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Effect of dapagliflozin on rat liver ischemia-reperfusion injury

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Abstract

In recent years, liver transplantation has emerged as the standard therapy for several liver disorders. Throughout the procedure, the transplanted liver tissue is subjected to varying degrees of ischemia-reperfusion (IR) damage. Consequently, there has been a long-standing pursuit of substances that can alleviate the harm caused by IR. In our investigation, we employed dapagliflozin as a potential therapeutic agent. Eighteen Wistar rats were divided into three groups (n = 6), including treatment, IR, and control that did not undergo surgical intervention. Two days prior to surgery, the treatment group received dapagliflozin at a dosage of 10.00 mg kg^{-1} orally. During surgery, liver ischemia was induced for 1 hr, followed by a 24-hr reperfusion period. The IR group exhibited elevated levels of alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, lactate dehydrogenase, and malondialdehyde compared to the control group. In contrast, the treatment group showed levels of these factors that were closer to those of the control group. While total protein, albumin, and total anti-oxidant capacity decreased in the IR group, this decline was less significant in the treatment group. Analysis of oxidative stress in liver tissue revealed that the treatment group had increased anti-oxidant capacity, and exhibited less oxidative stress compared to the IR group. Furthermore, dapagliflozin was found to reduce the degree of liver edema, necrosis, and vascular hyperemia following IR. Overall, dapagliflozin demonstrates the potential to lessen liver damage, enhance liver tissue regeneration, and mitigate the consequences associated with liver impairment.

Introduction

Over the last 50 years, liver transplantation has become the standard treatment for advanced liver diseases, acute liver failure, and liver tumors. In Iran, the leading causes for liver transplantation are hepatitis B (31.20%), cryptogenic cirrhosis (26.90%), and auto-immune hepatitis (13.40%).[1,2] For nearly 50 years, the immune mechanisms influencing liver transplant acceptance or rejection have been understood. However, certain factors can still adversely affect transplant outcomes by impairing liver tissue function.[3] Restoring blood flow to the transplanted liver can lead to ischemia-reperfusion (IR) injury, which recruits neutrophils and activates Kupffer cells, resulting in liver cell death due to a severe inflammatory response.[3,4]

Recent advances in post-liver transplant treatment, including immunosuppressive drugs, like prednisolone, have reduced acute liver transplant rejection rates by approximately 30.00% globally.[2] Improvements in surgical techniques, medical care, infection control, and drug development have also enhanced post-transplant liver tissue survival. However, current immunosuppressive protocols have not effectively managed chronic liver rejection and can lead to serious complications, such as systemic infections and cancer.[5] During transplantation, the liver tissue experiences IR injury, activating the immune system, which can trigger acute rejection or complicate chronic rejection. Notably, both humoral and cellular responses of the immune system are activated during IR injuries.[6]

Ischemia-reperfusion injury is defined as a cellular damage that occurs within an organ when blood supply is restored following a period of ischemia, thereby re-establishing oxygenation in tissue that has undergone hypoxic shock.[7] This phenomenon was initially described by Toledo-Pereyra *et al*. as a significant pathological condition associated with liver transplantation.[8] In such instances, the transplanted hepatic tissue may experience congestion, progressive thrombosis, or necrosis, ultimately

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culminating in organ dysfunction and failure.[9] Ischemia-reperfusion liver injuries are classified into two categories, including warm IR and cold storage injuries, with warm IR being an unavoidable process in liver transplantation and related conditions, including circulatory shocks, liver sinusoid obstruction, toxic liver injury, and Budd-Chiari syndrome.[10] During ischemia and low oxygen conditions, reactive oxygen species (ROS) are produced in liver cells.[11] These ROS significantly contribute to ischemic damage. The reduced oxygen supply to aerobic liver cells, including sinusoidal endothelial cells, Kupffer cells, hepatocytes, and stellate cells, leads to decreased adenosine triphosphate production and increased ROS due to the mitochondrial electron transport chain inactivation.[12] This inactivation disrupts ion homeostasis and decreases energy levels, resulting in cell swelling and narrowing of hepatic sinusoidal lumens.[10,13] Increased intra-cellular calcium concentration damages mitochondria, releasing more ROS, which oxidizes plasma membrane lipids and proteins, leading to apoptosis or necrosis.[14] Although reperfusion is essential for rescuing ischemic tissue, it can cause additional damage due to the ROS production, which is still debated.[15] When ROS levels exceed the capacity of internal anti-oxidants, oxidative damage occurs, leading to cytotoxicity and tissue injury.[16] Free radicals mediate reperfusion injury, causing lipid and protein peroxidation.[17] Instead of alleviating shock symptoms, reperfusion can exacerbate conditions, leading to sinusoidal endothelial cell swelling, vasoconstrictors increase, vasodilators reduction, and ultimately reduced oxygenation and continued ischemic shock.[18]

