Al-killidar *et. al.,* Babcock Univ. Med. J.2025 8(2):217-225
https://doi.org/10.38029/babcockuniv.med.j..v8i2.1021
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Empagliflozin attenuates inflammation and myocardial injury in a murine model of sepsis

Al-killidar SM[1], Muhammad-Baqir BM[2]ID

[1]*Southern Primary Health Sector in Najaf, Iraq*
[2]*Department of Clinical Pharmacy, Faculty of Pharmacy, University of Kufa, Iraq*

Submitted: 1st April 2025
Accepted: 11th July 2025
Published: 31st December 2025
ID: Orcid ID

Abstract
Objective: This study aimed to evaluate the cardioprotective and anti-inflammatory effects of Empagliflozin in a murine model of polymicrobial sepsis induced by caecal ligation and puncture (CLP).
Methods: Thirty-five male Swiss albino mice were randomly assigned into five groups (n = 7): control, sham, sepsis, vehicle (DMSO), and Empagliflozin (10 mg/kg/day for 3 days, intraperitoneally). Sepsis was induced via CLP. Blood and cardiac tissues were collected 24 hours post-CLP for analysis. Serum cardiac troponin I (cTn-I) and tissue levels of NF-κB, TNF-α, and FoxO3 were measured using ELISA. Histopathological evaluation of cardiac tissues was conducted and scored using a standardised injury scale.
Results: The sepsis and vehicle groups showed significantly elevated levels of cTn-I (4.13 ± 0.32 ng/mL and 4.08 ± 0.29 ng/mL), NF-κB, TNF-α, and FoxO3 compared to the control and sham groups (all $p < 0.01$). Empagliflozin treatment significantly reduced these markers (cTn-I: 2.15 ± 0.22 ng/mL; $p = 0.012$ vs. sepsis). Histologically, Empagliflozin-treated hearts showed reduced myocardial damage (score: 1.14 ± 0.18) compared to the sepsis (3.14 ± 0.26) and vehicle (3.00 ± 0.24) groups.
Conclusion: Empagliflozin attenuated cardiac inflammation and injury in a mouse model of sepsis. These preclinical findings support further mechanistic research and warrant clinical investigation of Empagliflozin as a potential adjunctive therapy in septic cardiomyopathy.

Keywords: Empagliflozin, Sepsis-induced cardiomyopathy, Cecal ligation and puncture (CLP), Inflammation, FoxO3

Plain English Summary

Sepsis is a life-threatening condition caused by an overwhelming response to infection, often leading to damage in vital organs like the heart. This study tested whether Empagliflozin, a drug commonly used to treat type 2 diabetes, could help protect the heart during sepsis in mice. The researchers gave Empagliflozin to mice before inducing sepsis and found that it lowered key markers of heart damage and inflammation. Mice treated with Empagliflozin also had healthier heart tissue under the microscope compared to untreated mice. These results suggest that Empagliflozin might be useful in reducing heart injury in sepsis and could be studied further in human patients in the future.

Introduction

Sepsis is a major complication in critically ill patients with infections, trauma, burns, or shock. It arises from an imbalanced host response to infection and can lead to multi-organ failure and death (1). Globally, sepsis accounts for up to 19.7% of all fatalities, highlighting its significant burden on public health (2). Experimental models such as lipopolysaccharide (LPS) administration (3), intravenous pathogen injection (4), caecal ligation and puncture (CLP) (5), and colon ascendens stent peritonitis (6) have been developed to investigate sepsis pathophysiology and test potential therapeutic agents.

Sepsis can profoundly impair cardiac function, a condition termed septic cardiomyopathy. This is

Correspondence:
Al-killidar Safwa M
Southern Primary Health Sector in Najaf
Iraq
+9647807880777, Safwa.alkillidar@student.uokufa.edu.iq

driven by a cascade of events including the release of inflammatory cytokines (e.g., TNF-α), mitochondrial dysfunction, complement activation, oxidative stress, and apoptosis (7, 8). Among the numerous mediators involved in the septic response, cytokines, damage- and pathogen-associated molecular patterns (DAMPs and PAMPs), nitric oxide, and transcriptional factors such as NF-κB play central roles in driving inflammation and tissue damage (7). These mechanisms culminate in myocardial injury, often reflected by elevated levels of cardiac troponin I (cTn-I), a highly specific biomarker of cardiomyocyte damage (9).

