

Original Research Article

Gemigliptin attenuates hepatic damage in cecal ligation and puncture sepsis in mice

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Sent for review: 29 April 2026

Revised accepted: 22 July 2026

Abstract

Purpose: To investigate the hepatoprotective benefit of gemigliptin in limiting sepsis-induced hepatic injury.

Methods: A total of 24 male Albino Swiss mice were randomly assigned into 4 groups (n = 6). Group 1 was control; mice underwent laparotomy without cecal ligation and puncture (CLP), group 2 underwent CLP, group 3 received dimethyl sulfoxide (DMSO) 1 h before CLP induction, and group 4 received gemigliptin (30 µg/g) intraperitoneally, 1 h before CLP. After 24 h, the mice were euthanized, and serum AST and ALT levels were determined. Also, liver tissues were assessed for biomarkers like NF-κB, MDA, caspase-3, and p-mTOR. Histological examination of hepatic tissues was conducted using hematoxylin and eosin (H & E) stain.

Results: ALT, AST, NF-κB, MDA, caspase-3, and hepatic damage scores were significantly higher compared to control following CLP induction. Furthermore, treatment with gemigliptin significantly lowered serum ALT, AST, NF-κB, MDA, caspase-3 and hepatic damage scores. Also, gemigliptin significantly decreased p-mTOR levels compared to groups 2 and 3.

Conclusion: Gemigliptin significantly reduces serum ALT, AST, NF-κB, MDA, caspase-3, hepatic damage scores, and p-mTOR levels when compared with group 2 or group 3.

Keywords: Cecal ligation and puncture, Gemigliptin, Liver, Oxidative stress, p-mTOR

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INTRODUCTION

Sepsis is an extensive inflammatory reaction to infections, often regarded as the primary cause of death among patients in emergency departments worldwide [1]. Sepsis is considered the main cause of mortality, surpassing cancer and cardiovascular illnesses in certain situations, and increases the costs of healthcare in intensive care units [2]. Previous studies have established that sepsis is the predominant reason for death in non-coronary critical care units [3]. Several factors, including an uncontrolled inflammatory

response, antibiotic resistance, and poor anti-infection therapy, are linked to high death rates from severe sepsis in critical care units [4]. Sepsis adversely affects various body organs, like the hepatic, neural, cardiac, renal, and pulmonary tissues [5]. The liver is structurally unique, has a rich blood supply, and performs several activities, such as cytokine synthesis, coordination of immunological responses, and bacterial elimination, serving as a pivotal center for regulating immunity and inflammation [6]. Sepsis-induced liver injury (SILI) is a type of secondary liver damage characterized by hepatic

dysfunction, abnormal liver biochemistry results, and increased risk of liver failure [7]. In hospitals, sepsis leads to many hepatic diseases, like septic cholestasis, hypoxic hepatitis, and secondary sclerosing cholangitis [8]. Autophagy is crucial for maintaining cellular balance by breaking down long-lived proteins and injured organelles in response to external stimuli [9]. Recent findings indicated that autophagy stimulation mitigates apoptosis and enhances the recovery process from hepatic injury [10]. The mammalian target of rapamycin kinase (mTOR), a crucial autophagy controller, is suppressed to initiate autophagy [11]. Oxidative stress and inflammation are closely interconnected pathways, with inflammation representing the earliest response during the initial stages of sepsis. Reactive oxygen species (ROS) are generated as a result of this inflammatory reaction. Excessive ROS generation contributes to liver injury by initiating and amplifying inflammatory processes, leading to increased production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) [12]. Multiple studies have demonstrated that nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is crucial in the progression of multiple organ damage caused by sepsis [13]. Also, raised NF- κ B expression has been associated with sepsis-induced hepatic damage [14]. Inflammation linked to sepsis also induces cellular apoptosis [15], and suppression of caspase-3 activity significantly mitigates liver impairment generated by sepsis [16]. Gemigliptin is a strong, specific, and long-lasting dipeptidyl peptidase-4 (DPP-4) inhibitor [17]. It was introduced by LG Life Sciences (Seoul, Korea) and received approval from the Ministry of Food and Drug Safety in June 2012 for the management of type II diabetes mellitus (T2DM) [18]. A previous animal study has shown that suppression of DPP-4 by gemigliptin provides renoprotective effects against cisplatin-associated nephropathy in mice by reducing renal tubular cell death and inflammatory responses [19]. Also, gemigliptin had a cardioprotective effect against ischemia/reperfusion injury by significantly decreasing infarct size and improving heart function. Protective benefits were primarily independent of glycemic management and attributed to antioxidative and cardioprotective mechanisms [20]. Despite these benefits, the possible therapeutic effect of gemigliptin in sepsis-induced hepatic damage using the cecal ligation and puncture (CLP) model is poorly reported. Hence, this study investigated the hepatoprotective benefit of gemigliptin in limiting sepsis-induced hepatic injury.

