J Nephropharmacol. 2025:e12798.

https://jnephropharmacology.com DOI: 10.34172/npj.2025.12798

Journal of Nephropharmacology

Therapeutic potential of rosuvastatin in sepsis-induced acute kidney injury; evidence from an experimental animal study

Ghanim M. Al-ghanimi[1], **Ali M. Janabi**[2*]

[1]AL-Diwaniya Teaching Hospital, Al Diwaniya Health Directorate, Diwaniya, Iraq
[2]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, Najaf, Iraq

ARTICLE INFO

Article Type:
Original

Article History:
Received: 24 May 2025
Revised: 24 Jun. 2025
Accepted: 9 Jul. 2025
ePublished: 20 Sep. 2025

Keywords:
Kidney
Acute kidney injury
Nephroprotection
Sepsis
Inflammation
Oxidative stress
Rosuvastatin

ABSTRACT

Introduction: Sepsis-induced acute kidney injury (SI-AKI) is a critical complication contributing to high morbidity and mortality in septic patients. Rosuvastatin, a β-hydroxy β-methylglutaryl-CoA reductase inhibitor widely administered for hyperlipidemia, has demonstrated anti-inflammatory and organ-protective effects in various experimental models.

Objectives: This study aims to evaluate the therapeutic potential of rosuvastatin in ameliorating sepsis-induced AKI using an established experimental animal model.

Materials and Methods: This experimental animal study was conducted at the university of Kufa, Iraq. Twenty-four adult Swiss albino mice were divided into four groups randomly (n = 6 in each group): Sham group, cecal ligation and puncture (CLP), CLP + dimethyl sulfoxide (DMSO), and CLP + rosuvastatin. The sham group of mice had no CLP laparotomy operation. The CLP group had a midline laparotomy with cecum ligation and perforation. In the CLP + rosuvastatin and CLP + DMSO groups, respectively, a dose of rosuvastatin 10 mg/kg and DMSO was administered intraperitoneally one hour before the CLP process. Kidney function parameters, including serum urea, creatinine, kidney injury molecule-1 (KIM-1) levels, histopathological scores, and nuclear phosphorylated extracellular signal-regulated kinases 1 and 2 (p-ERK 1/2) expression, were measured and compared between four groups.

Results: The results demonstrated that sepsis induced by CLP significantly elevated all kidney function parameters, including serum urea, creatinine, KIM-1 levels, histopathological scores, and nuclear p-ERK1/2 expression. However, treatment with rosuvastatin markedly reduced these markers, restoring them to levels comparable to those observed in healthy control mice (sham group), indicating a protective effect of rosuvastatin against sepsis-associated kidney injury.

Conclusion: Our study showed that, CLP-induced sepsis caused significant kidney injury, as shown by increased serum markers, tissue damage, and p-ERK1/2 expressions. We also found, treatment with rosuvastatin effectively reduced these changes, restoring kidney function and structure to near-normal levels. These results highlight rosuvastatin's potential as a protective agent against sepsis-related AKI, likely through modulation of the ERK1/2 pathway.

Implication for health policy/practice/research/medical education:
In this experimental animal study, we found that administration of rosuvastatin significantly mitigated renal damage related to cecal ligation and puncture (CLP)-induced sepsis, improving both kidney function and tissue integrity toward normal levels. These findings suggest that rosuvastatin may offer protective benefits against sepsis-associated acute kidney injury, potentially by regulating the extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling pathway.

Please cite this paper as: Al-ghanimi GM, Janabi AM. Therapeutic potential of rosuvastatin in sepsis-induced acute kidney injury; evidence from an experimental animal study. J Nephropharmacol. 2025;14(x):e12798. DOI: 10.34172/npj.2025.12798.

Original

Introduction

Acute kidney injury (AKI) is a serious complication of critical illness (1) associated with significant morbidity and mortality in both short-term and long-term outcomes (2,3). This highly common and multifactorial renal disease is diagnosed using standardized criteria such as RIFLE (risk, injury, failure, loss, end-stage kidney disease), AKIN (acute kidney injury network), or KDIGO (kidney disease improving global outcomes) (3). A recent meta-analysis including 201 studies with 98,228 participants demonstrated that the overall incidence of any stage AKI is approximately 30%, with severe renal injury occurring

***Corresponding author**: Ali M. Janabi, Email: alim.hashim@uokufa.edu.iq

in 15% of cases. Furthermore, AKI-associated mortality was reported at 30%, with the odds of death being 3.4 times higher in patients with AKI compared to those without (4).

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (5,6). This condition results from an imbalance in the immune response that leads to widespread inflammation, profound alterations in microcirculation, and rapid progression to multiple organ failure (6,7). The current clinical definition, known as sepsis-3, emphasizes the presence of organ dysfunction measured by an increase of two or more points in the sequential organ failure assessment (SOFA) score (8). Sepsis represents the predominant cause of AKI in critically ill patients, accounting for nearly 50% of all AKI cases in intensive care settings, with mortality rates reaching 20% (9). Despite advances in understanding the pathophysiological mechanisms underlying sepsis-induced acute kidney injury (SI-AKI), its severity and complexity continue to pose significant challenges to clinicians (10). The complex interplay between inflammatory responses, oxidative stress, and microcirculatory dysfunction in SI-AKI has been extensively studied, yet there remains no exact and effective therapy available for its treatment or prevention. This therapeutic gap highlights the urgent need for novel approaches targeting the specific pathophysiological mechanisms of SI-AKI (11).

