly take places in underlying of hepatic resection, liver transplantation, or septic shock [1]. Hepatic IR-induced acute liver failure (ALF) is a prevalent clinical complication which associated with impairment in remote organs such as the lung, cardiac and kidneys [2,3].

It has been reported that the prevalence of hepatorenal syndrome (HRS) varies from 40 to 85% [4]. Acute kidney injury (AKI) is an important side effect subsequent orthotopic liver transplantation associated with increased mortality among patients [5].

It has been revealed, reactive oxygen species (ROS), inflammation, vasoactive peptides, and adenosine triphosphate (ATP) depletion are contributed in the progression of IR-induced impairments [6]. Moreover, Ca^{2+} overload in the cell, stimulation of intrarenal adenosine, and superoxide-induced membrane changes are contributed in ischemic damage [7]. These events exacerbate renal injury via lipids peroxidation, protein oxidation, and DNA destruction [8]. The production of malondialdehyde (MDA), as an aldehyde can be used to evaluate of the level of oxidative stress [9] and especially to evaluate of the lipid peroxidation [10].

Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are three key antioxidant enzymes against free radicals or reactive species in the cells [11]. SOD activates the dismutation of the superoxide anion into hydrogen peroxide (H_2O_2) and molecular oxygen. Then, CAT converts H_2O_2 into H_2O and O_2. GP_X also catalyzes the reduction of lipidic or nonlipidic hydroperoxides as well as H_2O_2 via oxidization of glutathione [12].

Three nitric oxide synthase (NOS) isoforms including endothelial NOS (eNOS), inducible NOS (iNOS), and neuron NOS (nNOS) have been identified in the kidney [13]. NO is a key regulator of intrarenal hemodynamics and glomerular filtration rate (GFR) in HRS [14].

Zinc (Zn) is one of the most important trace element [15] in all tissues, secretions, and liquids [16]. It is necessary for growth, development [17], metabolism, detoxification, signaling pathways, and gene modulation [18]. Zn also has various biological processes including protein synthesis, proliferation, redox homeostasis [19], and antioxidant functions [20] by maintain of cell membrane, induction of metallothionein (MT) content [21,22] or suppression of calcium influx [23]. Inadequate of Zn augments oxidative stress, and provokes oxidative stress in the hepatocytes of rats [24]. It has been determined that Zn has defensive properties against ethanol [25]-chlorpyrifos-induced hepatic damage [26], ethanol-induced acute stomach insult [27], IR-induced cardiac [28] and renal injuries [29].

One experimental study indicated that IR damage leads to a substantial increase in the serum concentrations of blood urea nitrogen (BUN), creatinine (Cr), while these markers decreased by $ZnCl_2$ administration prior to IR injury. In addition, it is reported that exogenous $ZnCl_2$ administration enhanced the decreased action of SOD, CAT and GP_X subsequent renal IR-induced injury. Furthermore, structural changes such as kidney apical microvillus border loss, nuclear condensation, cellular edema, loss of nuclei, and hemorrhage were take placed after renal IR injury which improved by $ZnCl_2$ [30]. In according of our search, it is not previous publication in this underlying and for first time we study the protective role of $ZnSO_4$ on some complications in renal including oxidative stress, biochemical factors disturbances and histopathological alterations following liver IR injury, and particularly role of ZnSO4 in acute tubular injury.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 200–250 g were procured from Shahrekord (Shahrekord, Iran) and acclimatized for 1 week before the experiment. Animals were housed in an air-conditioned room with 12/12 h light and dark cycles, and controlled temperature around (22 ± 2 °C). The rats were housed in cages, and fed with a standard rat chow, and tap water *ad libitum*, and fasted overnight before the procedures, but had free access to water. All protocols were done in accordance of The Ethics Committee of Yasuj University of Medical Sciences (IR.YUMS.REC.1400.006).

2.2. Experimental design

In this experiment, 28 rats were accidently divided into four groups (n = 7 for each group): Sham group: rats obtained normal saline (N/S, 2 ml/day, seven successive days, ip) before surgery [31], next laparotomy was done, but not underwent to IR. IR group: rats obtained N/S (2 ml/day) as mentioned previous, then were subjected to 45min of liver ischemia accompanied by 60min reperfusion. $ZnSO_4$ (heptahydrate) pretreatment group: rats obtained $ZnSO_4$ (5 mg/kg, 7 days, ip) prior surgery, subsequently they underwent to

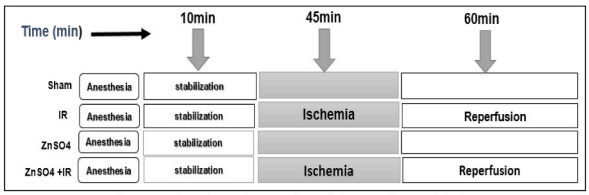

Fig. 1. The schematic overview of the experimental design.

laparotomy without ischemia induction. $ZnSO_4$ pretreatment + IR group: rats obtained $ZnSO_4$ (5 mg/kg, 7 days, ip) before surgery, then the IR protocol was done as indicated in Fig. 1.