EXPERIMENTAL

Animals

A total of 24 adult male Swiss Albino mice (8 – 12 weeks, 22 – 35 g) were randomly and equally assigned into 4 groups (n = 6). The animals were procured from the Animal House Facility at the Faculty of Pharmacy, University of Kufa. All animals were kept under standardized laboratory conditions (24 ± 2 °C, ambient humidity of 55 – 63 %, and a 12 h light / dark cycle). Each animal was housed individually in distinct cages, with free access to standard feed and potable water throughout the study period. Ethical approval was obtained from the Institutional Animal Care and Use Committee (IACUC), University of Kufa (approval no: 2365), and the study complied with the internationally accepted guide for the care and use of laboratory animals [21].

Drug preparation

Gemigliptin (Targetmol®) is soluble in DMSO at 122.5 mg/mL and was freshly prepared before administration. The dose was given intraperitoneally at 30 μ g/g body weight.

Study design

Following a 7-day initial adaptation, a total of 24 adult Swiss Albino mice were divided into 4 groups (n = 6) using the block randomization technique with an open-label framework. Under anesthesia, group 1 (control) underwent laparotomy without cecal ligation and puncture (CLP). To create an acute liver injury (ALI) model, the CLP approach was used for induction (group 2). One hour before CLP surgery, a single intraperitoneal injection of DMSO in an equivalent volume was administered to group 3. Based on a prior study, group 4 received one intraperitoneal dose of gemigliptin (30 μ g/g) 1 h before CLP induction [22].

Technique

The cecal ligation and puncture (CLP) procedure was utilized to create sepsis. The mice were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) [23]. The abdominal wall of each mouse was shaved and disinfected with 10 % povidone-iodine solution, followed by a midline incision of 1 – 1.5 cm. The cecum was carefully exposed, tied beneath the ileocecal valve, and subjected to a dual puncture, and a minimal quantity of feces was expelled through the two apertures. The cecum was subsequently repositioned anatomically, and the abdominal wall was closed. Thereafter, normal saline (20

mL/kg body weight) was administered to compensate for fluid loss and maintain hydration during the procedure [24].

Sampling techniques

Twenty-four hours after CLP operation, the animals were euthanized, and tissue and blood specimens were obtained.

Blood specimen collection

Blood samples (1 mL) were collected by direct cardiac puncture following euthanasia, 24 h after CLP, from each animal. The samples were transferred into gel tubes and centrifuged at 6,000 rpm for 10 min to separate the serum. Serum ALT and AST levels were then measured spectrophotometrically.

Tissue sample collection

The liver of mice was excised 24 h after CLP operation and split in two. The first part of the liver was used for histopathology, while the second part of the tissue was homogenized and frozen at -80 °C to determine the levels of NF- κ B (Cat. No. SL0723Mo), caspase-3 (Cat. No. SL0679Mo), MDA (Cat. No. SL0370Mo), and p-mTOR (Cat. No. SL1130Mo) using enzyme-linked immunosorbent assay (ELISA) with the various kits from SunLong Biotech Co., China.

Tissue preparation for histopathology

Following euthanasia, the liver was collected and rinsed with normal saline to remove residual blood and clots. The samples were then fixed in 10 % formalin, dehydrated through graded alcohol, cleared with xylene, and embedded in paraffin to form tissue blocks. Sections of 5 μ m thickness were prepared from these blocks and stained with hematoxylin and eosin (H & E). Histopathological alterations of hepatic tissues were scored according to the Batts-Ludwig scoring (necro-inflammatory activity grade). Grade 0 indicated no portal, periportal, and lobular activity; grade 1 (minimal patchy or infrequent), grade 2 (mild: some or all portal tract) with lobular activity, mild hepatocyte injury, grade 3 (moderate: all portal tracts), moderate lobular activity, and grade 4 (severe: may have bridging fibrosis) [25].