Statins, particularly rosuvastatin, have emerged as potential therapeutic agents for sepsis-related conditions due to their pleiotropic effects extending beyond lipid-lowering properties (12). These medications act by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis (13). The immunomodulatory and antioxidant properties of statins have been shown to modify inflammatory cell signaling of the immune response to infection, suggesting potential benefits in sepsis outcomes. Previous research has demonstrated that statin therapy might be beneficial when administered before sepsis onset or in its initial period (12). Notably, experimental studies with simvastatin, another member of the statin family, have shown renoprotective effects through antioxidant mechanisms in sepsis-induced AKI animal models (14). The statins for acutely injured lungs in sepsis (SAILS) trial investigated rosuvastatin's impact in patients with sepsis-associated acute respiratory distress syndrome, providing valuable insights into its potential application in sepsis-related organ dysfunction (15).

This study aims to investigate the therapeutic effects of rosuvastatin on SI-AKI using an established animal model, focusing on its impact on renal function. By elucidating the renoprotective mechanisms of rosuvastatin in sepsis, this research seeks to provide preclinical evidence supporting its potential application as a targeted therapy for SI-AKI, addressing a critical unmet need in critical care medicine.

Objectives

The objective of this study is to investigate the therapeutic effects of rosuvastatin on sepsis-induced AKI by evaluating its impact on kidney function, histopathological changes, and molecular markers in an established experimental mouse model of sepsis.

Materials and Methods

Study design and samples

This experimental animal study was conducted at the university of Kufa, Iraq, and the Institutional Animal Care and Use Committee (IACUC) approved it. Following one week of initial adaptation, 24 adult Swiss albino mice were divided into four groups randomly (n = 6 in each group); sham group, cecal ligation and puncture (CLP), CLP + dimethyl sulfoxide (DMSO), and CLP + rosuvastatin. The sham group of mice had no CLP laparotomy operation. The CLP group, on the other hand, had a midline laparotomy with cecum ligation and perforation. In the CLP + rosuvastatin group, one hour before the CLP process, a dose of rosuvastatin 10 mg/kg was administered intraperitoneal. For the DMSO group, one hour before the CLP procedure, the mice in the CLP + DMSO group were given an intraperitoneal injection of DMSO, a vehicle for rosuvastatin (16).

Animals' preparation

This experimental study was conducted on 24 male adult (age 8-11 weeks) Swiss albino mice weighing between 20-35 g, purchased from the animal facility at the College of Science, University of Kufa. The mice were maintained under normal conditions at a specified temperature of 25±4 °C, humidity levels of 55%–65%, and a 12-hour light/dark cycle. Before the study, the animals were housed in separate cages and offered a commercial mouse chow meal along with unrestricted access to drinking water.

Drug preparation

According to the manufacturer's instructions from MedChem Express, rosuvastatin has a solubility of 100 mg/mL in DMSO, which is the recommended solvent. Therefore, the solution should be prepared fresh shortly before use. The dose was administered intraperitoneally and calculated based on the mice's body weight (16).

Experimental procedure

A model of CLP is an experimentally created polymicrobial sepsis that simulates the human sepsis situation (17,18). It is used to study sepsis and associated multi-organ dysfunction because it is highly similar to the progression and characteristics, and exhibits a cytokine profile like that of human sepsis (17,19). Before the procedure, the mice were anesthetized with a mixture of 100 mg/kg ketamine and 10 mg/kg xylazine administered intraperitoneally (20). The cecum is reached via a 1-2 cm midline abdominal incision, and it is ligated just below

the ileocecal valve. The ligated section of the cecum is subsequently punctured twice with a G-20 needle and then repositioned into its original location. The abdomen was subsequently sutured with 5.0 medical sutures. The mice were administered a subcutaneous resuscitative dose of normal saline and observed every four hours for one day for various indicators of illness (21).

Blood sample collection and biochemical assessment of renal function tests

After 24 hours of CLP surgery, anesthesia was administered to the mice before blood samples were taken by direct heart puncture after scarification surgery. To obtain the serum, blood samples were centrifuged at 6000 rpm for 10 minutes. Then, a spectrophotometric technique was used to determine urea and creatinine levels at 550 nm absorbance (22). Commercial enzyme-linked immunosorbent assay (ELISA) kits from Bioassay technology laboratory, China, Cat. No. E0617Mo, following the manufacturer's instructions was used for kidney injury molecule-1(KIM-1) level assessment (23).

Tissue sampling for renal tissue histopathology

After 24 hours of CLP-induced polymicrobial sepsis, all the animals were euthanized, their kidneys were taken and rinsed with saline to remove any clots or erythrocytes. The renal tissue was divided and used to measure the P-ERK 1/2 level by immunohistochemistry and to examine renal tissue histopathology.

Tissue collection for histological analysis

Kidney tissue samples were immersed in 10% formalin for fixation, dehydrated by a variety of alcohol concentrations from 50% to 100%, cleared with xylene, embedded in paraffin, and sectioned into 5-micrometer-thick slices using a microtome (24). The sections were then stained with hematoxylin and eosin after deparaffinization. Then, we covered the stained tissue sections with mounting medium to preserve and protect the tissue, and next a pathologist examines the slide under a microscope. Damaged cells were analyzed in five distinct, non-overlapping views. The sections were graded using a score design to test the extent of renal injuries, such as inflammation, cellular edema, red cell extravasation, cytoplasmic eosinophilia, and damage percentage. The scoring system that was employed consisted of five scores: score 0; normal, score 1 <25% damage, score 2 (25%-50%) damage, score 3 (50%-75%) damage score 4 >75% damage (25).