Empagliflozin, a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, is approved for managing type 2 diabetes mellitus (10) and has demonstrated renal and cardiovascular protective effects beyond glycaemic control (11, 12). Clinical trials have shown that Empagliflozin reduces adverse cardiovascular outcomes, hospitalisations for heart failure, and cardiovascular mortality in patients with or without diabetes (13). Its cardioprotective effects are mediated through multiple mechanisms: improved myocardial energy efficiency via ketone utilisation (14, 15), reduced reactive oxygen species (ROS) production (16), decreased cardiac fibrosis (16, 17), and modulation of the sodium-hydrogen exchanger in the heart and kidney (18). Additionally, Empagliflozin has anti-inflammatory and anti-apoptotic effects, attributed in part to inhibition of NF-κB activation and suppression of cytokine production such as TNF-α (19, 20, 21, 22, 23, 24). It also influences transcriptional factors like FoxO3, which regulate immune function, oxidative stress response, autophagy, and programmed cell death (25).

Despite these known effects, the role of Empagliflozin in modulating sepsis-induced cardiac inflammation and injury remains underexplored. Most existing data focus on chronic cardiometabolic disease models or acute injury unrelated to sepsis (12, 16, 17). Moreover, while a few studies have shown reduced systemic inflammation with Empagliflozin in septic or LPS-induced models (19, 26, 27), the specific impact on cardiac biomarkers such as cTn-I, NF-κB, TNF-α, and FoxO3 in polymicrobial sepsis has not been systematically examined.

This study aims to evaluate the cardioprotective and anti-inflammatory effects of Empagliflozin in a mouse model of CLP-induced sepsis. By assessing myocardial injury and inflammation through biochemical and histological parameters, this study seeks to expand current understanding of Empagliflozin's therapeutic potential in acute septic states.

Materials and Methods

Animal Preparation

Thirty-five healthy male Swiss albino mice (30–35 g, 8–12 weeks old) were obtained from the Centre for Cancer Research in Iraq. Mice were housed in polypropylene cages under standard laboratory conditions (12-hour light/dark cycle, temperature 22–24 °C, humidity 60–65%) in the animal facility of the Faculty of Pharmacy, University of Kufa. Animals had unrestricted access to standard rodent chow and water throughout the study period, which spanned from October 19 to December 30, 2023.

Study Design

After a one-week acclimatisation, mice were randomly assigned to five groups (n = 7 per group). 1) Control group: Received no treatment or surgical procedure; served as baseline. 2) Sham group: Subjected to anaesthesia and laparotomy without CLP to control for surgical stress. 3) Sepsis group: Subjected to CLP without any pre-treatment to induce polymicrobial sepsis. 4) Vehicle group: Received dimethyl sulfoxide (DMSO, 1%, intraperitoneally) once daily for three days; final dose was administered 1 hour before CLP. 5) Empagliflozin group: Received Empagliflozin (10 mg/kg/day, intraperitoneally) for three consecutive days; final dose was given 1 hour before CLP (28). Dimethyl sulfoxide (DMSO) was used as the vehicle control because Empagliflozin is poorly soluble in aqueous solutions and was prepared in a minimal concentration of DMSO for intraperitoneal administration. The vehicle group thus controls for any potential effects of the solvent alone. The 10 mg/kg dosage of Empagliflozin was selected based on prior studies demonstrating its anti-inflammatory and cardioprotective effects in murine models (17, 26, 29).

The sample size (n = 7 per group) was determined through a priori power calculation using GPower software (version 3.1). Assuming an effect size of 1.5 for cytokine level changes (based on pilot data), an alpha level of 0.05, and a power of 0.80, a minimum of six animals per group was required. We included seven mice per group to account for potential experimental variability and dropout.

Cecal Ligation and Puncture (CLP) Procedure

Polymicrobial sepsis was induced via CLP as previously described (5, 30). Mice were anaesthetised with intraperitoneal ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (10 mg/kg) (30). After abdominal hair was shaved and disinfected with povidone-iodine, a 1–2 cm midline laparotomy was performed. The cecum was ligated just below the ileocecal valve using a 4-0 silk suture (Ethicon,

USA), avoiding intestinal obstruction. It was then punctured twice using a 22-gauge needle (BD PrecisionGlide®, USA), and a small amount of faecal content was extruded to ensure patency. The cecum was returned to the peritoneal cavity, and the incision was closed in two layers using 4-0 absorbable sutures. Postoperative resuscitation was achieved with 1 mL of 0.9% sterile saline injected subcutaneously.

