Immunopathologia Persa
http immunopathol.com
DOI:10.34172/ipp.2025.43864

Therapeutic potential of fimasartan as a novel angiotensin receptor antagonist in mitigating liver injury in a murine sepsis model; an experimental animal study

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Received 2 Mar. 2025
Revised: 30 Apr. 2025
Accepted 12 Sep. 2025
ePublished 20 Sep. 2025

Keywords: Fimasartan, Angiotensin II receptor blocker, Sepsis, Inflammation, Liver injury, Oxidative stress

Citation: Al-Shimary AM, Janabi AM, Ehrhardt C. Therapeutic potential of fimasartan as a novel angiotensin receptor antagonist in mitigating liver injury in a murine sepsis model; an experimental animal study. Immunopathol Persa. 2025;x(x):e43864. DOI:10.34172/ipp.2025.43864.

Abstract

Introduction: The angiotensin II type 1 receptor (AT1R) blockers play a crucial role in mediating inflammatory responses, and their blockade has emerged as a potential therapeutic strategy for mitigating sepsis-related organ damage, especially the liver. Fimasartan, a novel AT1R antagonist, has shown promise in preclinical studies for its anti-inflammatory properties and ability to improve survival in murine models of sepsis.

Objectives: This study aimed to explore the therapeutic potential of fimasartan in mitigating liver injury within a murine sepsis model.

Materials and Methods: This experimental study investigated the effects of fimasartan on sepsis-induced liver injury in 24 male albino Swiss mice, divided into four groups: Sham (laparotomy without cecal ligation and puncture [CLP]), CLP (cecal ligation and puncture to induce sepsis), vehicle (received dimethyl sulfoxide [DMSO]), and fimasartan-treated (received 3 mg/kg fimasartan intraperitoneal one hour before CLP). After 24 hours, the mice were sacrificed, and blood samples were analyzed for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and macrophage migration inhibitory factor (MIF) levels, while liver tissues were examined for biomarkers including intercellular adhesion molecule-1 (ICAM-1), interleukin-6 (IL-6), caspase-11, microtubule-associated protein 1A/1B-light chain 3 (LC3), malondialdehyde (MDA), superoxide dismutase (SOD), and Wnt/β-catenin genes. Histopathological analysis of liver tissues was also performed. The results were compared across groups to assess the therapeutic potential of fimasartan in mitigating sepsis-induced liver injury.

Results: The results demonstrated that following the CLP procedure, liver indicators such as ALT, AST, IL-6, ICAM-1, MIF, MDA, caspase-11, and liver injury scores were significantly elevated compared to the sham group. In contrast, treatment with fimasartan resulted in a marked reduction of these elevated levels compared to the CLP group. Additionally, CLP induction led to a significant decrease in hepatic levels of LC3, SOD, and Wnt/β-catenin signaling activity relative to the sham-operated controls. However, administration of fimasartan significantly reversed these reductions, highlighting its potential protective effects on liver function in sepsis.

Conclusion: Fimasartan demonstrated significant hepatoprotective effects in sepsis-induced liver injury. These findings suggest that fimasartan, an established angiotensin II receptor blocker already approved for hypertension management, could potentially be repurposed as an adjunctive therapy for patients with sepsis to mitigate liver dysfunction, a major contributor to sepsis mortality. Given the current limited therapeutic options for sepsis-induced organ damage, fimasartan represents a promising candidate for clinical trials, particularly in septic patients with early signs of liver involvement.

Introduction

Sepsis is a potentially life-threatening condition that arises from an uncontrolled immune response to infection, leading to significant damage to the body's tissues and organs; this severe reaction can result in increased morbidity and mortality if not recognized and treated promptly (1). The global incidence of this disease is approximately 508 cases per 100 000 people (2), and its pathophysiology involves a highly complex interplay of mechanisms, including immune response, mitochondrial dysfunction, autophagy, inflammatory response, and coagulation disorders (3). Previous studies documented that sepsis is the most common cause of death in non-coronary intensive care unit (ICU) (4). The higher mortality rate from severe sepsis in ICU is related to many factors, including an uncontrolled inflammatory response, multidrug resistance, in addition to ineffective anti-infection therapy (5).