Tissue sampling for immunohistochemistry

Immunohistochemical staining was performed to examine how phospho-ERK 1/2 is expressed in renal tissue. Sections of 3μm thickness embedded in paraffin were subjected to deparaffinization, rehydration, antigen repairing by exposure to heat for 20 minutes, and suppression of the activity of endogenous peroxidase with 3% H2O2 for three minutes. Incubate the sections with a 1:100 dilution of primary antibody [Phospho-ERK(p-ERK) 1/2 polyclonal antibody]. Once the slides have been washed, incubated for 30 minutes with a secondary antibody that has been conjugated, followed by additional washing and treatment with horseradish peroxidase for 30 minutes. Subsequently, for 10 minutes, the sections were placed in an incubator containing 3,3′-diaminobenzidine that had just been produced. Hematoxylin was then used as a counterstain. Finally, the slides were prepared for microscopic examination by clearing and mounting them (26). Phospho-ERK 1/2 protein expression was assessed using the H-score method (range; 0–300), computed by multiplying the staining intensity by the stained area percentage. Staining intensity was graded on a scale from 0 to 3, where 0 indicated absence of stains, 1 indicated weak staining, 2 indicated moderate, and 3 indicated strong staining. The proportion of positively stained cells was evaluated on a scale from 0% to 100% (27).

Analysis of p-ERK 1/2

The expression of phosphorylated extracellular signal-regulated kinases 1 and 2 (p-ERK 1/2) was evaluated using immunohistochemistry. The primary antibody, phospho-ERK 1/2 (Tyr204) polyclonal antibody, was purchased from Elabscience (China). The secondary antibody, Mouse/Rabbit PolyDetector Plus DAB HRP Brown, was obtained from BIO SB United States of America (USA).

Statistical analysis

Data analysis was performed using IBM SPSS Statistics software, version 27 (IBM Corp., USA). The Shapiro-Wilk test was applied to assess the normality of the data distribution. Both parametric and nonparametric statistical methods were initially employed; however, since the P-values were consistent across both approaches for all variables, parametric tests were chosen due to their greater precision and reliability in hypothesis testing. Group differences were evaluated using analysis of variance (ANOVA), followed by a Scheffé post hoc test to pinpoint specific differences between groups. A significance level of $P < 0.05$ was used for all statistical tests.

Results

This experimental study utilized 24 adult Swiss albino mice, ethically approved for study under institutional guidelines. Subjects were randomly assigned to four groups (n = 6 per group); sham group, serving as a surgical control; CLP, subjected to CLP to induce sepsis; CLP+DMSO, receiving the dimethyl sulfoxide vehicle; and CLP + rosuvastatin, administered a 10 mg/kg rosuvastatin one hour before the CLP process. The results indicated that the sham group exhibited substantially lower serum urea levels compared to the CLP group and the CLP and DMSO group, though not significantly different from

the CLP and rosuvastatin group. The CLP group showed markedly higher urea levels relative to both the CLP and rosuvastatin group and the Sham group, but no significant difference was observed when compared to the CLP and DMSO group. Conversely, the CLP and rosuvastatin group displayed significantly reduced urea levels compared to both the CLP group and the CLP and DMSO group (Table 1 and Figure 1).

Serum concentrations of serum creatinine were significantly elevated in both the CLP and CLP+DMSO groups relative to the Sham group, with no notable difference seen between the CLP and CLP+DMSO groups, as well as sham and CLP+rosuvastatin. Whereas pretreatment with rosuvastatin markedly reduced these serum markers compared to the CLP group. These findings indicate that rosuvastatin contributed to the preservation of renal function after CLP-induced sepsis (Table 2 and Figure 2).

Quantitative analysis revealed serum KIM-1 concentrations were significantly elevated in the CLP and CLP+DMSO groups compared to the sham cohort. No statistically significant variation occurred between the Sham and CLP + rosuvastatin groups, as well as between CLP and CLP+ DMSO. Notably, rosuvastatin pretreatment attenuated KIM-1 levels relative to untreated CLP mice, suggesting a renoprotective effect (Table 3 and Figure 3).

The distribution of histopathological scores varied notably among the four experimental groups. The sham group predominantly exhibited normal histology, with the majority of subjects showing no pathological changes and a small proportion displaying only mild alterations. In contrast, both the CLP and CLP+DMSO groups were characterized exclusively by highly severe histopathological damage, with no cases demonstrating normal or mild scores. The CLP+ rosuvastatin group showed a different pattern, with half of the subjects presenting normal histology and the other half exhibiting mild changes, while no moderate, severe, or highly severe damage was observed. These findings indicate that rosuvastatin treatment is associated with a marked reduction in histopathological injury compared to untreated or DMSO-treated CLP groups, suggesting a protective effect against tissue damage in this experimental model (Table 4 and Figure 4).