For induction of hepatic IR injury, following anesthesia with a mixture of ketamine (80 mg/kg, ip) and xylazine (10 mg/kg, ip) [32], rats subjected to operation. Briefly, midline laparotomy was performed, then portal triad (artery, vein, and bile duct) clamped with bulldog clamp for induction of partial ischemia (70%) of median and right lobes of liver for 45 min, then unclamped for 60 min [33]. Finally, blood specimens were collected from the heart for biochemical assessments. Furthermore, pieces of liver and kidney tissues were removed for determination of oxidative stress markers and histopathological analysis.

2.3. Biochemical analysis

To assessment of the serum biomarkers of hepatocyte injury including alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), ALP (alkaline phosphatase) and also evaluation of the renal parameters including BUN and Cr, blood was taken from the heart and allowed to clot formation, subsequently centrifuged at 5000×*g* for 10 min [34]. The above-mentioned parameters were evaluated by commercially assay kits (Pars Azmoon Co, Iran), and read by a biochemical autoanalyzer (BT-1500-A-A, Rome, Italy).

2.4. Preparation of kidney homogenate tissue

To measure the oxidative stress and antioxidant markers, one piece of kidney tissue quickly removed, weighed, and homogenized with a homogenizer (IKA Werke Ultra-Turrax T25 basic homogenizer; IKA Werke, Breisgau, Germany) in ice-cold phosphate-buffered saline solution (PBS) (10 mmol/L, pH: 7.4). The homogenate was centrifuged at 10000 g for 10 min at 4 °C and supernatant cultivate at −20 °C for assessment of oxidative stress parameters [35] by commercially kits as described below.

2.5. Evaluation of oxidative stress markers

2.5.1. Evaluation of superoxide dismutase activity

The activity of SOD in the kidney tissue was determined colorimetrically at the wavelength of 405 nm according to the manufacturer's instructions available kit (Cat #:15032, Nasdox, Iran) by ELISA reader (Biotek, Netherlands).

2.5.2. Measurement of glutathione peroxidase activity

The activity of GP_X in the kidney tissue was evaluated colorimetrically at the wavelength of 340 nm based on the manufacturer's instructions of available kit (Cat #: 15,082, Nagpix, Iran) by ELISA reader (Biotek, Netherlands).

2.5.3. Measurement of catalase activity

The activity of CAT in the kidney tissue was determined colorimetrically at the wavelength of 570 nm based on the manufacturer's instructions assay kit (Cat #: 15,052, Nactaz, Iran) by ELISA reader (Biotek, Netherlands).

2.5.4. Measurement of ferric reducing antioxidant power (FRAP)

To measurement the level of FRAP, tripyridyl-*s*-triazine (TPTZ) was used. For this aim, the supernatant of the homogenate kidney tissue was added to TPTZ solution 10 mM, Fe^{+3} 20 mM and acetate buffer 0.3 M, then temperature was increased to 37 °C. The FRAP level was determined by measuring the light absorption of compound at the wavelength of 593 nm by ELISA reader (Biotek, Netherlands). The conclusions were presented as to micro mole per gram tissue (μmol/g tissue) [36].

2.5.5. Evaluation of MDA

Lipid peroxidation was estimated by measuring of MDA generation [37]. Briefly, a total of 0.5 ml of supernatant of homogenate tissue of kidney was mixed with 2 ml of solution containing thiobarbituric acid (15% w/v), trichloroacetic acid (0.375% w/v), and 0.25 N HCl. The samples were boiled in a water bath for 15 min, cooled for 10 min in ice bath, and then centrifuged for 15 min at 2000 *g*. The absorbance was read at the wavelength of 535 nm by ELISA reader (Biotek, Netherlands) and presented as μmol/g tissue.

2.5.6. Measurement of NO

Nitrite level was calculated, as an index of NO formation according to the Griess reaction [38]. The level of NO metabolite (NOX) was expressed as μmol/g tissue using sodium nitrite as standard (0–100 μmol/L). The absorbance of the red product was measured at the wavelength of 570 nm by ELISA reader (Biotek, Netherlands).