The liver is a central organ that plays a crucial role in the progression of sepsis, and

Key point

In this experimental animal study, we found that fimasartan demonstrates significant hepatoprotective effects in sepsis-induced liver injury. If validated in human trials, this finding could introduce a readily available pharmacological option for preventing liver dysfunction in sepsis, potentially reducing mortality and improving outcomes in this high-risk population.

improving liver dysfunction has been linked to reduced morbidity and mortality rates (6,7). Sepsis-associated liver injury primarily manifests in two forms: cholestasis and hypoxic hepatitis (8). This liver damage is compounded by additional risks, including multi-organ dysfunction and drug toxicity, which arise from impaired hepatic biotransformation capabilities. Such impairments can lead to an increased mortality rate among affected patients (9). Sepsis activates multiple signaling pathways, including the Wnt/β-catenin pathway, which plays a significant role in the inflammatory response. Inhibiting the Wnt/β-catenin pathway has been shown to reduce inflammation and lessen organ injury induced by sepsis (10). Inflammation and oxidative stress are interconnected processes, with inflammation serving as the primary response during the early stages of sepsis. This inflammatory response triggers the generation of reactive oxygen species (ROS). When ROS production becomes excessive, it can initiate an inflammatory cascade and enhance the inflammatory response by releasing pro-inflammatory cytokines such as TNF-α and IL-6, ultimately resulting in liver damage (11).

Fimasartan is a newly developed angiotensin II type 1 receptor (AT1R) blocker (12) that has gained approval in South Korea for hypertension management, with additional approvals in countries such as India, Russia, and China. This medication not only effectively lowers blood pressure but also exhibits renoprotective properties, demonstrating a favorable safety and tolerability profile in clinical studies (13). Previous animal studies have shown that fimasartan effectively stabilizes atherosclerotic plaques and reduces myocardial injury by exerting anti-inflammatory effects (14,15). Additionally, a recent study demonstrated that fimasartan enhances kidney function in a rat model of renal ischemia-reperfusion injury (IRI) by modulating inflammatory responses, oxidative stress, and apoptotic markers (16). Despite the promising findings regarding fimasartan's protective effects, there is a notable absence of studies evaluating its therapeutic potential specifically in sepsis-related liver injury. This gap in the literature prompted us to conduct this study to investigate the impact of fimasartan on mitigating liver damage associated with sepsis.

Objectives

This study aimed to evaluate the therapeutic potential of fimasartan, a novel angiotensin receptor antagonist, in mitigating liver injury associated with sepsis in a murine model, while investigating its efficacy and safety profile as a treatment option for septic liver damage.

Materials and Methods

Study design and samples

This experimental study was conducted on 24 male albino Swiss mice (8–12 weeks old, weighing 25–35 g) obtained from the university of Kufa, faculty of sciences. The mice were housed under standard conditions, including a controlled temperature of 24 ± 2 °C, 60–65% humidity, and a 12-hour light/dark cycle. The animals were randomly divided into four groups (n = 6 mice per group); the sham group underwent a laparotomy without cecal ligation and puncture (CLP); the CLP group underwent the cecal ligation and puncture procedure; the Vehicle group received intraperitoneal dimethyl sulfoxide (DMSO); and the fimasartan-treated group received 3 mg/kg of fimasartan intraperitoneal one hour before the CLP procedure.

Material preparation

Materials were prepared as follows; fimasartan was obtained from Med Chem Express (MCE). Liver function tests, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were sourced from Mannheim. In addition, the enzyme-linked immunosorbent assay (ELISA) kits for interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), microtubule-associated protein 1A/1B-light chain 3 (LC3), macrophage migration inhibitory factor (MIF), and caspase-11 were purchased from SunLong Biotech CO. Malondialdehyde (MDA) and superoxide dismutase (SOD) ELISA kits were acquired from Bioassay Technology Laboratory (BT LAB). Primers for Wnt and β-catenin were obtained from Solarbio, China. Anesthesia was provided by xylazine (20 mg/mL) from Micropets and ketamine (100 mg/mL) from Alfasan.