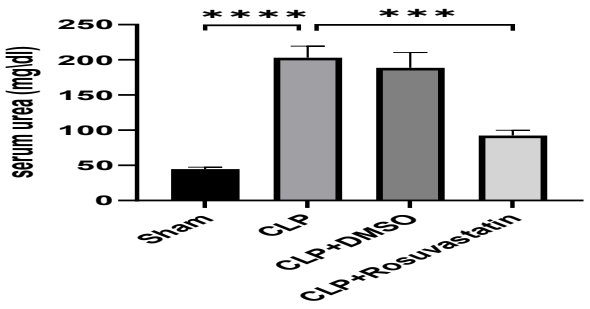

Figure 1. Comparison of serum urea levels between the four groups. CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide, ***$P < 0.001$.

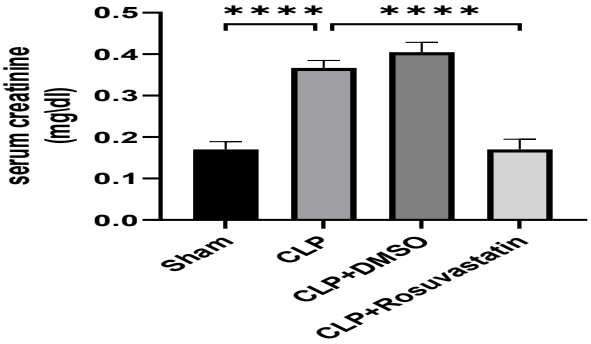

Figure 2. Comparison of serum creatinine levels between the four groups. CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide, ***$P < 0.001$.

The comparative analysis of nuclear p-ERK1/2 expression revealed distinct patterns across treatment groups. The Sham group exhibited negligible nuclear p-ERK1/2 expression, while the CLP and CLP and DMSO groups demonstrated significantly higher levels compared to Sham, with no discernible difference between these two intervention groups. In contrast, the CLP and rosuvastatin group showed a marked reduction in nuclear p-ERK1/2 expression relative to both the CLP and CLP and DMSO

Table 1. Comparative analysis of serum urea among treatment groups

	Group		Mean	SD	*P* value*
Serum urea (mg/dL)	Sham		44.71	6.75	<0.001
	CLP		203.04	40.25	
	CLP & DMSO		188.65	52.93	
	CLP & Rosuvastatin		92.48	18.35	
	First group	**Second group**	**Mean difference**		***P* value****
	Sham	CLP	153.33		<0.001
		CLP & DMSO	143.93		<0.001
		CLP & Rosuvastatin	47.77		0.163
	CLP	CLP & DMSO	14.39		0.914
		CLP & Rosuvastatin	110.56		<0.001
	CLP & DMSO	CLP & Rosuvastatin	96.16		0.001

CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide; SD, Standard deviation. *One-way ANOVA, **Post hoc Scheffe test.

Table 2. Comparative analysis of serum creatinine among treatment groups

	Group		Mean	SD	*P* value*
Serum creatinine (mg/dL)	Sham		0.17	0.04	<0.001
	CLP		0.36	0.04	
	CLP & DMSO		0.40	0.05	
	CLP & Rosuvastatin		0.17	0.06	
	First group	**Second group**	**Mean difference**		***P* value****
	Sham	CLP	0.19		<0.001
		CLP & DMSO	0.23		<0.001
		CLP & Rosuvastatin	0.00		>0.999
	CLP	CLP & DMSO	0.03		0.671
		CLP & Rosuvastatin	0.19		<0.001
	CLP & DMSO	CLP & Rosuvastatin	0.23		<0.001

CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide; SD, Standard deviation. *One-way ANOVA, **Post hoc Scheffe test.

Table 3. Comparative analysis of serum KIM-1 among treatment groups

	Group		Mean	SD	*P* value*
KIM-1 (ng/dL)	Sham		24.98	3.27	<0.001
	CLP		39.24	4.74	
	CLP & DMSO		37.56	6.90	
	CLP & Rosuvastatin		28.82	1.40	
	First group	**Second group**	**Mean difference**		***P* value****
	Sham	CLP	14.25		<0.001
		CLP & DMSO	12.57		0.001
		CLP & Rosuvastatin	3.83		0.557
	CLP	CLP & DMSO	1.67		0.937
		CLP & Rosuvastatin	10.41		0.008
	CLP & DMSO	CLP & Rosuvastatin	8.73		0.008

CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide; SD, Standard deviation; KIM-1; Kidney injury molecule-1. *One-way ANOVA, **Post hoc Scheffe test.

groups. Post hoc analysis indicated that rosuvastatin treatment was associated with substantially lower nuclear p-ERK1/2 levels compared to untreated CLP or DMSO-administered CLP models, whereas DMSO itself did not significantly alter expression levels relative to CLP alone. These findings suggest that rosuvastatin effectively attenuates injury-induced nuclear ERK1/2 phosphorylation in this experimental model (Table 5 and Figure 5).

The results of histopathology and photomicrographs of the renal section indicated that the sham group shows a negative nuclear p-ERK 1/2 expression (Figure 6). Furthermore, Figure 7 demonstrates the results of hematoxylin and eosin staining of renal tissues among the four treatment groups.