Efforts have long been made to utilize drugs and compounds that can reduce IR injury and facilitate liver transplantation.[19] Dapagliflozin, a sodium-glucose cotransporter 2 inhibitor, is a third-line treatment for diabetic patients. It prevents glucose reabsorption, leading to increased glucose excretion in urine and reduced blood glucose levels. This process also results in significant water loss, indicating that dapagliflozin acts as a diuretic.[20] Additionally, dapagliflozin lowers blood pressure and has been associated with a weight loss of 2 to 3 kg over 12 weeks.[21] While some studies suggest that sodium-glucose transporter inhibition reduces ROS production in diabetic kidneys, its role in liver IR remains unclear.[22]

While there is no direct study on dapagliflozin's effects on liver IR injury, several related studies provide insights. Lahnwong *et al*. have demonstrated that acute dapagliflozin administration offers cardioprotective effects in rats experiencing cardiac IR.[23] Similarly, Xiong *et al*. have investigated its role in diabetic rats, concluding that dapagliflozin protects the heart from myocardial IR injury by modulating endothelial nitric oxide synthase and inducible nitric oxide synthase expressions and inhibiting lipid peroxidation.[24] Furthermore, Chang *et al*. have reported its effectiveness in reducing renal IR injury.[22] Lastly, Phrueksotsai *et al*. found that 12 weeks of dapagliflozin treatment significantly improved liver fat content, reduced visceral fat and body weight, enhanced blood sugar control, and improved liver biochemistry in type 2 diabetic patients with non-alcoholic fatty liver disease.[25] Considering the protective effect of dapagliflozin on various organs, we hypothesized that dapagliflozin influences the liver's enzymatic, anti-oxidant, histo-pathological, and protein-producing status following IR. Therefore, this study aimed to investigate the effects of dapagliflozin on the liver in this context.

Materials and Methods

Animals and treatment. This study was conducted in accordance with ethical principles for laboratory animal research and received approval from the Research Ethics Committee of the University of Tabriz, Tabriz, Iran (Code: IR.TABRIZU.REC.1403.070). Eighteen mature male Wistar rats, aged 3 to 4 months and weighing between 200 and 250 g, were purchased and housed in the Laboratory Animal Care Center at the Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran. The rats were kept in specialized cages with a 12-hr light/dark cycle at a temperature of 23.00 - 25.00 ˚C, with free access to food and water. They were randomly divided into three groups of six, including control, IR, and treatment (IR with dapagliflozin). After a 1-week acclimatization period, the treatment group received 10.00 mg kg^{-1} of dapagliflozin (Gloxiga, Modava Pharmaceuticals, Hashtgerd, Iran) daily dissolved in distilled water *via* oral gavage for 2 days leading up to surgery.[22] The other groups were given distilled water in the same manner.

Surgery. Twenty-four hr after the last drug gavage, surgery was conducted to induce liver IR. The rats were anesthetized using 3.00% isoflurane (Supriya Lifescience Ltd., Mumbai, India) on oxygen *via* a novel mask, and anesthesia was maintained during the procedure with 2.00% isoflurane and oxygen).[7] A midline incision was made in the upper abdomen to expose the liver, and the hepatoduodenal ligament was cut to facilitate access to the vessels.[26] The branches of the left and middle portal veins and hepatic artery were ligated using an atraumatic vascular clamp (Fig. 1), confirming effective hepatic ischemia by observing the liver lobe's color change from dark red to pale white. After 1 hr, the clamp was removed, allowing for 24 hr of reperfusion. In the control group, a midline incision was made to expose the same vessels, but no obstruction or manipulation of hepatic blood flow was performed.[27,28] Subcutaneous sutures were applied using 4-0 polyglycolate suture material (Supa, Tehran, Iran) in a simple pattern, and skin closure were made with 4-0 monofilament polyamide suture material (Supa) in the same pattern. Post-surgery, rats were kept in separate cages and monitored until they regained full