Sample Collection and Preparation

Blood Samples

At 24 hours post-CLP, animals were anaesthetised and euthanised. Whole blood was collected via cardiac puncture and transferred to gel-containing serum tubes (without anticoagulant). Tubes were incubated at 37 °C for 30 minutes, then centrifuged at 4000 rpm for 20 minutes. The resulting serum was aliquoted and stored at −20 °C until analysis.

Cardiac troponin I (cTn-I) was quantified using ELISA kits (Mouse cTnI ELISA Kit, Cat. No. E-EL-M0043, Elabscience, China), following the manufacturer's instructions.

Heart Tissue Samples

Hearts were excised, washed in ice-cold PBS, and weighed. Each heart was bisected transversely:

The upper half was fixed in 10% buffered formalin for histology.

The lower half was washed, homogenised (1:10 w/v) in PBS with 1% Triton X-100 and protease inhibitor cocktail using a high-intensity ultrasonic processor (QSonica, USA), then centrifuged at 12,000 rpm for 15 minutes at 4 °C.

Supernatants were used to measure ELISA kits, as seen in Table 1.

Table 1: Supernatants for ELISA Kits

Marker	Kit Name	Catalogue No.	Manufacturer
NF-κB	Mouse NF-κB ELISA Kit	E-EL-M0664	Elabscience
TNF-α	Mouse TNF-α ELISA Kit	E-EL-M0049	Elabscience
FoxO3	Mouse FoxO3 ELISA Kit	MBS2515122	MyBioSource

Histological Evaluation

Formalin-fixed heart tissues were embedded in paraffin, sectioned at 5 µm using a rotary microtome, and stained with haematoxylin-eosin (H&E) and Masson's trichrome. Sections were examined under a light microscope (Olympus CX43, Japan) at ×400 magnification.

Myocardial injury was evaluated using a semi-quantitative scoring system adapted from Zingarelli et al. (31). A score of 0 indicated normal myocardial architecture with no observable damage. A score of 1 was assigned when focal necrosis and interstitial oedema were present. A score of 2 reflected hypertrophy of cardiomyocytes. A score of 3 denoted leukocyte infiltration accompanied by constriction bands, while a score of 4 represented the most severe injury, characterised by haemorrhage, extensive neutrophil infiltration, and band necrosis. Scoring was performed by two independent, blinded observers, with discrepancies resolved by consensus. Histopathological scoring was performed independently by two blinded pathologists, and any discrepancies were resolved by consensus.

Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Intergroup differences were assessed using one-way analysis of variance (ANOVA) followed by Bonferroni post hoc tests for multiple comparisons. Histopathological scores, which are ordinal, were analysed using the Kruskal-Wallis test followed by Dunn's multiple comparison test. Statistical significance was set at $p < 0.05$. All analyses were performed using GraphPad Prism version 8.1 (GraphPad Software Inc., USA).

Results

Effect of Empagliflozin on Serum cTn-I Levels

As shown in Figure 1, serum levels of cardiac troponin I (cTn-I) were significantly elevated in the sepsis group (4.13 ± 0.32 ng/mL) compared to the control (1.27 ± 0.19 ng/mL; $p = 0.003$) and sham groups (1.42 ± 0.24 ng/mL; $p = 0.006$). The vehicle group (4.08 ± 0.29 ng/mL) exhibited similarly elevated cTn-I levels relative to the control ($p = 0.004$) and sham ($p = 0.005$) groups. In contrast, the Empagliflozin-treated group demonstrated a significantly reduced cTn-I level (2.15 ± 0.22 ng/mL) compared to both the sepsis ($p = 0.012$) and vehicle ($p = 0.015$) groups, indicating attenuation of myocardial injury.

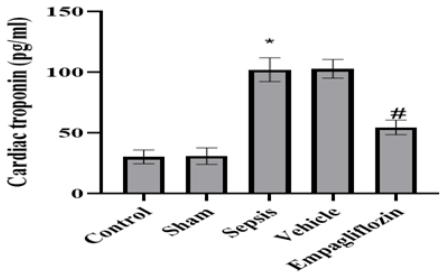

Figure 1: Serum levels of cTn-I across experimental groups (n = 7)
Data are presented as mean ± SEM. Statistical significance was determined by one-way ANOVA with a Bonferroni post hoc test

Effect of Empagliflozin on Cardiac NF-κB Expression
Tissue levels of NF-κB were significantly elevated in the sepsis group (3.92 ± 0.26 ng/mg protein) and vehicle group (3.85 ± 0.24 ng/mg) compared to the control (1.18 ± 0.15 ng/mg; p = 0.002 and p = 0.004, respectively) and sham groups (1.26 ± 0.14 ng/mg; p = 0.003 and p = 0.005). Empagliflozin treatment significantly reduced NF-κB levels (2.23 ± 0.18 ng/mg) versus both the sepsis (p = 0.014) and vehicle (p = 0.019) groups (Figure 2).