2.6. Histopathological analysis

For this purpose, liver and kidney tissues were isolated and fixed in 10% neutral formalin solution. Then, dehydrated through a graded series of alcohol, embedded in paraffin. Then, they were cut into 5 μm sections using a microtome (Leica RM 2125, Leica Microsystems Nussloch GmbH, Germany), and stained with Hematoxylin and Eosin [39]. In hepatic tissue, pathologic lesions such as vacuolization and congestion of sinusoids [40], and in renal tissue, microscopic changes specially necrosis of proximal, distal and collecting tubular cells and vacuolization of tubular cells [41] assessed under a digital research microscope (Olympus Bx51, Germany)

by a pathologist who was blinded to the groups.

2.7. Statistical analysis

The data were presented as mean ± SEM and evaluated by one-way analysis of variance (ANOVA) followed by Tukey post Hoc analysis test. $p < 0.05$ was regarded statistically significant.

3. Results

3.1. The impact of $ZnSO_4$ on serum levels of liver enzymes after IR-induced hepatic damage

As presented in Fig. 2 (A- C), the results of the present study expressed that the serum concentrations of liver enzymes of AST, ALT, and ALP were remarkably enhanced after hepatic IR insult in relative to sham group ($p < 0.01$ in three enzymes). The administration of $ZnSO_4$ (5 mg/kg, 7 days, ip) before IR damage significantly attenuated the levels of these enzymes in relative to IR group ($p < 0.05$ in three enzymes).

3.2. The impact of $ZnSO_4$ on serum levels of BUN and creatinine after IR-induced liver damage

As indicated in Fig. 3 (A and B), our findings showed that the serum concentrations of BUN and Cr elevated following IR-induced hepatic damage in comparison with the sham group ($p < 0.001$). Furthermore, the results of this study indicated that the $ZnSO_4$ pretreatment (5 mg/kg, seven days, ip) significantly decreased the levels of BUN and Cr in comparison with IR group ($p < 0.01$).

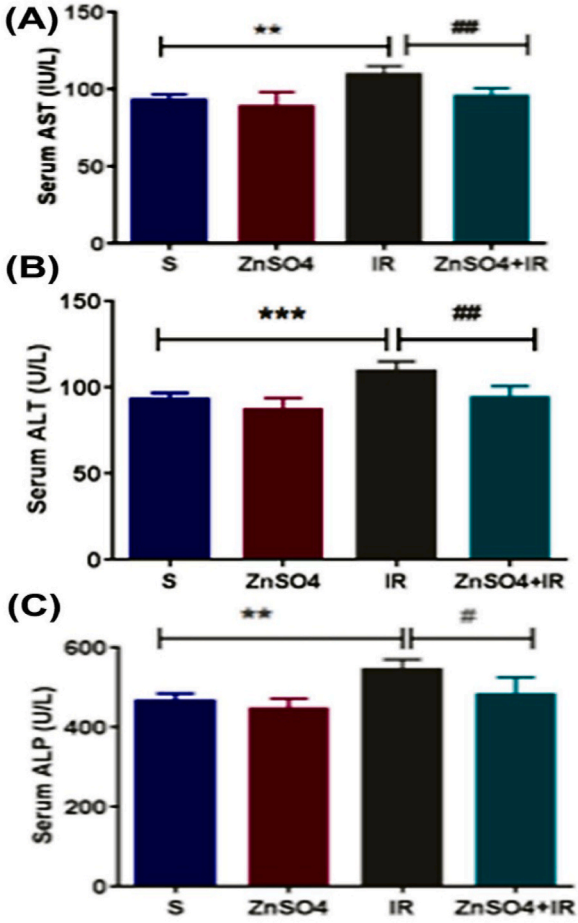

Fig. 2. Effects of $ZnSO_4$ (5 mg/kg, days, ip) on AST (A), ALT (B) and ALP (C) after IR-induced hepatic damage. Data demonstrated as mean ± SEM, n = 7. **$p < 0.01$ and ***$p < 0.001$ significant difference vs the sham group. #$p < 0.05$ and ##$p < 0.01$ significant difference vs the IR group. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