consciousness. Their body temperature was checked every 5 min, and an infra-red lamp was used to warm them if necessary. One hr after regaining consciousness, they were provided with water and food, kept in individual cages for 24 hr, and fed with rodent pellets.

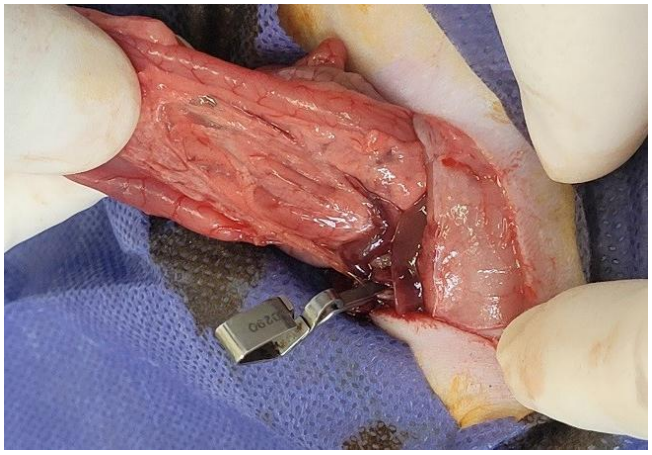

Fig. 1. Experimental hepatic ischemia in a rat. The branches of the left and middle portal veins and hepatic artery were ligated using an atraumatic vascular clamp after a midline celiotomy in rats.

Sampling. After 24 hr post-surgery, the rats were euthanized using a combination of ketamine (75.00 mg kg^{-1} body weight, Bremer Pharma GmbH, Warburg, Germany) and xylazine (7.50 mg kg^{-1} body weight, Alfasan, Woerden, Netherlands) administered *via* intraperitoneal injection. Following a repeated celiotomy and blood collection from the abdominal aorta, the animals were euthanized by dislocating the cervical vertebrae.[29] Blood samples were collected in gel-filled tubes for serum separation and left at room temperature (15.00 - 25.00 ˚C) for 15 to 30 min before being centrifuged at 3,000 rpm for 10 min.[30] The supernatant serum was then separated and frozen at – 20.00 ˚C before being transferred to a – 80.00 ˚C freezer for long-term storage. Biochemical kits were utilized to measure various parameters. After blood sampling, the liver tissue was carefully separated; one portion was placed in 10.00% formalin for fixation, while another was wrapped in aluminum foil, frozen in liquid nitrogen, and stored at – 80.00 ˚ C for biochemical analysis. Additionally, tissue sections from the formalin-fixed livers were stained with Hematoxylin and Eosin to assess histopathological parameters.

Serum and tissue biochemical analyses. All measurements were conducted using an autoanalyzer (Alcyon 300; Abbott, Chicago, USA) and commercial kits at a controlled temperature of 37.00 ˚C. Photometric methods are widely used in clinical chemistry for measuring the concentration of substances in a sample. These methods rely on the absorption of light at specific wavelengths. Serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) were assessed using photometric method recommended by the International Federation of Clinical Chemistry and Laboratory Medicine at a wavelength of 340 nm (Pars Azmoun Co., Tehran, Iran).[31,32] Serum alkaline phosphatase (ALP) levels were measured at 405 nm following the guidelines of the German Society of Clinical Chemistry (DGKC; Pars Azmoun Co).[33] Additionally, albumin (Alb) and total protein (TP) concentrations in serum and homogenized tissue were estimated photometrically at 570 and 546 nm using the Alb-bromocresol green reaction and Biuret method, respectively (Pars Azmoun Co.).[34] Total unconjugated (indirect) bilirubin levels in serum and conjugated (direct) bilirubin levels in serum and homogenized tissue were detected at 546 nm using the dichloroaniline method (Pars Azmoun Co.).[35] Lactate dehydrogenase (LDH) levels were measured at 340 nm using the DGKC method (Pishtaz Teb Zaman Diagnostics, Tehran, Iran).[36] Malondialdehyde (MDA) levels were assessed in serum and homogenized tissue at 532 nm (Pishtaz Teb Zaman Diagnostics).[37] The total anti-oxidant capacity (TAC) was detected at 600 nm (Navand Salamat Co., Urmia, Iran).[38] Finally, tissue glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase levels were measured at 412, 340, and 440 nm, respectively.[37,39]