Enzyme-linked immunosorbent assay (ELISA)

Each hepatic sample was weighed after cleaning with cold phosphate-buffered saline (PBS). Each sample was treated with PBS comprising 1 % Triton X and 1 % protease inhibitor cocktail at a

1:9 (weight:volume) proportion. The samples were homogenized using a high-intensity ultrasonic processor and subsequently spun at 3,000 rpm for 20 min at 4 °C. Aliquots of the supernatants were transferred into new Eppendorf tubes for the determination of NF- κ B, caspase-3, MDA, and p-mTOR levels using ELISA kits (SunLong Biotech Co., China).

Liver function tests

Serum AST and ALT were quantified spectrophotometrically.

Statistical analysis

Data were analyzed using GraphPad Prism (version 10.6.1; USA) and presented as mean $\pm$ standard error of the mean (SEM). One-way analysis of variance (ANOVA) and Bonferroni test were employed for multiple group comparisons. Kruskal–Wallis nonparametric test and Dunn's multiple comparisons test were used to assess histological variations among the groups. $p < 0.05$ was considered statistically significant.

RESULTS

Liver function

Serum levels of AST and ALT were significantly higher in groups 2 and 3 compared to group 1 ($p < 0.05$). However, there was no significant difference in serum AST and ALT levels between groups 2 and 3 ($p > 0.05$). Further treatment with gemigliptin significantly reduced serum AST and ALT levels compared to group 2 ($p < 0.05$; Figure 1).

Effect on NF- κ B marker

Groups 2 and 3 showed significantly higher NF- κ B compared to control ($p < 0.05$). There was no significant difference in NF- κ B between groups 2 and 3 ($p > 0.05$). Furthermore, treatment with gemigliptin significantly decreased NF- κ B levels within hepatic tissues compared to group 2 ($p < 0.05$; Figure 2).

Level of MDA

Groups 2 and 3 showed significantly higher hepatic tissue MDA concentrations compared to control ($p < 0.05$). However, there was no significant difference in MDA level between groups 2 and 3 ($p > 0.05$). Treatment with gemigliptin significantly reduced hepatic tissue MDA concentration compared to groups 2 and 3 ($p < 0.05$; Figure 3).

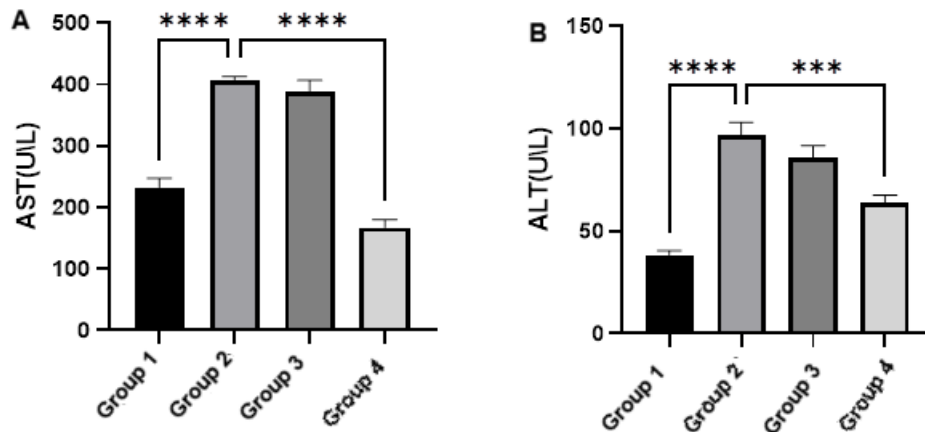


Figure 1: Serum AST and ALT levels. Group 1 (control), group 2 (CLP-induced), group 3 (CLP + DMSO), group 4 (CLP + gemigliptin). Data presented as mean $\pm$ SEM, *** p < 0.001, **** p < 0.0001 vs control