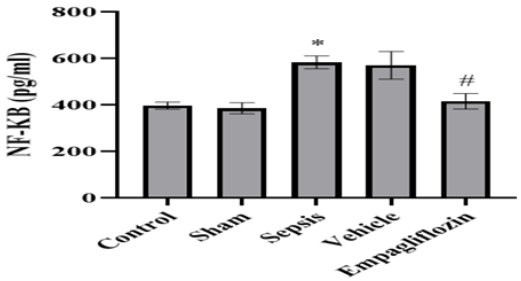

Figure 2: Cardiac NF-κB levels (ng/mg protein) measured by ELISA
Values are expressed as mean ± SEM. One-way ANOVA with Bonferroni correction

Effect of Empagliflozin on Cardiac TNF-α Levels
TNF-α concentrations followed a similar pattern (Figure 3). The sepsis (5.71 ± 0.36 ng/mg) and vehicle (5.64 ± 0.33 ng/mg) groups had significantly higher levels compared to the control (1.39 ± 0.12 ng/mg; both p = 0.001) and sham (1.48 ± 0.13 ng/mg; both p = 0.002) groups. Empagliflozin reduced TNF-α levels to 2.84 ± 0.25 ng/mg, significantly lower than those in the sepsis (p = 0.009) and vehicle (p = 0.011) groups.

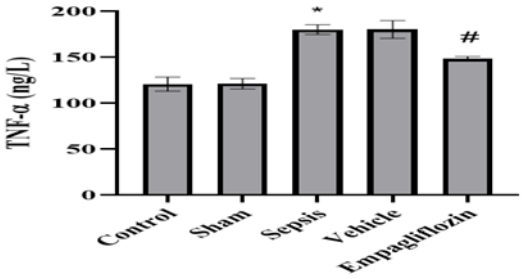

Figure 3: Tissue TNF-α levels (ng/mg protein) across groups
Bars represent mean ± SEM. One-way ANOVA and Bonferroni post hoc test applied

Effect of Empagliflozin on Cardiac FoxO3 Expression
As shown in Figure 4, FoxO3 levels were significantly increased in the sepsis (4.08 ± 0.28 ng/mg) and vehicle (3.99 ± 0.25 ng/mg) groups compared to the control (1.22 ± 0.15 ng/mg; both p = 0.002) and sham (1.35 ± 0.17 ng/mg; p = 0.003 and p = 0.005). The Empagliflozin group showed significantly lower FoxO3 expression (2.09 ± 0.20 ng/mg) compared to sepsis (p = 0.013) and vehicle (p = 0.016) groups.

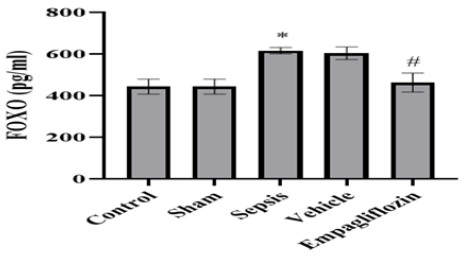

Figure 4: Tissue FoxO3 levels (ng/mg protein) determined by ELISA. Data are mean ± SEM (n = 7)

Histopathological Evaluation of Myocardial Tissue

Histological examination revealed that the control and sham groups showed normal myocardial architecture (score 0) (Figure 5A–B). Myocardial tissue from the sepsis (Figure 5C) and vehicle (Figure 5D) groups displayed severe cardiac injury, including leukocyte infiltration, constriction bands, and interstitial oedema (mean score: 3.14 ± 0.26 and 3.00 ± 0.24, respectively). The Empagliflozin-treated group (Figure 5E) showed markedly reduced myocardial damage, with only mild oedema, vascular congestion, and minimal inflammatory cell infiltration (score: 1.14 ± 0.18).