Histopathological studies. To thoroughly investigate tissue reactions, liver tissue samples were meticulously collected and fixed in 10.00% buffered formalin, ensuring a volume at least 10 times that of the samples. After 24 hr, the formalin was replaced, and a series of preparation steps, including dehydration with ascending alcohols, clarification with xylene, and alcohol removal in a tissue processor was conducted. The samples were then embedded in paraffin, and sections of 4.00 to 5.00 microns were prepared using a microtome. These sections were placed in an oven at 56.00 ˚C for 30 min before undergoing conventional Hematoxylin and Eosin staining. Histhopatological parameters, including cell swelling, hyperemia, edema, and necrosis, were assessed by a pathologist who was unaware of the groups, and the lesions were graded from zero to three based on the severity.

Statistical analysis. For statistical analysis, GraphPad Prism (version 8.0; GraphPad Software Inc., San Diego, USA) Software was employed to analyze data. Serum and tissue biochemical factors were analyzed utilizing one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test to assess differences between groups. Results were expressed as mean ± standard deviation, with significance set at $p < 0.05$. Additionally, histopathological data were analyzed using non-parametric tests. The Kruskal-Wallis test was used to assess differences in histopathological parameters among three groups. Following the significant Kruskal-Wallis result, *post hoc* pairwise comparisons were conducted using Mann-Whitney U test with Holm-Bonferroni correction, reporting results as mean rank at a 95.00% confidence level.

Results

Serum biochemical analysis. The study assessed various biochemical markers across three experimental groups. The AST is an enzyme found in various tissues, including the liver, heart, and muscles. Elevated levels can indicate liver damage or disease, making it a critical marker in clinical diagnostics. The mean AST levels were 127.83 in the control group, 340.40 in the IR group, and 280.50 in the dapagliflozin group, with significant differences observed ($p < 0.05$). The ALT is primarily found in the liver, and its levels are often measured alongside AST to evaluate liver health. A higher ALT level can suggest liver inflammation or damage. Similarly, ALT levels were 57.66 (control), 183 (IR), and 138.33 (treatment), also showing significant differences ($p < 0.05$). The alkaline phosphatase is another enzyme that plays a role in breaking down proteins. Its levels can indicate liver or bone disorders. For alkaline phosphatase, the averages were 331.17 (control), 515.80 (IR), and 504.16 (treatment), again with significant differences ($p < 0.05$). Total protein and Alb levels are crucial for evaluating nutritional status and liver function. The study also found TP levels of 6.96 (control), 6.12 (IR), and 6.36 (treatment), with significant differences ($p < 0.05$). The Alb levels were 2.50 (control), 2.04 (IR), and 2.13 (treatment), showing significant differences ($p < 0.05$). Bilirubin is a by-product of red blood cell breakdown, and its levels can indicate liver function and hemolysis. Total bilirubin levels averaged 0.35 (control), 0.66 (IR), and 0.42 (treatment), with significant differences noted ($p < 0.05$). Direct bilirubin levels were 0.16833 (control), 0.38 (IR), and 0.23 (treatment), also with significant differences ($p < 0.05$). The LDH is an enzyme involved in energy production. Elevated levels can indicate tissue damage or disease. The LDH levels were 350 (control), 785.20 (IR), and 573.50 (treatment), indicating significant differences ($p < 0.05$). In contrast, MDA levels were 2.51 (control), 2.70 (IR), and 2.68 (treatment), showing no significant differences ($p > 0.05$). The MDA is a marker of oxidative stress, and its levels can indicate cellular damage. Finally, TAC levels were 0.57 (control), 0.52 (IR), and 0.55 (treatment), also with no significant differences ($p > 0.05$; Fig. 2).