Discussion

The study findings revealed that CLP-induced sepsis

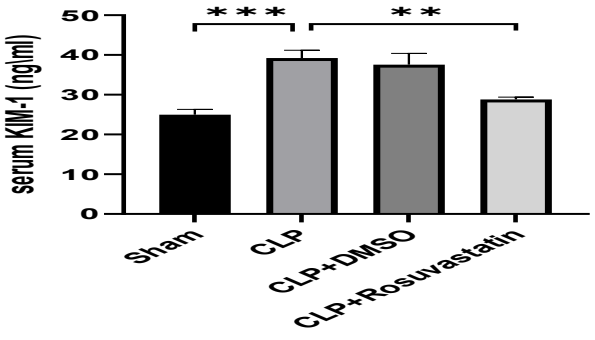

Figure 3. Comparison of serum KIM-1 levels between the four groups. CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide; KIM-1; Kidney injury molecule-1. **$P < 0.01$, ***$P < 0.001$.

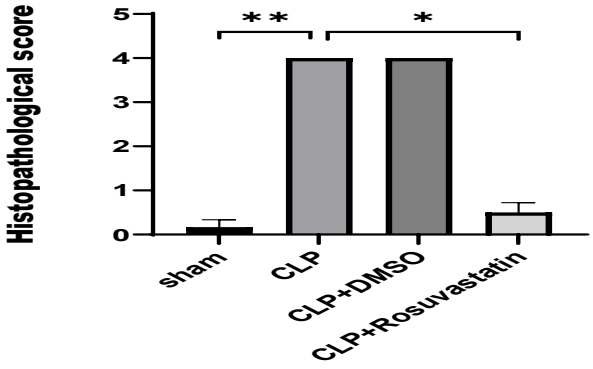

Figure 4. Comparison of histopathological damage score between the four groups. CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide.*$P < 0.05$, **$P < 0.01$.

Table 4. Distribution of histopathological damage among the four experimental groups

Score	Treatment group							
	Sham		CLP		CLP + DMSO		CLP + Rosuvastatin	
	No.	%	No.	%	No.	%	No.	%
Normal (0)	5	83.33	0	0	0	0	3	50
Mild (1)	1	16.67	0	0	0	0	3	50
Moderate (2)	0	0	0	0	0	0	0	0
Severe (3)	0	0	0	0	0	0	0	0
Highly severe (4)	0	0	6	100	6	100	0	0
Total	6	100	6	100	6	100	6	100

CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide.

Table 5. Comparative analysis of nuclear p-ERK1/2 expression H-score among treatment groups

	Group		Mean	SD	*P* value*
H-score of nuclear p-ERK1/2	Sham		0.00	0.00	<0.001
	CLP		48.00	16.54	
	CLP & DMSO		50.00	22.58	
	CLP & Rosuvastatin		12.50	14.74	
	First group	**Second group**	**Mean difference**		***P* value****
	Sham	CLP	48.00		<0.001
		CLP & DMSO	50.00		<0.001
		CLP & Rosuvastatin	12.50		0.608
	CLP	CLP & DMSO	2.00		0.997
		CLP & Rosuvastatin	35.50		0.009
	CLP & DMSO	CLP & Rosuvastatin	37.50		0.006

CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide; SD, Standard deviation; p-ERK1/2, Phosphorylated ERK1/2. *One-way ANOVA, **Post hoc Scheffe test.

resulted in a significant increase in renal function indices, encompassing serum urea and creatinine concentrations, KIM-1 levels, histopathological assessment scores, and nuclear p-ERK1/2 expression. However, administration of rosuvastatin led to a substantial attenuation of these indicators, restoring them to levels approximating those of healthy control (sham group) mice, thereby demonstrating a renoprotective effect of rosuvastatin in the context of sepsis-associated kidney injury.

The significant reduction in serum urea and creatinine levels observed in our rosuvastatin-treated septic mice

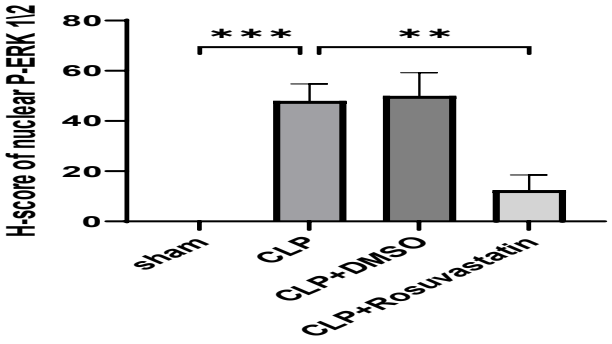

Figure 3. Comparison of nuclear p-ERK1/2 expression H-score between the four groups. CLP, Cecal ligation and puncture; DMSO, Dimethyl sulfoxide; p-ERK1/2, Phosphorylated ERK1/2. **$P < 0.01$, ***$P < 0.001$.

aligns with some previous findings but contrasts with others in the existing literature. Recent research by Tang et al, demonstrated that rosuvastatin administration substantially mitigated inflammation and improved renal function in a relevant model of sepsis, supporting our observations of normalized renal function markers (28). Similarly, an earlier study by Yasuda et al with simvastatin in CLP models found significant improvements in serum BUN and creatinine levels, suggesting a class effect of statins in sepsis-induced AKI (29). However, these findings stand in contrast to a trial secondary analysis by Hsu et al, which concluded that rosuvastatin treatment in patients with sepsis-associated acute respiratory distress syndrome (ARDS) did not protect against de novo AKI or worsening of preexisting AKI (15). This discrepancy may be attributed to differences in study populations, with our preclinical model potentially capturing early intervention effects not replicable in clinical scenarios where treatment often begins after kidney injury has been established. The contradicting findings highlight the complex relationship between rosuvastatin and kidney function in inflammatory states, which appears to be influenced by the timing of intervention, dosage considerations, and baseline kidney function.