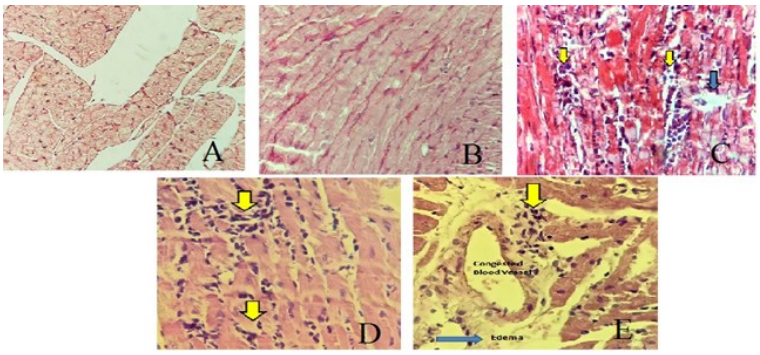

Figure 5: Representative histological sections of cardiac tissue (H&E and trichrome stain, ×400)

(A) Control; (B) Sham; (C) Sepsis; (D) Vehicle; (E) Empagliflozin. Yellow arrows indicate leukocyte infiltration; blue arrows show oedema/congestion

These observations were supported by quantitative scoring (Table 2) and statistical comparison (Figure 6). Histopathological scores were significantly lower in the Empagliflozin group compared to the sepsis ($p = 0.008$) and vehicle ($p = 0.010$) groups.

Table 2: Summary of Myocardial Histological Injury Scores (n = 7)

Group	Histological Score (Mean ± SEM)
Control	0.00 ± 0.00
Sham	0.00 ± 0.00
Sepsis	3.14 ± 0.26
Vehicle	3.00 ± 0.24
Empagliflozin	1.14 ± 0.18

Semi-quantitative histological scoring of cardiac injury using the Zingarelli scale. Lower scores indicate less myocardial damage

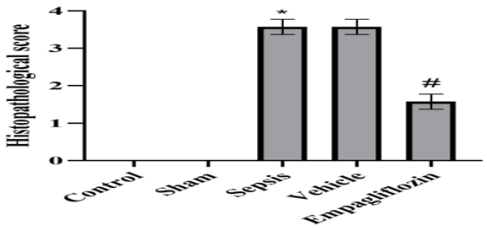

Figure 6: Mean myocardial injury scores across groups

Error bars represent SEM. Kruskal-Wallis test followed by Dunn's post hoc test

Discussion

This study provides evidence that Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, mitigates cardiac injury and inflammation in a murine model of polymicrobial sepsis induced by caecal ligation and puncture (CLP). Treatment with Empagliflozin significantly reduced serum cTn-I and tissue levels of NF-κB, TNF-α, and FoxO3, and improved histopathological features of myocardial injury. These findings align with previous preclinical studies reporting the anti-inflammatory and cardioprotective effects of Empagliflozin in models of cardiac stress, including doxorubicin-induced cardiotoxicity and cisplatin-related cardiac injury (17, 29).

A key mediator of the inflammatory response in sepsis is NF-κB, a transcription factor that regulates genes involved in cytokine release, apoptosis, and immune activation (22, 32). Elevated cardiac NF-κB levels in the untreated sepsis and vehicle groups in our study confirm its central role in myocardial inflammation. Notably, Empagliflozin significantly attenuated NF-κB expression, corroborating findings from Lee et al., who demonstrated that Empagliflozin suppresses NF-κB phosphorylation in LPS-activated macrophages via inhibition of IKK activity (24). Similar reductions in NF-κB signalling have also been observed in septic renal tissues following Empagliflozin administration (26). These anti-inflammatory effects may underlie the observed reduction in TNF-α, a major pro-inflammatory cytokine implicated in septic cardiomyopathy and vascular dysfunction (23, 33, 34).

In addition to its immunomodulatory action, Empagliflozin has been shown to preserve mitochondrial integrity and reduce oxidative stress in cardiac tissue (16, 18, 35). This is especially relevant in sepsis, where mitochondrial dysfunction contributes to impaired myocardial energetics and contractile failure (7, 8). Though our study did not directly assess mitochondrial function, the significant reduction in cTn-I, a marker of cardiomyocyte injury, and improved histological architecture suggest that Empagliflozin may protect cardiac mitochondria indirectly by blunting upstream inflammatory cascades.

The observed downregulation of FoxO3 in the Empagliflozin-treated group is particularly intriguing. FoxO3 is a transcription factor involved in oxidative stress response, apoptosis, and immune regulation (25), and its expression is reportedly upregulated in septic conditions (36, 37). Our findings provide some of the first in vivo evidence that Empagliflozin may suppress FoxO3 expression during sepsis. Given the limited literature on this interaction, the modulation of FoxO3 may represent a novel pathway through which Empagliflozin exerts anti-apoptotic effects. This warrants further investigation using mechanistic studies, including gene knockdown models and proteomic profiling.