Liver tissue biochemical analysis. The study results revealed the following averages: The average TP levels were 106.16 in the control group, 105.50 in the IR group, and 105.60 in the dapagliflozin-treated group. Notably, there were no significant differences among these groups ($p > 0.05$). The MDA levels were significantly different among the groups. The control group had a mean MDA

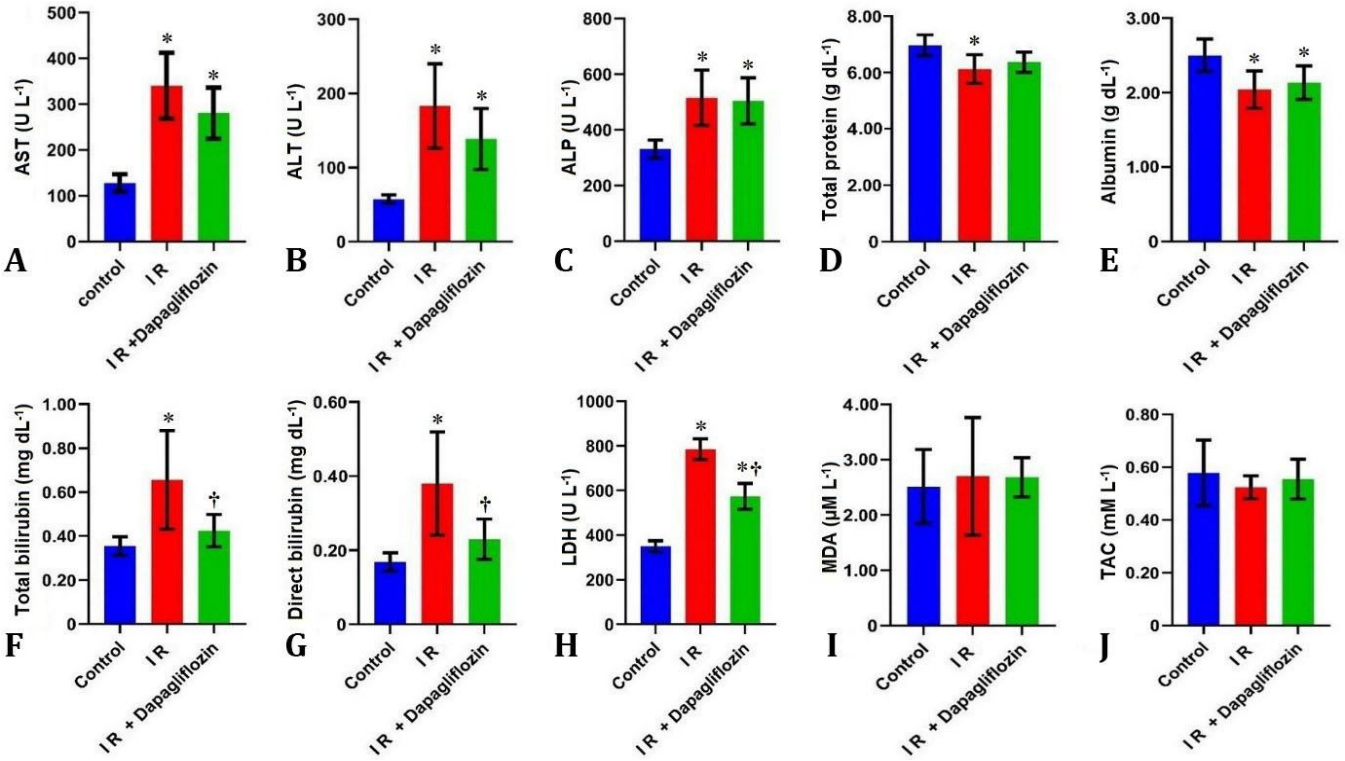

Fig. 2. Comparison of biochemical factors including **A)** Aspartate transaminase (AST); **B)** Alanine transaminase (ALT); **C)** Alkaline phosphatase (ALP); **D)** Total protein; **E)** Albumin; **F)** Total bilirubin, **G)** Direct bilirubin; **H)** Lactate dehydrogenase (LDH); **I)** Malondialdehyde (MDA), and **J)** total anti-oxidant capacity (TAC) levels in serum of different groups of rats.
* indicates significant difference with control group ($p < 0.05$) and † indicates significant difference with ischemia-reperfusion (IR) group ($p < 0.05$).