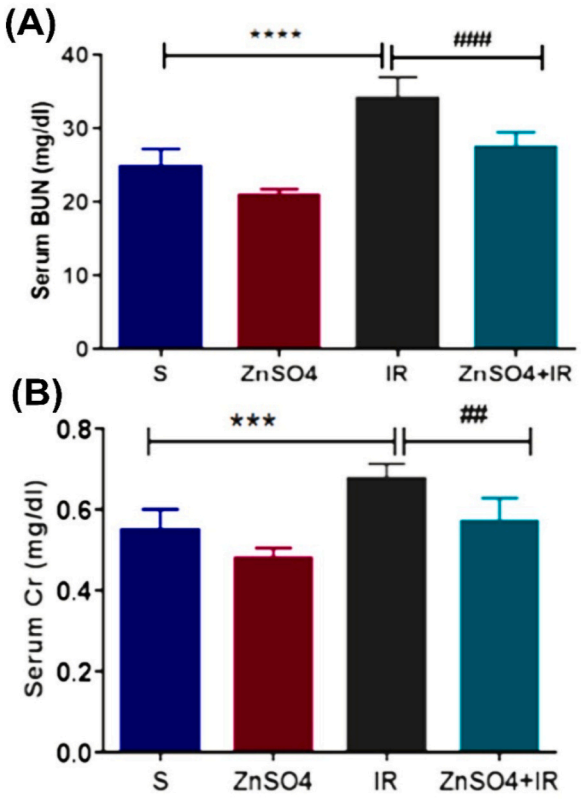

Fig. 3. Effects of $ZnSO_4$ (5 mg/kg, 7 days, ip) on serum concentrations of BUN (A) and Cr (B) after IR-induced liver damage. Data showed as mean ± SEM, n = 7. ***p < 0.01 and ****p < 0.001 significant difference vs the sham group and ##P < 0.01 and ###P < 0.001 significant difference vs the IR group. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; BUN: Blood urea nitrogen; Cr: Creatinine.

3.3. The impact of $ZnSO_4$ on SOD, CAT and GP_X in renal tissue after IR-induced liver insult

As indicated in Fig. 4 (A-C), the antioxidant enzymes activity of SOD (A), CAT (B) and GP_X (C) in homogenate renal tissue after liver IR procedure reduced in IR group versus the sham group ($p < 0.01$). The findings of this experimental study also showed that the administration of $ZnSO_4$ (5 mg/kg, seven days, ip) prior to IR damage, profoundly enhanced the activity of above-mentioned enzymes in relative to IR group ($p < 0.05$).

3.4. The impact of $ZnSO_4$ on FRAP in kidney tissue after IR-induced liver insult

As presented in Fig. 5, following liver IR procedure the concentration of FRAP in kidney tissue decreased in IR group in comparison with the sham group ($p < 0.01$). The results of this study also indicated that pretreatment with $ZnSO_4$ (5 mg/kg, 7 days, ip), dramatically increased the concentration of FRAP in $ZnSO_4$+IR group in relative to IR group ($p < 0.01$).

3.5. The impact of $ZnSO_4$ on NO in kidney tissue after IR-induced liver damage

As presented in Fig. 6, following hepatic IR insult phenomenon, the concentration of NO metabolite in kidney tissue reduced in IR group in comparison with the sham group ($p < 0.01$). The findings of this study also presented that $ZnSO_4$ (5 mg/kg, 7 days, ip), dramatically increased the concentration of NO metabolite in $ZnSO_4$+IR group in relative to IR group ($p < 0.05$).

3.6. The impact of $ZnSO_4$ on MDA in renal tissue following IR-induced liver injury

As presented in Fig. 7, our data revealed that the concentration of MDA in kidney tissue enhanced in IR group in relative to the sham group ($p < 0.01$). Our reports also indicated that $ZnSO_4$ (5 mg/kg, 7 consecutive days, ip), significantly attenuated the concentration of MDA in $ZnSO_4$+IR group versus the IR group ($p < 0.05$).