Our finding that rosuvastatin treatment significantly reduced KIM-1 levels in septic mice represents an important contribution to understanding statin effects on

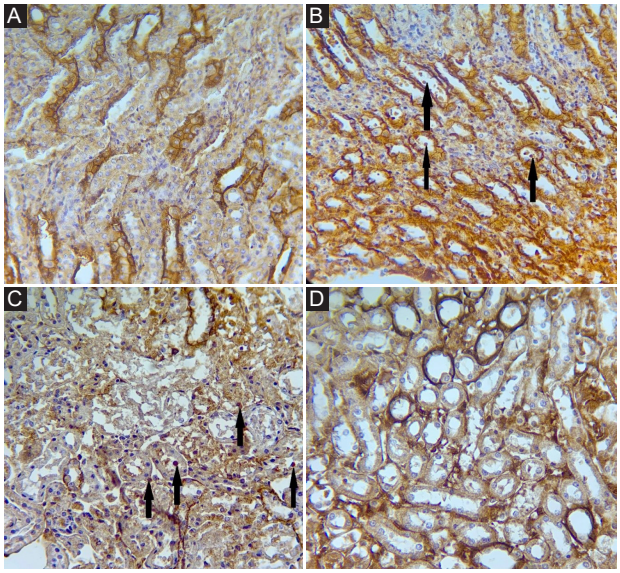

Figure 6. Histopathology and photomicrographs of the renal section. IHC ×400 (A), CLP group positive nuclear p-ERK 1/2 expression (black arrows), IHC ×400 (B), CLP + DMSO group positive nuclear p-ERK 1/2 expression. IHC ×400, and (C), CLP + Rosuvastatin-treated group showing negative nuclear p-ERK 1/2 expression, IHC, ×400 (D).

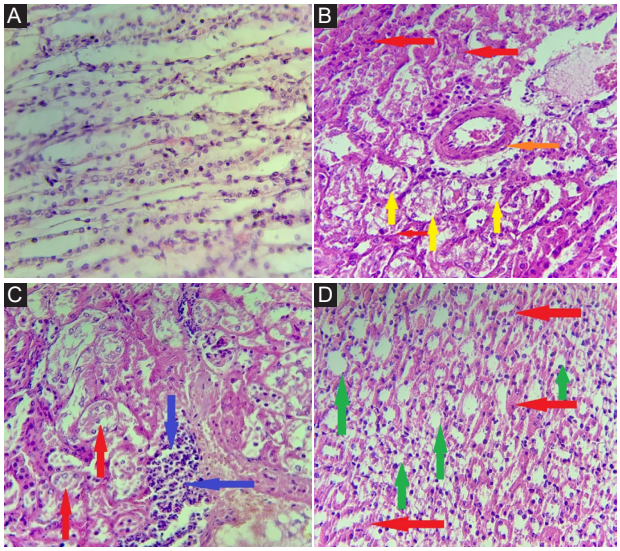

Figure 7. Hematoxylin and eosin staining of renal tissues among the four treatment groups. The results demonstrated that in the sham group, the kidney cross-section showed normal histological structure (magnification; 400× [A]). In the control group, cellular swelling and increased cytoplasmic eosinophilia (red arrows), cytoplasmic vacuolization (yellow arrow), and vascular congestion (orange arrow) (magnification: 400× [B]). In the DMSO group, damaged tubules (red arrow) and inflammation (blue arrow) (magnification: 400× [C]). In the rosuvastatin-treated group, the kidney cross-section displayed a damage score of 1, affecting 20% of the renal tubules; a damaged tubule (red arrow), and a normal tubule (green arrow) (magnification: 400× [D]).

specific biomarkers of tubular injury. Previous research has not extensively examined rosuvastatin's specific effects on KIM-1 in sepsis models, making our findings particularly notable. The observed KIM-1 reduction parallels reported effects of simvastatin in similar experimental models, where it attenuated CLP-induced tubular damage and reversed renal tubular hypoxia (29). These consistent findings across statin types suggest a shared mechanism potentially involving improvements in intrarenal microvascular perfusion, as previously demonstrated in simvastatin studies. However, caution in interpreting these findings is warranted, given real-world data linking rosuvastatin to increased risks of hematuria and proteinuria compared to other statins like atorvastatin, particularly at higher doses. The contrasting effects observed between controlled experimental settings and clinical populations underscore the importance of dose-dependent considerations in rosuvastatin's renoprotective capacity, with our model potentially representing optimal dosing conditions that may not always translate to clinical practice where dosing must be carefully calibrated to baseline kidney function, as illustrated by case reports of rosuvastatin-associated worsening of kidney function in patients with preexisting chronic kidney disease (30).