level of 0.26, while the IR group had 0.39, and the treatment group had 0.31. This indicates significant oxidative stress in the IR group compared to the control ($p < 0.05$). The SOD levels were measured at 5.62 (control), 5.21 (IR), and 5.52 (treatment). The differences were significant, suggesting that dapagliflozin may help maintain SOD levels in the face of oxidative stress ($p < 0.05$). The mean GPx levels were 7.61 (control), 7.21 (IR), and 7.38 (treatment), with significant differences noted ($p < 0.05$). This indicates that GPx activity was reduced in the IR group, highlighting the impact of oxidative stress. The TAC averages were 1.16 (control), 1.14 (IR), and 1.18 (treatment), showing no significant differences ($p > 0.05$). This suggests that while there was oxidative stress, the overall anti-oxidant capacity remained relatively stable across groups. Lastly, the mean catalase levels were 15.31 (control), 13.26 (IR), and 13.99 (treatment), with significant differences observed ($p < 0.05$). This indicates that catalase activity was compromised in the IR group, but dapagliflozin treatment appeared to offer some protective effect (Fig. 3).

Histopathological findings. The results of the histopathological study are summarized in Table 1, presented as mean rank, and illustrated in Figure 4. In the control group, liver tissue sections exhibited an almost normal structure, with no evidence of edema or necrosis. Only mild hyperemia was noted in two cases, and cellular swelling was observed in one case. Conversely, the IR group displayed more significant lesions, including cellular swelling, vascular hyperemia, moderate necrosis, and mild to moderate edema. In the treatment group, the observed lesions were generally milder compared to the IR group, with instances of cellular swelling, hyperemia, mild to moderate edema, and mild necrosis. Statistical analysis indicated that IR group had significant cell swelling compared to the other groups ($p < 0.05$). Hyperemia in the IR group was significantly greater than the control group ($p < 0.05$). Both the IR and treatment groups showed significantly more edema than the control group ($p < 0.05$). There was no statistically significant difference in terms of necrosis ($p > 0.05$).