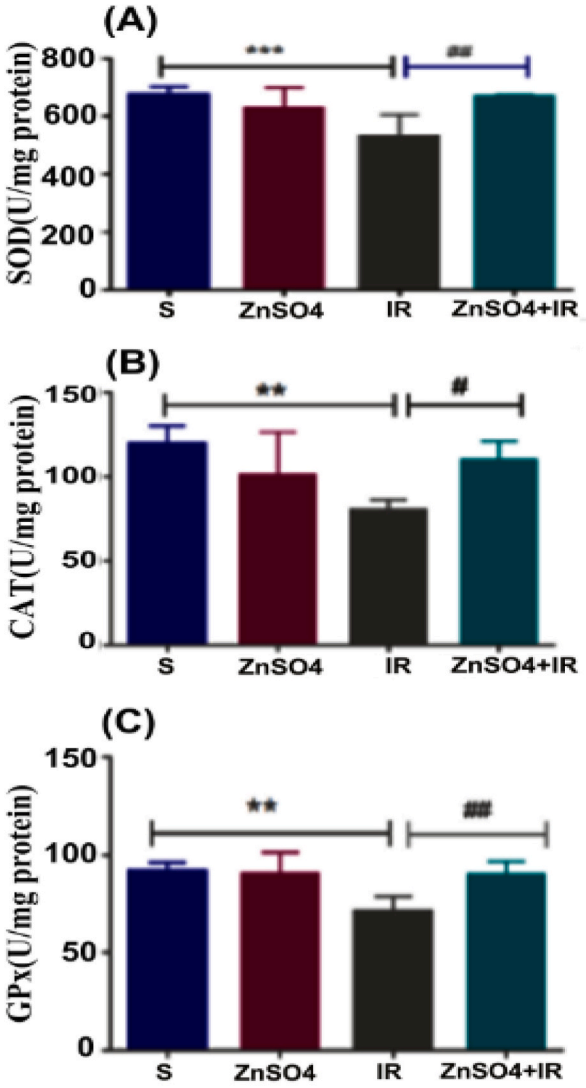

Fig. 4. Effects of $ZnSO_4$ (5 mg/kg, 7 days, ip) on SOD (A), CAT (B) and GPx (C) in kidney tissue after IR-induced liver damage. Data indicated as mean ± SEM, n = 7. **p < 0.01 significant difference vs the sham group and ##P < 0.01 significant difference vs the IR group. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; SOD: Superoxide dismutase; CAT: Catalase; GP_X: Glutathione peroxidase.

3.7. The impact of $ZnSO_4$ on histological alterations of liver beyond IR-induced liver damage

As shown in Fig. 8, our model of partial hepatic IR injury induced disarrangement in the architecture of liver tissue such as cell vacuolization (white arrow), and congestion of sinusoids (black arrow) in comparison with the sham group. $ZnSO_4$ (5 mg/kg, 7 days, ip) significantly improved the vacuolization and congestion of sinusoids alterations of liver tissue in comparison with IR group.

3.8. The impact of $ZnSO_4$ on histological alterations of kidney after IR-induced liver injury

Our model of partial hepatic IR injury (45 min ischemia followed by 60 min reperfusion) induced necrosis of renal architecture destruction including proximal, distal and collecting tubules (black arrow), hyaline cast (blue arrow), cell vacuolization and glomerular sclerosis (white arrow) in comparison with sham group. As shown in Fig. 9, $ZnSO_4$ (5 mg/kg, 7 days, ip) significantly improved proximal, distal and collecting tubules, hyaline cast, cell vacuolization and glomerular sclerosis alterations of renal tissue in relative to IR group.

4. Discussion

Previous studies demonstrated the beneficial effects of zinc supplementations on renal IR injury [6,42]. However, in according of

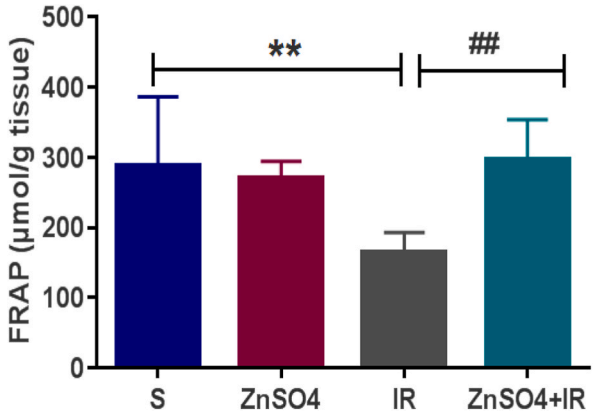

Fig. 5. Effects of $ZnSO_4$ (5 mg/kg, 7 days, ip)) on FRAP in kidney tissue after IR-induced hepatic damage. Data expressed as mean ± SEM, n = 7. **p < 0.01 significant difference vs the sham group and ##p < 0.01 significant difference vs the IR group. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; FRAP: Ferric reducing antioxidant power.