CLP procedure

The CLP procedure was conducted following established protocols. Mice were anesthetized via intraperitoneal injection with a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg). A 1 cm incision was made in the abdomen, allowing exposure of the cecum. The cecum was then ligated below the ileocecal valve, and a double puncture was performed using a 20-gauge needle. After the procedure, the cecum was returned to its anatomical position, and the abdominal wall was closed with 6.0 surgical sutures. Post-operatively, all mice were returned to their cages with access to food and water for a 24-hour recovery period (6,7).

Hepatic histopathological examination

Hepatic tissues underwent histopathological examination by first being fixed in 10% formaldehyde, then dehydrated and cleared. The tissues were embedded in paraffin blocks and sectioned into 5-micrometer thick slices. Liver sections were stained using hematoxylin and eosin

(H&E). The degree of liver tissue damage was scored on a scale from 0 to 3 based on pathological changes such as vacuoles, ballooning, apoptosis, and necrosis. The scoring system categorized tissue damage as follows; score 0 for normal tissue, score 1 for mild damage, score 2 for moderate damage, and score 3 for severe damage (17).

Data collection and outcomes

Upon completion of the experiment, all animals were sacrificed after 24 hours. Blood samples were collected to measure AST, ALT, and MIF. Liver tissue samples were obtained to assess ICAM-1, IL-6, caspase-11, LC3, MDA, SOD, and the Wnt/β-catenin genes. A portion of the liver was reserved for histopathological examination. The collected data were then compared across different groups to evaluate the effects of the treatment.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.5 software. Quantitative data are presented as mean ± standard error of the mean (SEM). Analysis of variance (ANOVA) followed by the Bonferroni test was used for statistical comparisons. For histological score changes, the Kruskal-Wallis test was employed. A p-value of less than 0.05 was considered statistically significant, denoted as $*P<0.05$, $**P<0.01$, and $***P<0.001$.

Results

The results indicated that 24 male albino Swiss mice (8–12 weeks old, weighing 25–35 grams) were divided into four groups of sham, CLP, CLP with DMSO, and CLP with fimasartan (n = 6 mice per group). Statistical comparison tests confirmed that the frequency distribution of all dependent variables—including AST, ALT, MIF, ICAM-1, IL-6, caspase-11, LC3, MDA, SOD, Wnt/β-catenin, and liver injury scores—differed significantly among the groups. In the CLP and CLP with DMSO groups, markers associated with liver injury and inflammation, including enzyme indicators and pro-inflammatory cytokines, were elevated compared to the sham group. Administration of fimasartan in the CLP model resulted in marked improvements, as evidenced by trends toward normalization of these markers. Additionally, measures of autophagy, oxidative stress, apoptotic activity, and components of the Wnt/β-catenin signaling pathway were significantly disrupted following CLP induction, with fimasartan treatment demonstrating a restorative effect (Table 1).

The results indicated that after conducting CLP, the liver enzymes such as ALT, AST, IL-6 and ICAM-1 significantly increased compared to the sham group. However, following fimasartan treatment, these levels were significantly lowered compared to the CLP group, revealing that fimasartan has protective properties against CLP-induced hepatic injury (Figure 1).

Experimental results demonstrated that hepatic MIF, MDA, caspase 11, and liver injury score rose significantly in mice following CLP compared to the sham group. However, treatment with fimasartan notably reduced these elevated indicators (Figure 2).

Experimental results revealed that CLP induction markedly reduced hepatic levels of LC3 (an autophagy marker), SOD (a key antioxidant enzyme), and Wnt/β-catenin signaling activity compared to sham-operated controls. However, fimasartan administration significantly increased these reductions, restoring LC3 expression, SOD activity, and Wnt/β-catenin pathway activation in CLP-exposed subjects. This reversal suggests fimasartan mitigates CLP-induced liver injury by restoring autophagy flux, enhancing antioxidant defenses, and activating prosurvival Wnt/β-catenin signaling, mechanisms critical for counteracting sepsis-associated oxidative stress, cellular dysregulation, and impaired tissue repair (Figure 3).