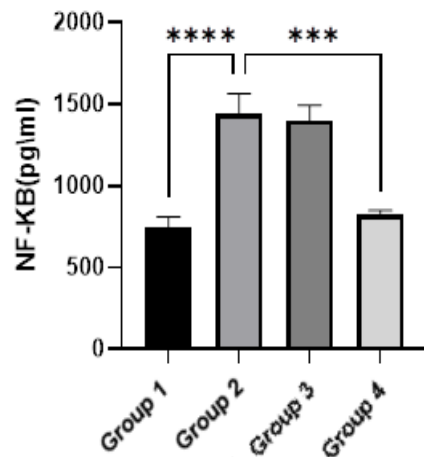


Figure 2: Hepatic NF-kB level. Group 1 (control), group 2 (CLP-induced), group 3 (CLP + DMSO), group 4 (CLP + gemigliptin). Data presented as mean $\pm$ SEM, *** p < 0.001, **** p < 0.0001 vs control

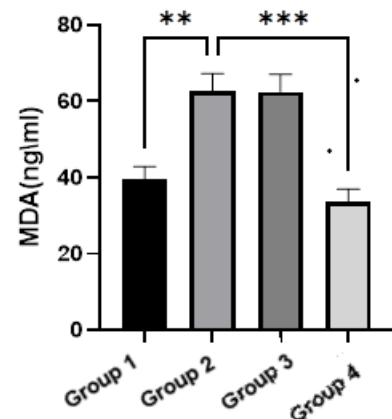


Figure 3: Level of hepatic MDA. Group 1 (control), group 2 (CLP-induced), group 3 (CLP + DMSO), group 4 (CLP + gemigliptin). Data expressed as mean $\pm$ SEM, ** p < 0.01, *** p < 0.001 vs control

Level of caspase-3 marker

Groups 2 and 3 showed significantly higher levels of caspase-3 compared to control group (p < 0.05). There was no significant difference in level of caspase-3 between groups 2 and 3 (p > 0.05). Furthermore, treatment with gemigliptin significantly reduced level of caspase-3 compared to groups 2 and 3 (p < 0.05; Figure 4).

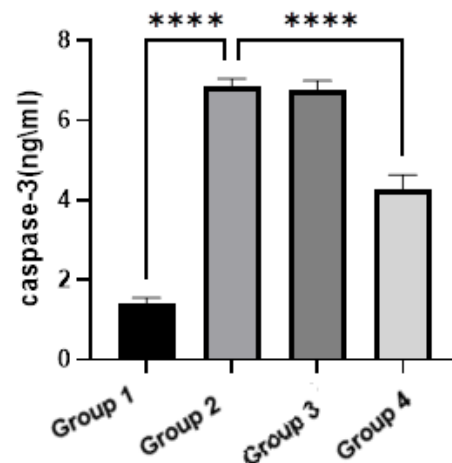


Figure 4: Level of hepatic caspase-3. Group 1 (control), group 2 (CLP-induced), group 3 (CLP + DMSO), group 4 (CLP + gemigliptin). Data expressed as mean $\pm$ SEM, **** p < 0.0001 vs control

Level of p-mTOR

Groups 2 and 3 showed significantly lower p-mTOR levels compared to control (p < 0.05), and no significant difference between groups 2 and 3 (p > 0.05). Treatment with gemigliptin significantly decreased p-mTOR levels compared to groups 2 and 3 (p < 0.05; Figure 5).

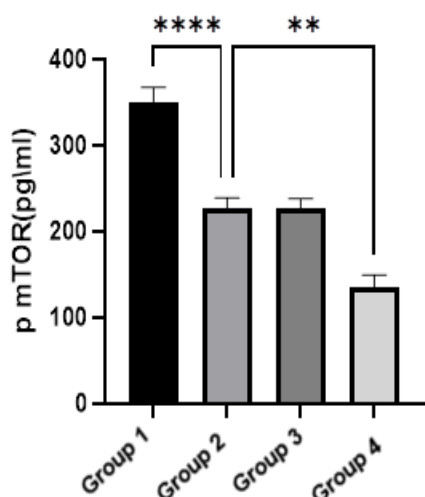


Figure 5: Level of hepatic p-mTOR. Group 1 (control), group 2 (CLP-induced), group 3 (CLP + DMSO), group 4 (CLP + gemigliptin). Data expressed as mean $\pm$ SEM, ** $p < 0.01$, **** $p < 0.0001$ vs control

Histopathological evaluation

Histopathological examination indicated that liver tissues of group 2 (Figure 6 A) and 3 (Figure 6 B) showed significant tissue damage, pronounced inflammation, and vascular congestion, as opposed to the typical hepatic architecture of group 1 (Figure 6 C). Treatment with gemigliptin significantly lowered histological damage induced by CLP (Figure 6 D).