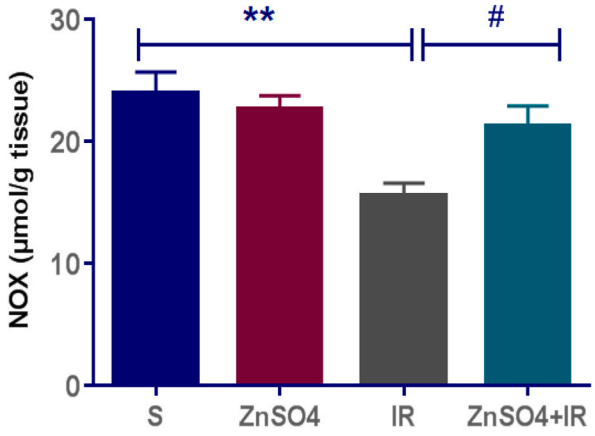

Fig. 6. Effects of $ZnSO_4$ (5 mg/kg, 7 days, ip) on NO metabolite in kidney tissue after IR-induced liver damage. Data indicated as mean ± SEM, n = 7. **p < 0.01 significant difference vs the sham group and #p < 0.05 significant difference vs the IR group. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; NO: Nitric Oxide.

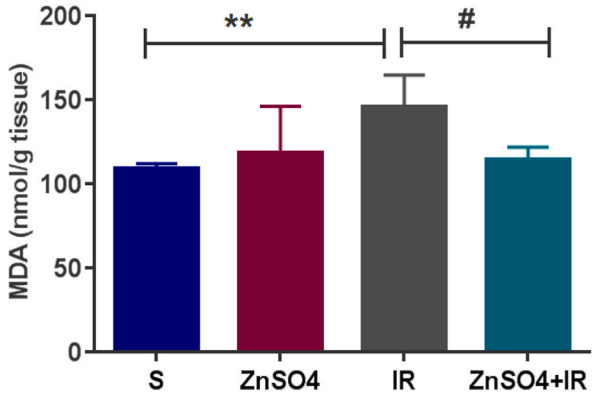

Fig. 7. Effects of $ZnSO_4$ (5 mg/kg, 7 days, ip) on MDA in kidney tissue after IR-induced hepatic damage. Data expressed as mean ± SEM, n = 7. **p < 0.01 significant difference vs the sham group and #p < 0.05 significant difference vs the IR group. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; MDA: Malondialdehyde.

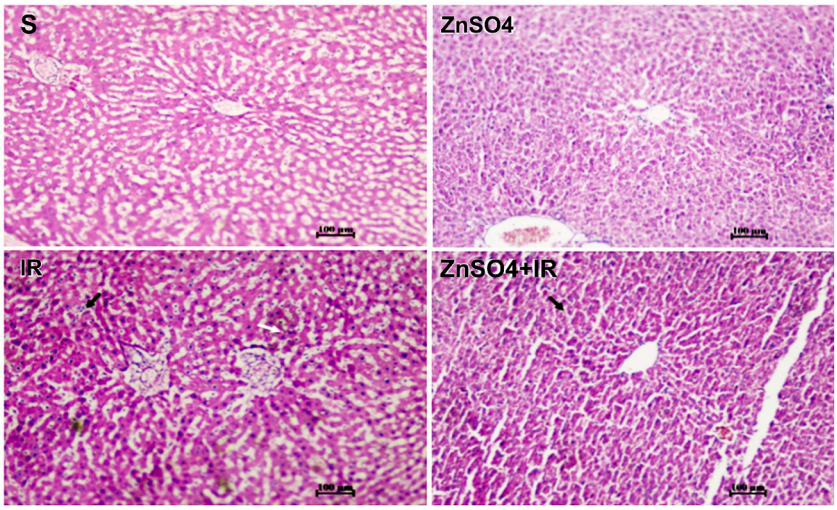

Fig. 8. The impact of $ZnSO_4$ (5 mg/kg, 7 days, ip) on liver tissue subsequent IR-induced hepatic damage. (Hematoxylin and Eosin staining, magnification 100x). Sham group (S) has normal architecture; IR group Displays cell vacuolization (white arrow) and congestion of sinusoids (black arrow). $ZnSO_4$ group has normal architecture. $ZnSO_4$+IR group displays normal structure. S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; ip: Intraperitoneally.