Histopathological examination revealed that livers

Table 1. Frequency distribution of biochemical and histological markers among studied mice subjected to CLP

Dependent variable	Experimental group				*P* value*
	Sham	CLP	CLP+DMSO	CLP+Fimasartan	
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	
ALT (U/L)	93.66 (6.59)	307.66 (15.06)	308.33 (24.32)	229.33 (13.41)	<0.001
AST (U/L)	327.33 (37.73)	1331.33 (47.98)	1319.0 (40.24)	896.50 (88.15)	<0.001
IL-6 (ng/L)	20.10 (1.57)	53.16 (6.65)	51.66 (5.31)	35.31 (2.95)	<0.001
ICAM-1 (ng/L)	158.00 (19.51)	382.66 (47.48)	385.66 (31.31)	239.43 (20.37)	<0.001
MIF (pg/mL)	185.16 (18.90)	357.33 (25.81)	317.16 (15.73)	263.33 (15.35)	<0.001
LC-3 (pg/mL)	36.20 (2.28)	21.76 (2.64)	18.58 (2.08)	31.76 (1.94)	<0.001
MDA (nmol/mL)	3.97 (0.26)	5.66 (0.29)	5.40 (0.37)	4.18 (0.27)	0.001
SOD (ng/mL)	1.61 (0.08)	1.08 (0.07)	1.08 (0.10)	1.51 (0.05)	<0.001
Caspase-11 (ng/mL)	0.92 (0.09)	1.95 (0.23)	1.89 (0.19)	1.15 (0.28)	<0.001
Δ CT Wnt	7.40 (0.48)	4.25 (0.29)	4.52 (0.50)	6.32 (0.39)	<0.001
Δ CT B-catenin	6.97 (0.54)	4.39 (0.26)	5.16 (0.39)	6.14 (0.31)	<0.001
Liver injury score	0 (0)	2.83 (0.16)	2.83 (0.16)	1.66 (0.21)	<0.001**

CLP: Cecal ligation and puncture; DMSO: Dimethyl sulfoxide; SEM: Standard error of mean; AST: Aspartate transaminase; ALT: Alanine transaminase; IL-6: Interleukin-6; ICAM-1: Intercellular adhesion molecule-1; LC3: microtubule-associated protein 1A/1B-light chain 3; MIF: Macrophage migration inhibitory factor; MDA: Malondialdehyde; SOD: Superoxide dismutase. *ANOVA; **Kruskal-Wallis.

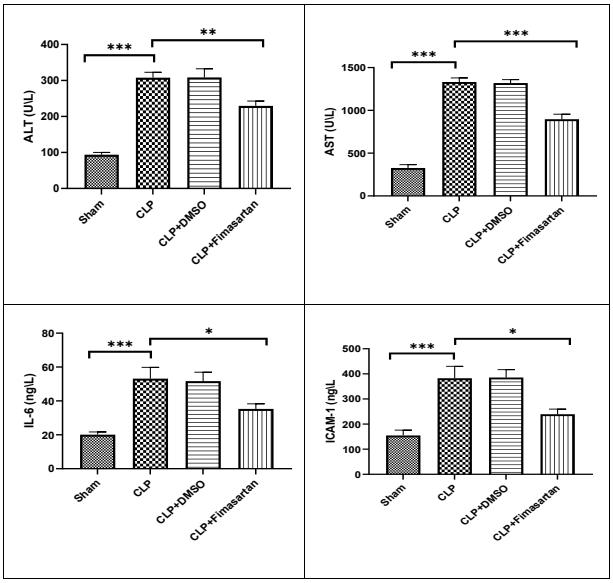

Figure 1. The effect of fimasartan on ALT, AST, hepatic IL-6, and hepatic ICAM-1. CLP; Cecal ligation and puncture, DMSO; Dimethyl sulfoxide, AST; Aspartate transaminase, ALT; Alanine transaminase, IL-6; Interleukin-6, ICAM-1; Intercellular adhesion molecule-1. *$P < 0.05$, **$P < 0.01$, ***$P<0.001$.