Empagliflozin's impact on cardiac injury in sepsis has growing translational relevance. While it is widely recognised for reducing cardiovascular mortality in patients with diabetes and heart failure (12, 13, 21), its application in acute inflammatory syndromes like sepsis remains underexplored. A limited number of studies have reported beneficial effects of SGLT2 inhibitors in septic contexts (19, 26, 27); however, conflicting evidence exists. For instance, some rodent studies in early LPS-induced endotoxemia have not shown significant improvements in survival or organ injury following Empagliflozin administration, possibly due to differences in timing, dosage, or models used (38, 39). These discrepancies underscore the importance of context-specific validation.

Despite promising results, this study has limitations. First, the observation window was limited to 24 hours post-CLP, and long-term cardiac outcomes were not evaluated. Second, while biomarker and histological changes were assessed, molecular mechanisms, such as mitochondrial bioenergetics, oxidative stress markers, or pathway-specific gene expression, were not explored. Third, only a single dose of Empagliflozin (10 mg/kg) was tested, precluding a dose-response analysis. Lastly, although animal models offer valuable insights, their translation to human sepsis, especially regarding pharmacodynamics and immune responses, requires cautious interpretation.

In summary, our findings demonstrate that Empagliflozin exerts protective effects on the septic heart by reducing inflammation and cardiomyocyte injury, likely via NF-κB, TNF-α, and possibly FoxO3 modulation. This adds to a growing body of literature supporting the pleiotropic benefits of SGLT2 inhibitors. Future studies should explore dose-dependent effects, elucidate downstream molecular pathways, and evaluate Empagliflozin in combination with conventional sepsis therapies. Its potential as an adjunctive therapy in human septic cardiomyopathy merits further investigation.

Study limitations

This study has several limitations. Only a single dose of Empagliflozin (10 mg/kg) was evaluated, precluding assessment of dose-dependent effects. Additionally, all animals were male; therefore, potential sex-based differences in drug response and inflammation were not examined. These factors may limit the generalizability of our

findings and should be addressed in future studies.

Conclusion

Empagliflozin reduced inflammatory markers (NF-κB, TNF-α, and FoxO3) and cardiac injury (cTn-I levels and histopathological scores) in a murine CLP model of sepsis. These findings suggest that Empagliflozin may confer cardioprotective and anti-inflammatory effects in the setting of sepsis. While the results are promising, they are based on a preclinical model, and further studies are needed to elucidate the underlying mechanisms, explore dose-response relationships, and determine clinical relevance in human sepsis.

List of Abbreviations

ANOVA: Analysis of Variance
cTn-I: Cardiac Troponin I
CLP: Caecal Ligation and Puncture
DAMP: Damage-Associated Molecular Pattern
DMSO: Dimethyl Sulfoxide
ELISA: Enzyme-Linked Immunosorbent Assay
FoxO3: Forkhead Box O3
H&E: Haematoxylin and Eosin
HFrEF: Heart Failure with Reduced Ejection Fraction
IKK: IκB Kinase
IL-6: Interleukin 6
LPS: Lipopolysaccharide
NF-κB: Nuclear Factor Kappa B
PAMP: Pathogen-Associated Molecular Pattern
PBS: Phosphate-Buffered Saline
ROS: Reactive Oxygen Species
SGLT2: Sodium-Glucose Cotransporter 2
SEM: Standard Error of the Mean
TNF-α: Tumour Necrosis Factor Alpha

Declarations

Ethics approval and consent to participate

All experimental procedures were approved by the Animal Care and Use Committee of the University of Kufa (Approval No. PHARM/ACUC/2023/019) and conducted in accordance with international guidelines for the care and use of laboratory animals. Efforts were made to minimise animal suffering and to reduce the number of animals used.

Consent for Publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution Non-Commercial 4.0 license.

Availability of Data

Data for this work is available from the authors and may be provided upon reasonable request.

Conflicts of Interest

None.

Funding

None.

Authors' contributions

ASM conceptualised and designed the study, supervised all stages of the research, and critically revised the manuscript for intellectual content.

MBM conducted the animal experiments, performed biochemical and histological analyses, analysed the data, and drafted the initial version of the manuscript.

Both authors contributed to data interpretation, reviewed the final manuscript, and approved it for submission.

Acknowledgments

The authors acknowledge the technical support provided by the Laboratory Unit of the Department of Clinical and Laboratory Sciences, Faculty of Pharmacy, University of Kufa. We also thank the staff of the animal house for their assistance with animal care. Special thanks to [Insert any mentor, statistician, or institution] for their guidance and input during the study design and analysis phases.