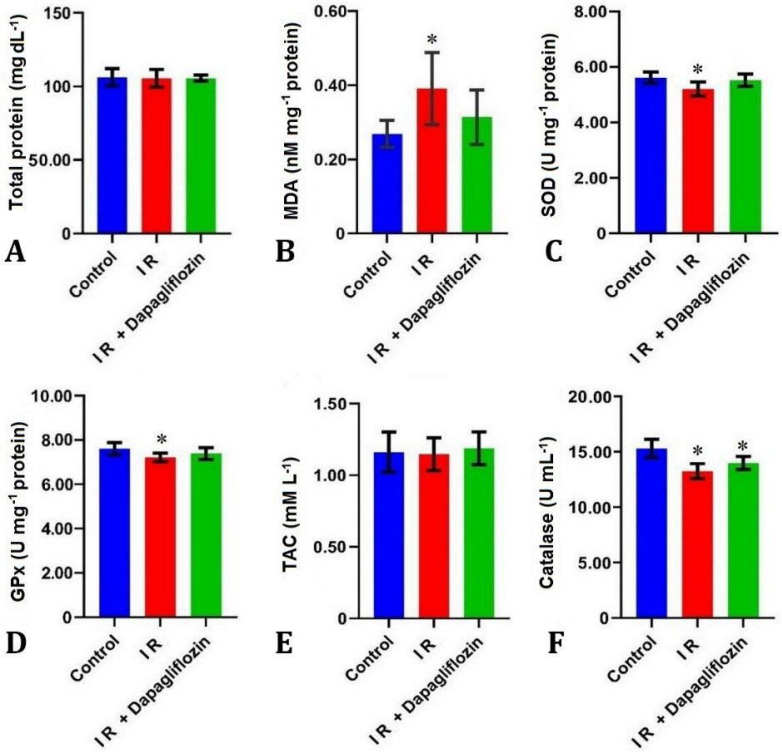

Fig. 3. Comparison of biochemical factors including **A)** Total protein, **B)** Malondialdehyde (MDA), **C)** Superoxide dismutase (SOD), **D)** Glutathione peroxidase (GPx), **E)** Total anti-oxidant capacity (TAC), and **F)** Catalase levels in liver tissue of different groups of rats. IR: Ischemia-reperfusion.
* indicates significant difference with control group ($p < 0.05$).

Table 1. Mean rank of damage based on histopathologic evaluation in the groups being compared.

Groups	Cell swelling	Hyperemia	Edema	Necrosis
Control	2.88[a]	3.00[a]	2.50[a]	4.00[a]
Ischemia-reperfusion	10.13[b]	9.50[b]	8.50[b]	9.25[a]
Treatment	6.50[a]	7.00[ab]	8.50[b]	6.25[a]

[a,b] Different superscript letters in each column indicate significant difference ($p < 0.05$).

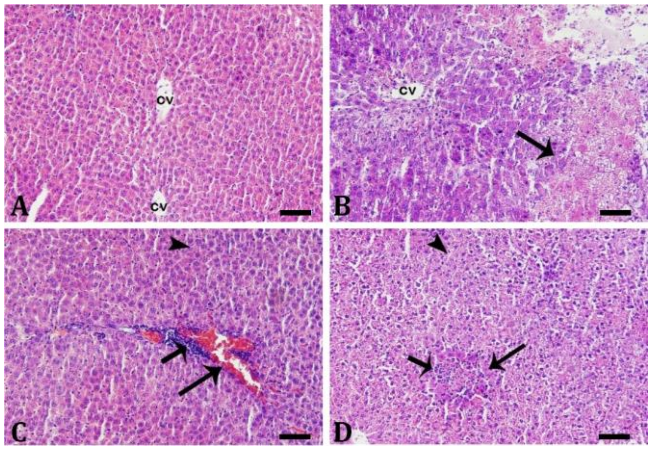

Fig. 4. Liver tissue sections from rats. **A)** The control group displays an almost normal structure. **B)** In the ischemia-reperfusion (IR) group, ischemic necrosis (arrow) is evident in the hepatocytes. **C)** The IR group also shows pathological lesions, including cellular swelling (arrowhead), vascular hyperemia (large arrow), and moderate edema (small arrow). **D)** In the treatment group, pathological lesions are present, including cellular swelling (arrowhead), focal necrosis (large arrow), and mild to moderate edema (small arrow). CV: Central vein. (Hematoxylin and Eosin staining, bars = 60.00 µm).

Discussion

A significant contributor to IR injury is oxidative stress, which arises from an imbalance between the production and accumulation of ROS.[40] When ROS concentrations exceed the control capacity of internal defense mechanisms, such as anti-oxidants, including tocopherols, ascorbic acid, and GPx, and intra-cellular enzymes, like SOD and catalase, oxidative damage to proteins, lipids, and DNA may occur, leading to cytotoxicity and tissue damage.[16] Free radicals serve as the primary mediators of circulatory damage, resulting in the peroxidation of tissue lipids and proteins.[17] In such instances, the plasma marker MDA, a widely recognized indicator of lipid peroxidation, exhibits a significant increase.[41] While tissue MDA did not show significant differences, serum MDA concentration was higher in the IR group compared to the control group, with a smaller increase in the treatment group. Supporting this, the catalase enzyme results indicated a more pronounced and significant decrease in the IR group than treatment group. The analysis of SOD and GPx also revealed significant differences, with both parameters decreasing in the IR group compared to the control group. However, the dapagliflozin-treated group experienced a smaller decrease in these two factors. In their 2013 study, Sahin *et al*. investigated the effects of dexmedetomidine on IR in rats, revealing that this condition led to increased serum MDA levels and decreased activity of SOD, GPx, and catalase, along with observable vascular damage in the IR group.[42] These findings help validate our data. Similarly, Köken and Inal found a significant increase in LDH and ALT levels in the IR group compared to the control group.[43] In contrast, Jaeschke *et al*. specifically examined anti-oxidant changes during IR in isolated rat livers and concluded that oxidative stress does not contribute to liver injury in this condition, which may explain the lack of significant differences in oxidative stress between our experimental groups.[44] Furthermore, a 2024 study reported that dapagliflozin reduced LDH levels associated with renal injury, increased anti-oxidant capacity, and suppressed the inflammatory response in a rat model of renal IR.[45] These beneficial effects of dapagliflozin on renal injury align with our findings on liver injury. However, the inconsistencies in anti-oxidant capacity results across different studies may be attributed to confounding factors. Although the analysis of TAC did not show significant differences, it indicated that oxidative stress was greater in the IR group than dapagliflozin group. The LDH levels were significantly elevated in the IR group, with a lesser increase observed in the dapagliflozin-treated group, which is in consistence with the aforementioned study.