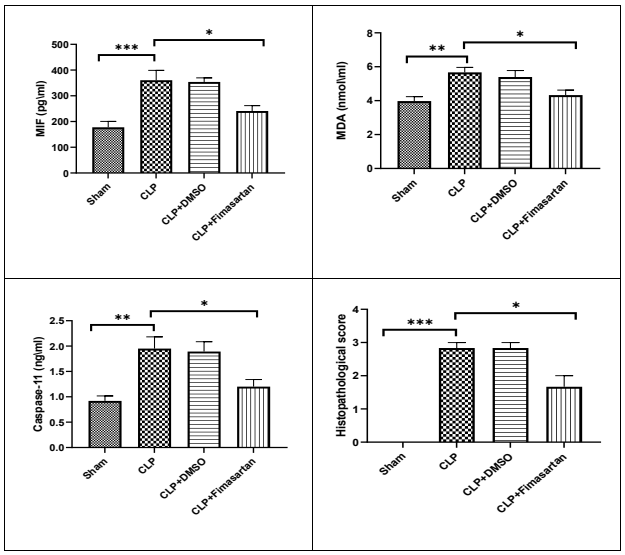

Figure 2. The effect of fimasartan on MIF, MDA, caspase11, and liver injury score. DMSO; Dimethyl sulfoxide, LC3; microtubule-associated protein 1A/1B-light chain 3, SOD; Superoxide dismutase. *$P < 0.05$, **$P < 0.01$, ***$P<0.001$.

subjected to CLP exhibited severe damage, marked by pronounced inflammation, apoptotic bodies, pyknosis, and necrosis, in stark contrast to the normal tissue architecture observed in the sham group. Notably, treatment with fimasartan led to a significant attenuation of these histopathological changes, indicating a protective effect against CLP-induced liver injury. This reduction in tissue damage suggests that fimasartan may mitigate the inflammatory and apoptotic processes triggered by CLP, thereby preserving liver integrity (Figure 4 A-E).

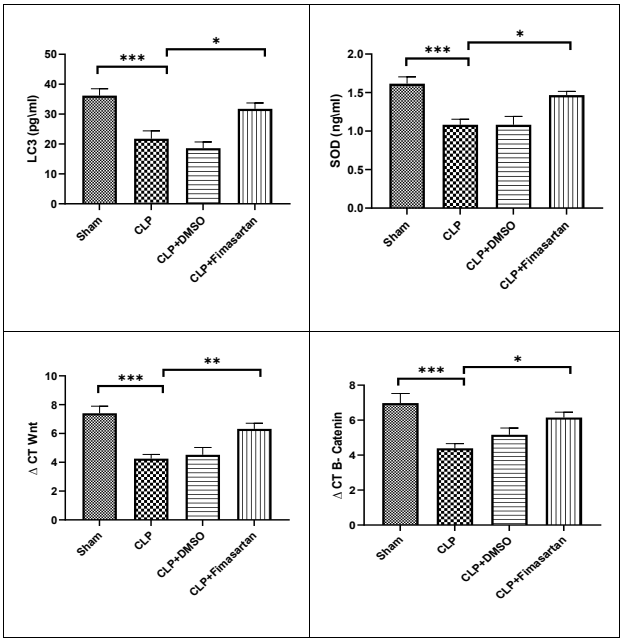

Figure 3. The effect of fimasartan on LC3, SOD, and Wnt/β-catenin. CLP; Cecal ligation and puncture, DMSO; Dimethyl sulfoxide, LC3; microtubule-associated protein 1A/1B-light chain 3, SOD; Superoxide dismutase. *$P < 0.05$, **$P < 0.01$, ***$P<0.001$.

Discussion

In our study, fimasartan was administered to mitigate sepsis-induced liver injury. Pretreatment with fimasartan significantly reduced serum ALT and AST levels compared to the CLP group, demonstrating its potential hepatoprotective properties. This protective effect may stem from fimasartan's antagonism of angiotensin II type 1 (AT1) receptors, which reduced hepatic tissue deterioration (18,19). Angiotensin II plays a significant role in the production of pro-inflammatory mediators and ROS (20). This process leads to inflammation and oxidative stress, which can cause tissue damage (21). Additionally, inhibiting angiotensin II has been shown to reduce the levels of various pro-inflammatory mediators (22).