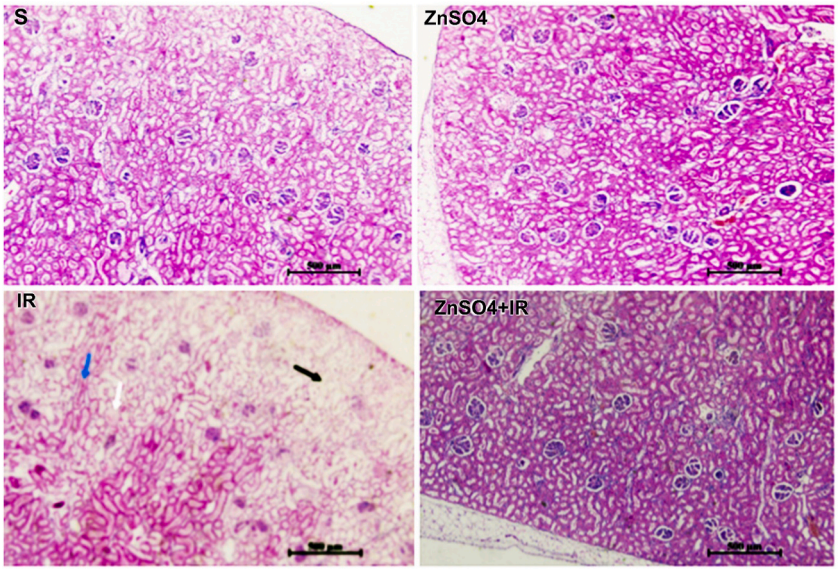

Fig. 9. The impact of $ZnSO_4$ (5 mg/kg, 7 days, ip) on kidney tissue beyond IR-induced liver damage. (Hematoxylin and Eosin staining, magnification 500x). Sham group (S) has normal structure (glomeruli and tubules); IR group displays necrosis of proximal, distal and collecting tubular cells (black arrow), hyaline cast (blue arrow), cell vacuolization, and glomerular sclerosis (white arrow). $ZnSO_4$ group has normal architecture. $ZnSO_4$+IR group has normal structure (except neutrophil infiltration (green arrow). S: Sham; $ZnSO_4$: Zinc sulfate; IR: Ischemia/reperfusion; ip: Intraperitoneally. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

our knowledge, the effect of this trace element on hepato-renal damage after 45 min hepatic ischemia tracked by 60 min reperfusion has not been investigated. Based on our findings, administration of $ZnSO_4$ before IR can be protect the renal damage through attenuating of renal function parameters such as BUN and Cr, enhancing the activity of SOD, CAT, and GP_X, elevating the contents of FRAP and NO, diminishing the MDA levels, and alleviating the structural transformations of the renal parenchyma.

Hepatocytes have various enzymes which contribute in a wide range of metabolic pathways. These enzymes are very sensitive indicators for detection of liver disorders [43]. It is reported that blood concentrations of liver enzymes of AST, ALT and ALP elevated beyond IR-induced liver insult [44]. Our findings manifested a significant elevation in the serum concentrations of aforementioned enzymes subsequent IR-induced liver damage in rats. This study demonstrated that exogenous $ZnSO_4$ administration significantly reduced the serum levels of AST, ALT and ALP in comparison with IR group.

In agreement with preceding documentations [6,45], we detected an increase in serum levels of BUN and Cr after 45min liver ischemia. But, the amount of Cr was lower in comparison with BUN. In this regard, it has been shown that the serum quantity of Cr, may be affected by multiple factors such as reducing the serum protein level, decreasing hepatic conversion of creatine to Cr, and increasing renal tubular secretion of Cr following liver injury [46]. It is revealed that $ZnCl_2$ administration before kidney IR injury significantly decreased the elevated serum concentration of BUN [7]. In addition, it is determined that zinc preconditioning dose dependently attenuated the levels of urea and Cr subsequent renal IR damage [47]. In agreement, in this study we found a reduction in the serum concentrations of BUN and Cr beyond administration of $ZnSO_4$ relative to IR group.

Earlier investigation expressed mild to moderate transformations in the architecture of the renal tissue next liver IR damage [48]. Furthermore, it is described that 45 min of liver ischemia caused renal architecture dysfunction [49]. On the other hand, it has been shown that mice underwent to liver IR developed histological dysfunctions such as proximal tubular cell necrosis, cortical tubular ectasia, and granular bile/heme cast formation in the kidney [4]. This effect may be related to splanchnic vasodilation after portal hypertension (26), which associated with systemic hypotension, and activation of renin angiotensin system due to intrarenal ischemia. Ischemia eventually leads to renal tubular necrosis and other impairments in this organ [50].

Our histopathological evaluation revealed several remarkable alterations including proximal, distal and collecting tubular necrosis, hyaline cast, cell vacuolization, glomerular sclerosis, and tubular dilation in the kidney tissue after hepatic IR damage. Our study also showed that $ZnSO_4$ improved previously stated alterations in kidney tissue. In this regard, it has been indicated that Zn decreases the lipid peroxidation as well as the consolidation of cytoplasmic, and mitochondrial membranes which ultimately preserves the architecture of renal tissue [30].