The improvement in histopathological scores and reduction in nuclear p-ERK1/2 expression demonstrated in our rosuvastatin-treated septic mice provide mechanistic insights into its renoprotective effects. These findings are consistent with recent investigations showing that rosuvastatin administration hampered organ dysfunction and mitigated inflammation in relevant models of sepsis (28). The modulation of the ERK1/2 signaling pathway by rosuvastatin appears to be a crucial mechanism underlying its protective effects, as it aligns with previous observations that statins prevent NF-κB (nuclear factor-κB) activation in macrophages, thereby reducing inflammatory cytokine production. The histopathological improvements we observed mirror findings from simvastatin studies that demonstrated attenuation of sepsis-induced tubular damage and restoration of renal vascular integrity (29). The parallel improvements in histopathology and molecular signaling suggest that rosuvastatin's renoprotective effects likely operate through multiple complementary mechanisms involving both anti-inflammatory actions and direct effects on renal vasculature. However, the balance of evidence suggests that these benefits may be context-dependent, as exemplified by studies indicating that rosuvastatin's effects on kidney integrity vary based on dosage and baseline kidney function. The molecular mechanisms we've identified through p-ERK1/2 expression analysis provide a foundation for understanding the conditions under which rosuvastatin might confer optimal renoprotection in sepsis-associated kidney injury, while acknowledging the need for careful consideration of patient-specific factors in clinical applications.

Conclusion

The findings conclusively demonstrate that CLP-induced sepsis precipitated significant renal dysfunction,

evidenced by elevated serum urea, creatinine, KIM-1, histopathological damage, and nuclear p-ERK1/2 overexpression. Rosuvastatin administration attenuated these perturbations, restoring biomarker and tissue integrity metrics to near-Sham levels, thereby confirming its renoprotective efficacy in this model. This normalization of molecular, biochemical, and structural parameters suggests rosuvastatin mitigates sepsis-associated AKI through ERK1/2 pathway modulation, potentially disrupting inflammatory and apoptotic cascades. These preclinical insights position rosuvastatin as a promising therapeutic candidate for sepsis-induced AKI, warranting further investigation into its clinical translation and precise mechanisms of action, including targeted studies on oxidative stress regulation and cytokine signaling networks.

Acknowledgments

The authors gratefully acknowledge the support and facilities provided by the University of Kufa, Iraq, where this experimental animal study was conducted. We also extend our sincere appreciation to the Institutional Animal Care and Use Committee (IACUC) for their approval and oversight, ensuring that all procedures complied with ethical standards for the humane treatment of animals throughout the study. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

Authors' contribution

Conceptualization: All authors.
Data curation: All authors.
Formal analysis: Ghanim M. Al-ghanimi.
Investigation: Ghanim M. Al-ghanimi.
Methodology: Ghanim M. Al-ghanimi.
Project management: Ali M. Janabi.
Resources: All authors.
Supervision: Ali M. Janabi.
Validation: Ali M. Janabi.
Writing–original draft: Ghanim M. Al-ghanimi.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Ethical issues

The research and the protocol of this study followed the guidelines of animal studies and were approved by the Ethics Committee of the Institutional Animal Care and Use Committee (IACUC) at Kufa University, Iraq, with an ethical approval code of (approval number 2123) on January 23, 2025. We also followed the guidelines related to animal experiments, approved by the United States National Institutes of Health (NIH, 1978). Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Funding/Support

The authors did not receive any source of funding

References

1. Rosner MH, La Manna G, Ronco C. Acute Kidney Injury in the Geriatric Population. Contrib Nephrol. 2018;193:149-160. doi: 10.1159/000484971.
2. Birkelo BC, Pannu N, Siew ED. Overview of Diagnostic Criteria and Epidemiology of Acute Kidney Injury and Acute Kidney Disease in the Critically Ill Patient. Clin J Am Soc Nephrol. 2022;17:717-735. doi: 10.2215/CJN.14181021.
3. Koeze J, Keus F, Dieperink W, van der Horst IC, Zijlstra JG, van Meurs M. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. BMC Nephrol. 2017;18:70. doi: 10.1186/s12882-017-0487-8.
4. Meena J, Kumar J, Kocharlakota JP, Gupta H, Mittal P, Kumar A, et al. Acute Kidney Injury in Neonates: A Meta-Analysis. Pediatrics. 2024;154:e2023065182. doi: 10.1542/peds.2023-065182.
5. Tong DL, Kempsell KE, Szakmany T, Ball G. Development of a Bioinformatics Framework for Identification and Validation of Genomic Biomarkers and Key Immunopathology Processes and Controllers in Infectious and Non-infectious Severe Inflammatory Response Syndrome. Front Immunol. 2020;11:380. doi: 10.3389/fimmu.2020.00380.
6. Schlapbach LJ, Trück J, Roger T. Editorial: The Immunology of Sepsis-Understanding Host Susceptibility, Pathogenesis of Disease, and Avenues for Future Treatment. Front Immunol. 2020;11:1263. doi: 10.3389/fimmu.2020.01263.
7. Man A, Grigorescu BL. To be or not to be… Sepsis? a Daily Challenge in ICU. J Crit Care Med (Targu Mures). 2020;6:80-83. doi: 10.2478/jccm-2020-0012.
8. Fujishima S. Organ dysfunction as a new standard for defining sepsis. Inflamm Regen. 2016;36:24. doi: 10.1186/s41232-016-0029-y.
9. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int. 2019;96:1083-1099. doi: 10.1016/j.kint.2019.05.026.
10. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol. 2012;2:1303-53. doi: 10.1002/cphy.c110041.
11. Wang L, Li J, Liao R, Li Y, Jiang L, Zhang Z, et al. Resolvin D1 attenuates sepsis induced acute kidney injury targeting mitochondria and NF-κB signaling pathway. Heliyon. 2022;8:e12269. doi: 10.1016/j.heliyon.2022.e12269.
12. Piechota M, Barylski M, Hannam S, Piechota-Urbańska M, Banach M. Rationale of statin therapy in septic