Interleukin-6 plays a significant role in tissue injury and inflammation, ultimately leading to apoptosis (23). Our study found that fimasartan significantly reduced IL-6 levels compared to the CLP group. This result aligns with a recent study by Abbas et al (16) and Cho et al (24), which demonstrated that fimasartan effectively lowers IL-6 levels in renal tissue during ischemia-reperfusion. Particularly, Abbas et al showed that fimasartan treatment maintained normal kidney morphology and significantly lowered the levels of proinflammatory cytokines, including IL-6, compared to control and vehicle-treated groups (16). Similarly, Cho et al found that high-dose fimasartan treatment attenuated the upregulation of tumor necrosis factor (TNF)-α, IL-1β, and IL-6 in ischemic kidneys (24). This protective mechanism appears particularly relevant in the context of the CLP model, which induces

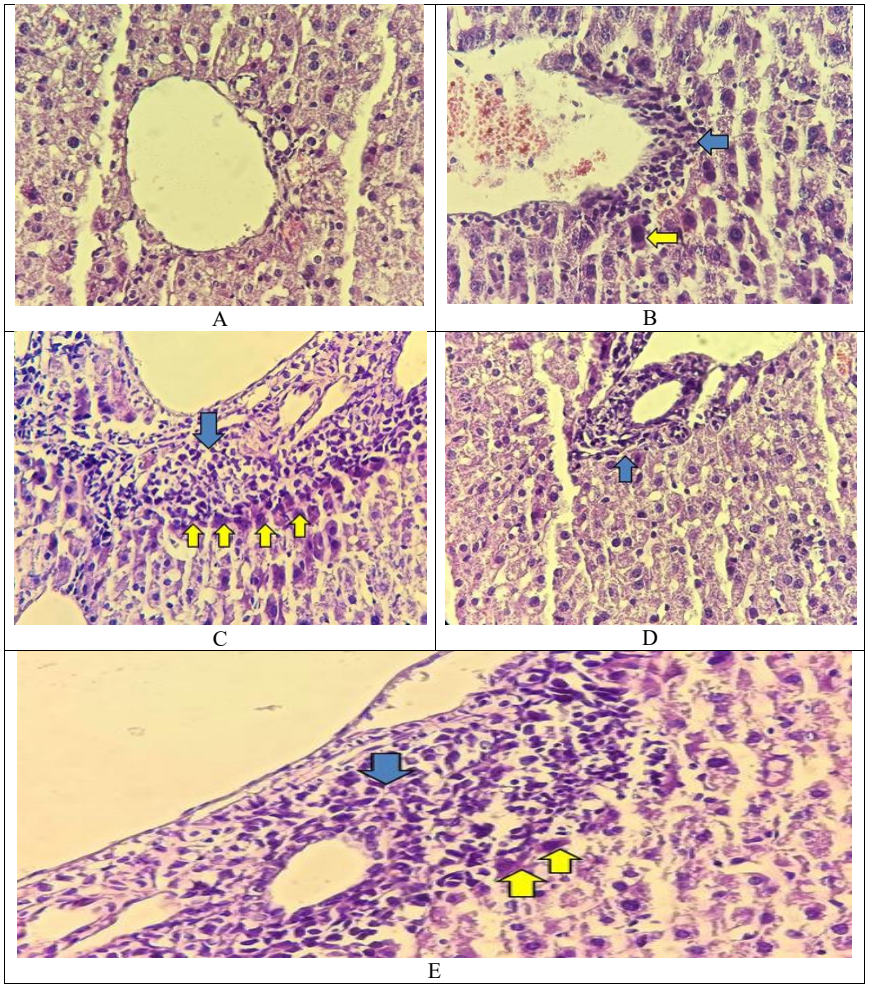

Figure 4. Histopathological examination of liver tissues from mice in the sham group, the CLP group, and the fimasartan-treated group. A) Representative image of score 0 of hepatic tissue for the sham group demonstrated intact lobular structure and hepatic plates, with no evidence of necrosis or inflammation seen (H&E ×400). B) A representative image of score 3 of hepatic tissue for DMSO group demonstrated severe centrilobular chronic inflammatory cell infiltration (blue arrow), with focal areas of hepatocyte nuclear pyknosis and cytoplasmic eosinophilia (apoptotic bodies) in the interface area with necrosis (yellow arrows) (H&E ×400). C) A representative image of score 3 of hepatic tissue for CLP group demonstrated severe periportal chronic inflammatory cell infiltration (blue arrow), with focal areas of hepatocyte nuclear pyknosis and cytoplasmic eosinophilia (apoptotic bodies) and necrosis in the interface area (yellow arrows) (H&E ×400). D) A representative image of score 1 of hepatic tissue for fimasartan group demonstrated mild periportal chronic inflammatory cell infiltration (blue arrow) (H&E ×400). E) A representative image of score 2 of hepatic tissue for fimasartan group demonstrated moderate periportal chronic inflammatory cell infiltration (blue arrow), with focal areas of hepatocyte nuclear pyknosis and cytoplasmic eosinophilia (apoptotic bodies) in the interface area (yellow arrows) (H&E ×400)