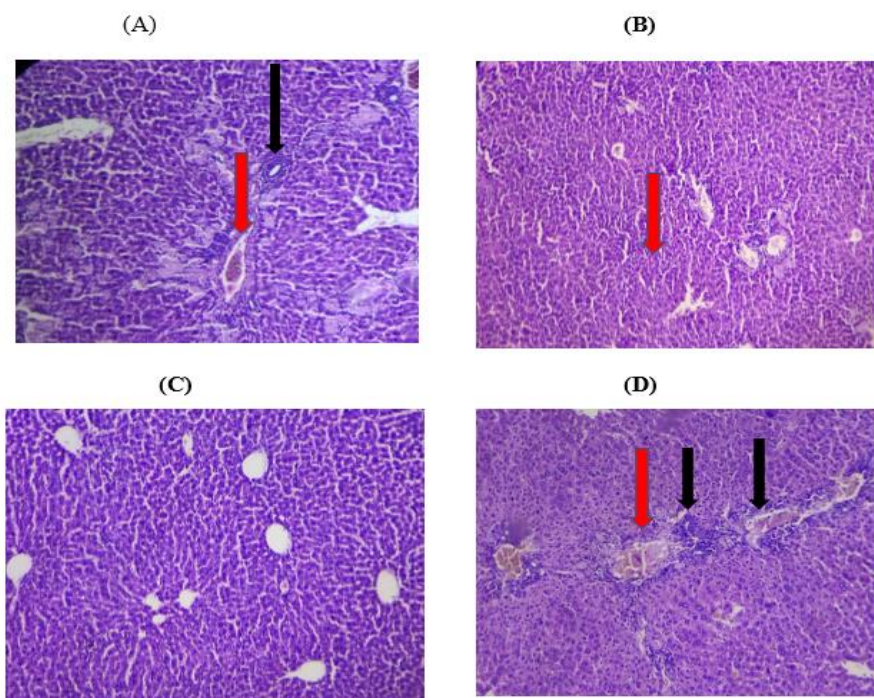


Figure 6: Histopathological findings. Necro-inflammatory grade for group 1 (C) was 0, group 2 (A) was 3, group 3 (B) was 2 group 4 (D) was 0. Liver tissue with vascular congestion (red arrow) and inflammation (black arrow)

DISCUSSION

Sepsis is a critical health disorder characterized by elevated death rates due to abnormal immunological response to infection, resulting in damage to multiple organs, including the liver [26]. Sepsis continues to be a major clinical challenge in hospitals due to high occurrence and mortality rates. Despite advances in sepsis management, including antimicrobial therapy and supportive treatments, there is still a lack of specific therapies targeting organ damage. The liver, as a key organ responsible for detoxifying endogenous and exogenous substances, is particularly affected during sepsis and is of particular concern [27]. Sepsis-induced liver injury (SILI) is defined as hepatic injury resulting from sepsis, through either direct or indirect mechanisms, potentially resulting in biochemical alterations, liver damage, or hepatic failure [28]. The liver is a crucial organ that significantly influences the progression of sepsis, and improving hepatic function has been associated with decreased death rates [29]. Gemigliptin was used in this study to alleviate sepsis-induced hepatic damage. Pretreatment with gemigliptin significantly lowered serum AST and ALT concentrations compared to group 2 (CLP group), indicating its possible protective effects on the liver. This protective benefit may be attributed to improved mitochondrial function and inhibition of reactive oxygen species (ROS) generation [30].

This study revealed that NF- κ B was significantly higher in group 2 compared to control. This finding is consistent with a previous study demonstrating that NF- κ B is elevated following ischemia-reperfusion injury to the kidney in a rat model [31]. NF- κ B plays a crucial role in myocardial ischemia/reperfusion damage, tissue damage, and inflammation [32]. The study revealed that gemigliptin significantly reduced NF- κ B concentrations compared to group 2, which is in agreement with a previous study [33].