Ischemia-reperfusion is generally associated with an increase in liver enzymes in serum, reflecting damage to liver tissue and the subsequent release of the enzymes into the bloodstream.[46] He *et al*. conducted a systematic review and meta-analysis, concluding that dapagliflozin significantly reduces liver enzymes and metabolic indices while improving body composition, indicating its potential therapeutic efficacy.[47] The results indicated that liver enzyme levels in the IR group were significantly higher than those in the control group. Conversely, dapagliflozin has been shown to partially modulate this increase in liver enzyme levels, particularly ALT.[48] This is why the dapagliflozin-treated group exhibited liver enzyme levels that were closer to those of the control group, suggesting a protective effect.

Despite, the results indicated no significant difference in serum TP levels among the studied groups, liver tissue damage in the IR group resulted in decreased production of liver proteins; however, dapagliflozin was not able to completely prevent this decrease. Several studies showed that liver tissue damage, particularly in the context of inflammatory and chronic liver diseases, significantly impairs the production of liver proteins. In patients with advanced chronic liver disease, Alb synthesis rates were found to be low, correlating negatively with liver function scores.[49] This indicates that liver damage directly affects the liver's ability to produce essential proteins. It has been shown that patients with decompensated alcoholic liver disease exhibit reduced synthetic rates for both Alb and fibrinogen, further highlighting the impact of liver damage on protein production.[50]

The observed increase in total bilirubin and conjugated bilirubin in the IR group can also be attributed to liver damage. Notably, the dapagliflozin-treated group exhibited a smaller increase in these parameters, suggesting that the

drug may mitigate liver damage, and consequently, the appearance of blood parameters indicative of liver injury. This conclusion is further supported by findings related to LDH, a marker of tissue damage, which increased more significantly in the IR group compared to the treatment group. In a study involving rats, dapagliflozin reduced oxidative stress and inflammation, suggesting a protective role against liver damage that could affect bilirubin metabolism. The drug activates the AMP-activated protein kinase/NOD-like receptor protein-3 (AMPK/NLRP3) signaling pathway, which is crucial in reducing inflammation and oxidative stress in the liver.[51] By improving liver function, dapagliflozin may help maintain normal bilirubin levels, as liver health is essential for bilirubin processing. The liver histology results indicated that the IR group showed significant issues, including cellular swelling, vascular hyperemia, moderate necrosis, and mild to moderate edema. Notably, cellular cwelling and hyperemia in the dapagliflozin-treated group were generally milder. Overall, these findings suggest that dapagliflozin effectively reduces the damaging effects of IR, highlighting its potential as a therapeutic option for liver damage. It is worth noting that this study also had limitations. Among them, we can point out the failure to assess the metabolic and hydration status of the rats and possible effects of dapagliflozin on that during the experiment.

In conclusion, hepatic IR leads to considerable damage and disruption of liver tissue and function. Dapagliflozin was shown to alleviate liver damage associated with this condition by modulating various injury markers, including liver enzymes, proteins, oxidative stress, anti-oxidant capacity, LDH, and catalase levels. Furthermore, dapagliflozin aids in maintaining the histological integrity of liver cells.

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Conflict of interest

The authors declare no competing interest.

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