patients. Curr Vasc Pharmacol. 2013;11:795-800. doi: 10.2174/1570161111311050018.
13. de Jesus Oliveira FM, Gonçalves-de-Albuquerque CF, de Moraes IMM, Reis PA, Rocha VN, Bozza PT, et al. Simvastatin Posttreatment Controls Inflammation and Improves Bacterial Clearance in Experimental Sepsis. Mediators Inflamm. 2020;2020:1839762. doi: 10.1155/2020/1839762.
14. Santos Fdo N, Watanabe M, Vasco CF, Fonseca CD, Vattimo Mde F. [Antioxidant protection of statins in acute kidney injury induced by sepsis]. Rev Esc Enferm USP. 2014;48:820-6.
15. Hsu RK, Truwit JD, Matthay MA, Levitt JE, Thompson BT, Liu KD. Effect of Rosuvastatin on Acute Kidney Injury in Sepsis-Associated Acute Respiratory Distress Syndrome. Can J Kidney Health Dis. 2018;5:2054358118789158. doi: 10.1177/2054358118789158.
16. Naito Y, Katada K, Takagi T, Tsuboi H, Kuroda M, Handa O, et al. Rosuvastatin reduces rat intestinal ischemia-reperfusion injury associated with the preservation of endothelial nitric oxide synthase protein. World J Gastroenterol. 2006 Apr 7;12:2024-30. doi: 10.3748/wjg.v12.i13.2024.
17. Doi K, Leelahavanichkul A, Yuen PS, Star RA. Animal models of sepsis and sepsis-induced kidney injury. J Clin Invest. 2009;119:2868-78. doi: 10.1172/JCI39421.
18. Buras JA, Holzmann B, Sitkovsky M. Animal models of sepsis: setting the stage. Nat Rev Drug Discov. 2005;4:854-65. doi: 10.1038/nrd1854.
19. Dejager L, Pinheiro I, Dejonckheere E, Libert C. Cecal ligation and puncture: the gold standard model for polymicrobial sepsis? Trends Microbiol. 2011;19:198-208. doi: 10.1016/j.tim.2011.01.001.
20. Jabber H, Mohammed B, Hadi NR. Investigating the renoprotective effect of C21 in male mice with sepsis via modulation of p-AKT/PI3K expression. J Med Life. 2023;16:203-209. doi: 10.25122/jml-2022-0299.
21. Dahlke K, Sommerfeld O, Wrann C, Riedemann N, editors. Polymicrobial sepsis via Cecum Ligation and Puncture (CLP) procedure in mice. Infection; 2009: urban & vogel neumarkter strasse 43, d-81673 Munich, Germany.
22. Alkhafaji GA, Janabi A. GIP/GLP-1 dual agonist tirzepatide ameliorates renal ischemia/reperfusion damage in rats. Int J App Pharm. 2025;17:165-73.
23. Alaasam ER, Janabi AM, Al-Buthabhak KM, Almudhafar RH, Hadi NR, Alexiou A, et al. Nephroprotective role of resveratrol in renal ischemia-reperfusion injury: a preclinical study in Sprague-Dawley rats. BMC Pharmacol Toxicol. 2024;25:82. doi: 10.1186/s40360-024-00809-8.
24. Q Jallawee H, Janabi AM. Trandolapril improves renal ischemia-reperfusion injury in adult male rats via activation of the autophagy pathway and inhibition of inflammation, oxidative stress, and apoptosis. J Biosci Appl Res. 2024;10:114-27.
25. Mohammed TJ, Hadi NR, Al-Yasiri I, Yousif NG, Jasim A, Alamran F, et al. Critical role of Ghrelin in downregulation of the inflammatory response after renal injury. Vasc Investig Ther. 2018;1:68-73.
26. Lee EG, Pang TW, Nelson J, Andrew M, Harper M. Comparison of mounting methods for the evaluation of fibers by phase contrast microscopy. Ann Occup Hyg. 2011;55:644-57. doi: 10.1093/annhyg/mer015.
27. Abbas LM, Al-Mudhafar RH, Al-Mudhafar DH, Hadi NR. Ranolazine protects the kidney from ischemia/reperfusion injury in adult male rats by modulation of inflammatory and oxidative pathways and suppression of Notch2/Hes1 signaling pathway. Sys Rev Pharm. 2021;12:481-93.
28. Tang Z, Ning Z, Li Z. The beneficial effects of Rosuvastatin in inhibiting inflammation in sepsis. Aging (Albany NY). 2024;16:10424-10434. doi: 10.18632/aging.205937.
29. Yasuda H, Yuen PS, Hu X, Zhou H, Star RA. Simvastatin improves sepsis-induced mortality and acute kidney injury via renal vascular effects. Kidney Int. 2006;69:1535-42. doi: 10.1038/sj.ki.5000300.
30. Sheth CT, Khorsan R. Rosuvastatin Associated Acute on Chronic Kidney Failure. Proceedings of UCLA Health. 2024;28.