The study further showed that gemigliptin significantly reduced hepatic MDA levels. Elevated MDA concentration is associated with coronary heart disease, with a high diagnostic accuracy as a non-invasive biomarker of oxidative stress for assessing disease progression and cardiovascular risk in patients with coronary artery disease (CAD). These findings suggest that the reduction in MDA levels following gemigliptin treatment may reflect its antioxidant potential to mitigate oxidative damage associated with sepsis [34].

A recent study indicated that DPP-4 inhibitors such as gemigliptin mitigated oxidative stress, using oxidative markers such as MDA, liver steatosis, inflammation, and fibrosis in CDAHFD-caused NAFLD mice [22]. To examine the effect of apoptosis on hepatic damage relating to CLP induction, the concentrations of caspase-3 in liver tissues were examined. The results showed that hepatic caspase-3 concentrations were significantly higher following CLP induction compared to control. A recent study demonstrated that elevated blood caspase-3 concentrations were significantly correlated with higher early death in individuals with severe spontaneous intracerebral hemorrhage, signifying increased apoptotic activity and poorer clinical outcomes [35].

A new study utilizing a rat model of thioacetamide-related hepatic fibrosis revealed that gemigliptin administration significantly inhibited hepatocyte apoptosis by modulating the caspase-3 pathway, resulting in decreased caspase-3-mediated cell death. The findings indicated that the anti-fibrotic activity of gemigliptin involves a reduction of caspase-3 activation, hence enhancing its protective function against hepatic injury [36].

Another significant finding was the reduction of p-mTOR concentrations in hepatic tissue of mice following CLP induction compared to control. Inhibition of the p-mTOR pathway is associated with accelerated autophagy in cecal ligation and puncture, resulting in myocardial diseases [37].

In this study, p-mTOR level was significantly lower in the gemigliptin-treated group compared to the CLP group. This finding is in agreement with a previous study that showed that sitagliptin (another DPP-4 inhibitor) enhances heart function, regulates glucose balance, mitigates β -cell dysfunction, and reduces p-mTOR activation in obese female mice [38]. Another study demonstrated that sitagliptin significantly ameliorates the development of hepatic steatosis and insulin resistance in a murine model by inhibiting inflammatory responses and decreasing p-mTOR levels [39]. Following treatment with gemigliptin, a further decrease in p-mTOR levels was observed. This represents a unique discovery, as no previous study has assessed the effect of gemigliptin on the liver p-mTOR pathway during cecal ligation and puncture-related sepsis in mice. However, further studies are needed to clarify the potential role of the p-mTOR pathway in hepatoprotective effects. In a more recent study, vildagliptin demonstrated hepatoprotective effects in sepsis-induced hepatic damage in a murine model [40], consistent with findings of the present study. Furthermore, this study showed that pretreatment with gemigliptin significantly reduced the histological score of tissue damage. This enhancement may be due to its capacity to diminish oxidative stress and mitigate inflammation, hepatic steatosis, fibrosis, and regulate apoptotic markers [22,36]. Therefore, gemigliptin showed significant hepatoprotective effect in sepsis-associated liver damage. This supports the idea that DPP-4 inhibitors reduce oxidative stress, inflammation, and apoptosis, preventing hepatic damage.

Limitations of the study

The study has some limitations. The study was limited to the evaluation of a single dose of gemigliptin, precluding the assessment of dose-response relationships and the therapeutic implications of delayed administration. The assessment conducted 24 h after CLP induction provided insights into early hepatic alterations; however, it did not account for long-term effects such as mortality or the progression of severe liver damage. Although gemigliptin exhibited potential hepatoprotective activity in sepsis, its safety profile requires more examination and should be pursued in future studies.

CONCLUSION

Treatment with gemigliptin alleviates sepsis-induced hepatic damage by reducing inflammatory markers, p-mTOR, oxidative stress,

suppressing apoptosis, and preserving hepatic integrity.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

Ethical approval for this study was obtained from the Institutional Animal Care and Use Committee (IACUC) of the University of Kufa (approval no. 2365).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Use of AI

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors contributed equally to this article. Abeer A. Alsabak was responsible for data collection, statistical analysis, and drafting the manuscript. Ali M. Janabi contributed to the main idea, study design, and critical revision of the manuscript.

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