polymicrobial sepsis, a condition where IL-6 serves as both a marker and mediator of severity (25).

We also investigated the effect of fimasartan on the pro-inflammatory marker MIF in cases of sepsis and the results showed that administration of fimasartan significantly lowered serum levels of MIF. This inhibition of MIF notably reduced the production of ROS and nitric oxide synthase (26). In addition, the administration of fimasartan significantly reduced hepatic ICAM-1 levels compared to the sepsis group. ICAM-1 is recognized as a critical factor that is elevated during sepsis, in conjunction with other pro-inflammatory mediators. The increase in ICAM-1 contributes to a pro-coagulation state and the recruitment of polymorphonuclear leukocytes, ultimately leading to necrosis and apoptosis of endothelial cells (27). This finding aligns with a previous study by Hong et al that documented fimasartan's ability to decrease ICAM-1 levels in mice with carotid injury (28). This result further supports fimasartan's potential therapeutic applications beyond hypertension management, particularly in conditions where inflammatory processes contribute to disease pathogenesis. The established safety profile of fimasartan, combined with its demonstrated efficacy in blood pressure reduction and organ protection, makes it an attractive candidate for treating conditions with underlying inflammatory components (29,30). These findings warrant further investigation into fimasartan's effects on specific inflammatory mediators in various clinical settings to fully elucidate its therapeutic potential.

To investigate the role of pyroptosis in liver injury induced by the CLP procedure, we assessed the levels of caspase-11 in hepatic tissue. Our results demonstrated a significant increase in hepatic caspase-11 levels associated with the CLP procedure, which is consistent with findings

from previous studies (17). Pretreatment with fimasartan demonstrated a significant reduction in hepatic caspase-11 levels, a finding that has not been previously explored in the literature. It is well-documented that lipid peroxidation leads to increased production of ROS, which can cause severe mitochondrial damage in hepatocytes, ultimately resulting in apoptosis or necrosis (31,32). Additionally, to evaluate the role of oxidative damage, we measured MDA levels alongside the activity of the antioxidant enzyme SOD. Our findings indicated that fimasartan significantly reduced MDA levels and increased SOD activity in treated mice. These results are consistent with a previous study that reported fimasartan markedly decreased renal MDA levels while elevating SOD activity in a rat model of nephrotoxicity (33). Moreover, the present study found that fimasartan significantly increased LC3 autophagy levels compared to the CLP group. To date, no previous studies have specifically examined the impact of fimasartan on LC3 autophagy. Autophagy plays a protective role in preventing liver failure by degrading damaged mitochondria and inhibiting apoptosis. Notably, blocking the autophagy process in the liver has been shown to accelerate death in septic mice, highlighting its critical role in survival during sepsis (34).

The most notable finding in our study was the significant elevation of Wnt/β-catenin levels in the liver tissue of mice subjected to the CLP procedure compared to the sham group. The upregulation of the canonical Wnt pathway was linked to an increase in pro-inflammatory cytokine production and a decrease in anti-inflammatory cytokine production (35). Fimasartan administration significantly reduced the expression of Wnt and β-catenin, maintaining these levels close to those observed in the sham group. This is a novel finding, as no prior studies have examined the effect of fimasartan on the hepatic Wnt/β-catenin signaling pathway during sepsis. Elevated Wnt/β-catenin signaling has been implicated in sepsis-induced inflammation and organ injury, with studies showing that its inhibition reduces inflammation and tissue damage. For instance, β-catenin inhibitors have been shown to alleviate inflammatory responses and improve outcomes in sepsis models by reducing cytokine production and tissue damage (10,36). Furthermore, while losartan, a different angiotensin receptor blocker, has been reported to inhibit Wnt pathway activation in a rat model of atrial fibrillation, this study highlights fimasartan's potential to modulate this pathway specifically in the context of sepsis (37). These findings suggest that targeting the Wnt/β-catenin signaling pathway with fimasartan may offer therapeutic benefits for managing sepsis-induced inflammation and organ injury, warranting further investigation into its mechanisms and broader clinical applications.