MDA, as an plentiful aldehyde [51] and a stable metabolite of the free radical mediated lipid peroxidation cascade, is a good marker which determines oxidative stress in clinical circumstances [52]. It has been indicated the level of MDA in tissue enhanced in the IR phenomenon [53,54]. In the present study, we showed $ZnSO_4$ significantly inhibited the increased MDA in the kidney tissue after liver partial ischemia (70%) followed by reperfusion.

Furthermore, it is indicated that the preservation of the renal tissue architecture later IR insult, partly is mediated by enhancing the antioxidant enzymes activity of SOD and CAT [55]. GP_X as a free radical scavenger enzyme neutralizes ROS such as lipid peroxides and H2O2 [56]. Earlier study revealed that the administration of Zn stimulates the activity of antioxidant enzymes of SOD, CAT, and GP_X following renal IR-induced impairment [30]. In this experiment, we revealed the activity of antioxidant enzymes of SOD, CAT and GPx, as well as, the content of FRAP attenuated in the renal tissue after hepatic IR-induced damage. Moreover, we observed that administration of $ZnSO_4$ prior to IR surgery significantly increased the activity of SOD, CAT, GPx and concentration of FRAP rather than to untreated of IR group. These observations in line with former research that implied $ZnSO_4$ preserved the liver against IR-induced damage through augmenting the antioxidant enzymes activity of SOD, CAT and GP_X in rats [1].

NO has important function in regulation of glomerular hemodynamics. It ameliorates renal blood flow (RBF) and GFR by vasodilation effect [13]. It has been described that NO generation was impaired after endothelial cells dysfunction [57] and attenuating of endogenous NO production participates in development of IR insult [49]. One study showed that eNOS activation possibly protects liver against remote ischemic preconditioning [58]. In this study, we observed a significantly reduction in NO metabolite contents in the kidney tissue beyond hepatic IR injury. It is speculated that this attenuation may be related to disturbance in histology of kidney and endothelial cells following liver IR damage. Furthermore, our findings indicated that $ZnSO_4$ pretreatment significantly increased the decreased renal tissue level of NO metabolite. Limitations of this study included: First; the results of this study obtained from animal's male and female rats excluded from this study, second; time of ischemia/reperfusion, third; literatures review and references were based on only English papers.

5. Conclusion

As shown in Fig. 10, $ZnSO_4$ as an important trace element and antioxidant can be protect the kidneys against complications of hepatic IR-induced damage such as disturbance in renal functions tests, oxidative stress imbalance and renal function destruction through decreasing the BUN and Cr levels, increasing the antioxidant enzymes activity of SOD, CAT, and GPx, as well as FRAP and NO metabolite content in renal tissue. Moreover, our study showed that $ZnSO_4$ improved histopathological changes of renal tissue beyond

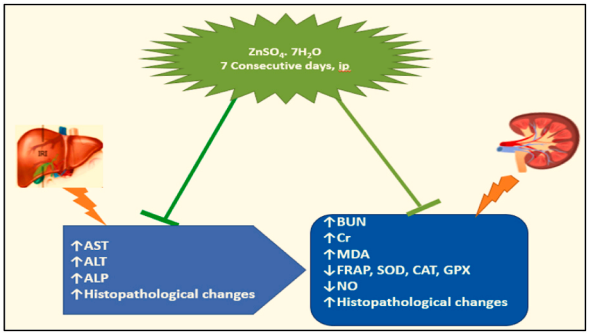

Fig. 10. Schematic overview of the effects of $ZnSO_4$ on renal damage after liver IR injury.

hepatic IR phenomenon. Therefore, $ZnSO_4$ can be considered a good candidate for attenuating of side effects of hepato-renal syndrome following liver IR injury. Although, further investigations are needed.

Declarations

Author contribution statement

Izadpanah Gheitasi: Conceived and designed the experiments, Wrote the paper.
Amir Hossein Doustimotlagh: Contributed reagents, materials, analysis tools or data.
Esmaeel Panahi Kokhdan: Performed the experiments, Contributed reagents.
Ghaidafeh Akbari: Conceived and designed the experiments, Analyzed and interpreted the data; Wrote the paper.
Mehrzad Jafari Barmak: Analyzed and interpreted the histopathology data.

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Conflict of interest

The authors declared no conflict of interest.

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