Finally, our findings revealed that pretreatment with fimasartan significantly lowered the histopathological score of tissue injury. This improvement is likely due to its ability to block AT1 receptors, along with its effects on reducing oxidative stress, suppressing inflammation, and regulating apoptotic markers (16,18).

Overall, the findings suggested that fimasartan exhibits significant hepatoprotective effects in sepsis-induced liver injury, positioning it as a potentially valuable therapeutic agent in this context. This conclusion aligns with broader evidence that angiotensin receptor blockers (ARBs) can mitigate liver damage by modulating the renin-angiotensin-aldosterone system, reducing oxidative stress, inflammation, and apoptosis. However, contrasting data highlight concerns about fimasartan's hepatotoxicity in certain patients, as rare cases of drug-induced liver injury have been documented, with delayed onset compared to other ARBs. These cases underscore the need for careful monitoring of liver function during fimasartan use, particularly in individuals with underlying liver conditions or a history of sensitivity to ARBs. In conclusion, while fimasartan's hepatoprotective potential in sepsis is promising, its safety profile warrants further investigation to balance its therapeutic benefits against the risk of adverse effects.

Conclusion

In conclusion, this study provides compelling evidence for the hepatoprotective effects of fimasartan in sepsis-induced liver injury. The results demonstrate that the CLP procedure induces significant hepatic damage, as evidenced by elevated liver enzymes (ALT and AST), pro-inflammatory mediators (IL-6, ICAM-1, and MIF), oxidative stress marker (MDA), and inflammatory cell death pathway activation (caspase-11), accompanied by histologically confirmed liver injury. Fimasartan treatment effectively attenuated these detrimental changes, suggesting potent anti-inflammatory and hepatoprotective properties. Furthermore, the ability of fimasartan to reverse CLP-induced reductions in autophagy marker LC3, antioxidant enzyme SOD, and Wnt/β-catenin signaling activity indicates multiple mechanisms of action through which fimasartan confers liver protection during sepsis. These findings highlight fimasartan, an angiotensin II receptor blocker, as a potential therapeutic agent for sepsis-associated liver dysfunction, a significant cause of morbidity and mortality in sepsis patients. The multi-faceted protective effects observed, encompassing anti-inflammatory, antioxidant, and cell-signaling pathway modulation, suggest that fimasartan may offer broader protective benefits beyond its established antihypertensive effects, warranting further investigation into its potential clinical applications for sepsis management.

Limitations of the study

The use of a murine model may limit the generalizability of the findings to human patients, as physiological differences between species can affect drug metabolism and response. Additionally, the sample size of 24 male albino Swiss mice may not provide sufficient statistical

power to detect subtle effects or variations in response to fimasartan treatment. The study also employed a single dose of fimasartan administered one hour before CLP, which may not accurately reflect clinical scenarios where dosing regimens and timing can vary significantly.

Authors' contribution

Conceptualization: Adhwaa M. Al-Shimary and Ali M. Janabi.
Data curation: Adhwaa M. Al-Shimary.
Formal Analysis: Carsten Ehrhardt.
Investigation: Adhwaa M. Al-Shimary and Carsten Ehrhardt.
Methodology: Ali M. Janabi and Carsten Ehrhardt.
Project Management: Ali M. Janabi.
Resources: All authors.
Supervision: Ali M. Janabi and Carsten Ehrhardt.
Validation: Ali M. Janabi.
Writing–original draft: Adhwaa M. Al-Shimary.
Writing–reviewing and editing: All authors.

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), Kufa University, Iraq (Ethical code #20549). We 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).

Conflicts of interest

The authors declare no conflict of interest.

Funding/Support

The authors did not receive any source of funding.

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