References

1. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. American journal of respiratory and critical care medicine. 2003 Mar 1;167(5):695-701. https://doi.org/10.1164/rccm.200207-682OC
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11. https://doi.org/10.1016/S0140-6736(19)32989-7
3. Bertani B, Ruiz N. Function and biogenesis of lipopolysaccharides. Ecosal plus. 2018 Dec 31;8(1):10-128. https://doi.org/10.1128/ecosalplus.esp-0001-2018
4. Buras JA, Holzmann B, Sitkovsky M. Animal models of sepsis: setting the stage. Nature reviews Drug discovery. 2005 Oct 1;4(10):854-65. https://doi.org/10.1038/nrd1854
5. Rittirsch D, Hoesel LM, Ward PA. The disconnect between animal models of sepsis and human sepsis. Journal of Leucocyte

Biology. 2007 Jan;81(1):137-43. https://doi.org/10.1189/jlb.0806542
6. Maier S, Traeger T, Entleutner M, Westerholt A, Kleist B, Hüser N, Holzmann B, Stier A, Pfeffer K, Heidecke CD. Cecal ligation and puncture versus colon ascendens stent peritonitis: two distinct animal models for polymicrobial sepsis. Shock. 2004 Jun 1;21(6):505-12. https://doi.org/10.1097/01.shk.0000126906.52367.dd
7. Shang X, Li J, Yu R, Zhu P, Zhang Y, Xu J, Chen K, Li M. Sepsis-related myocardial injury is associated with Mst1 upregulation, mitochondrial dysfunction and the Drp1/F-actin signaling pathway. Journal of molecular histology. 2019 Apr 15;50(2):91-103. https://doi.org/10.1007/s10735-018-09809-5
8. Tan Y, Chen S, Zhong J, Ren J, Dong M. Mitochondrial injury and targeted intervention in septic cardiomyopathy. Current pharmaceutical design. 2019 May 1;25(18):2060-70. https://doi.org/10.2174/1381612825666190708155400
9. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Fröhlich M, Sinning CR. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. New England Journal of Medicine. 2009 Aug 27;361(9):868-77. https://doi.org/10.1056/NEJMoa0903515
10. Cheng ST, Chen L, Li SY, Mayoux E, Leung PS. The effects of empagliflozin, an SGLT2 inhibitor, on pancreatic β-cell mass and glucose homeostasis in type 1 diabetes. PloS one. 2016 Jan 25;11(1):e0147391. https://doi.org/10.1371/journal.pone.0147391
11. Górriz JL, Navarro-González JF, Ortiz A, Vergara A, Nunez J, Jacobs-Cachá C, Martínez-Castelao A, Soler MJ. Sodium-glucose cotransporter 2 inhibition: towards an indication to treat diabetic kidney disease. Nephrology Dialysis Transplantation. 2020 Jan 1;35(Supplement_1):i13-23. https://doi.org/10.1093/ndt/gfz237
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New england journal of medicine. 2015 Nov 26;373(22):2117-28. https://doi.org/10.1056/NEJMoa1504720
13. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W. Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine. 2020 Oct 8;383(15):1413-24. https://doi.org/10.1056/NEJMoa2022190
14. Al Jobori H, Daniele G, Adams J, Cersosimo E, Triplitt C, DeFronzo RA, Abdul-Ghani M. Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. Diabetes, Obesity and Metabolism. 2017 Jun;19(6):809-13. https://doi.org/10.1111/dom.12881
15. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a “thrifty substrate” hypothesis. Diabetes care. 2016 Jul 1;39(7):1108-14. https://doi.org/10.2337/dc16-0330
16. Oh CM, Cho S, Jang JY, Kim H, Chun S, Choi M, Park S, Ko YG. Cardioprotective potential of an SGLT2 inhibitor against doxorubicin-induced heart failure. Korean Circulation Journal. 2019 Jul 31;49(12):1183. https://doi.org/10.4070/kcj.2019.0180
17. Quagliariello V, De Laurentiis M, Rea D, Barbieri A, Monti MG, Carbone A, Paccone A, Altucci L, Conte M, Canale ML, Botti G. The SGLT-2 inhibitor empagliflozin improves myocardial strain, reduces cardiac fibrosis and pro-inflammatory cytokines in non-diabetic mice treated with doxorubicin. Cardiovascular diabetology. 2021 Jul 23;20(1):150. https://doi.org/10.1186/s12933-021-01346-y
18. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018 Oct;61(10):2108-17. https://doi.org/10.1007/s00125-018-4670-7
19. Soni S, Dyck JR. The multiple effects of SGLT2 inhibitors suggest potential benefit in COVID-19 patients. The Canadian journal of cardiology. 2020 Jul 24;36(10):1691-e3. https://doi.org/10.1016/j.cjca.2020.07.230
20. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. Circulation. 2019 Apr 23;139(17):1985-7. https://doi.org/10.1161/CIRCULATIONAHA.118.038881
21. Marx N, McGuire DK. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. European heart journal. 2016 Nov 7;37(42):3192-200. https://doi.org/10.1093/eurheartj/ehw110
22. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. Nature reviews immunology. 2003 Sep 1;3(9):745-56. https://doi.org/10.1038/nri1184
23. Majid DS. Tumor necrosis factor-α and kidney function: experimental findings in mice. InAdvances in TNF Family Research:

Proceedings of the 12th International TNF Conference, 2009 2010 Oct 22 (pp. 471-480). New York, NY: Springer New York. https://doi.org/10.1007/978-1-4419-6612-4_48
24. Lee AS, Chen WP, Kuo YL, Ho YJ, Lee SS, Su MJ. Thaliporphine preserves cardiac function of endotoxemic rabbits by both directly and indirectly attenuating NFκB signaling pathway. PLoS One. 2012 Jun 25;7(6):e39174. https://doi.org/10.1371/journal.pone.0039174
25. Matsuzaki T, Alvarez-Garcia O, Mokuda S, Nagira K, Olmer M, Gamini R, Miyata K, Akasaki Y, Su AI, Asahara H, Lotz MK. FoxO transcription factors modulate autophagy and proteoglycan 4 in cartilage homeostasis and osteoarthritis. Science translational medicine. 2018 Feb 14;10(428):eaan0746. https://doi.org/10.1126/scitranslmed.aan0746
26. Jawad AS, Hassan ES, Mohammad AR. Protective effect of empagliflozin from acute renal injury during endotoxemia in mice model. Lat Am J Pharm. 2022 Jan 1;41(2):463-71.
27. Makaro A, Świerczyński M, Pokora K, Sarniak B, Kordek R, Fichna J, Salaga M. Empagliflozin attenuates intestinal inflammation through suppression of nitric oxide synthesis and myeloperoxidase activity in in vitro and in vivo models of colitis. Inflammopharmacology. 2024 Feb;32(1):377-92. https://doi.org/10.1007/s10787-023-01227-8
28. Koyani CN, Plastira I, Sourij H, Hallström S, Schmidt A, Rainer PP, Bugger H, Frank S, Malle E, von Lewinski D. Empagliflozin protects heart from inflammation and energy depletion via AMPK activation. Pharmacological research. 2020 Aug 1;158:104870. https://doi.org/10.1016/j.phrs.2020.104870
29. El-Shafei AA, Hassan RM, Hosny SA. A comparative histological and immunohistochemical study on the possible therapeutic effects of empagliflozin and platelet-rich plasma against cisplatin induced cardiotoxicity in rats. Egyptian Journal of Histology. 2023 Mar 1;46(1):378-493.
30. Wellington D, Mikaelian I, Singer L. Comparison of ketamine–xylazine and ketamine–dexmedetomidine anesthesia and intraperitoneal tolerance in rats. Journal of the American association for laboratory animal science. 2013 Jul 1;52(4):481-7.
31. Zingarelli B, Salzman AL, Szabó C. Genetic disruption of poly (ADP-ribose) synthetase inhibits the expression of P-selectin and intercellular adhesion molecule-1 in myocardial ischemia/reperfusion injury. Circulation research. 1998 Jul 13;83(1):85-94. https://doi.org/10.1161/01.RES.83.1.85
32. Rossi AG, Hallett JM, Sawatzky DA, Teixeira MM, Haslett C. Modulation of granulocyte apoptosis can influence the resolution of inflammation. https://doi.org/10.1042/BST0350288
33. Chu WM. Tumor necrosis factor. Cancer letters. 2013 Jan 28;328(2):222-5. https://doi.org/10.1016/j.canlet.2012.10.014
34. Carbone M, Ly BH, Dodson RF, Pagano I, Morris PT, Dogan UA, Gazdar AF, Pass HI, Yang H. Malignant mesothelioma: facts, myths, and hypotheses. Journal of cellular physiology. 2012 Jan;227(1):44-58. https://doi.org/10.1002/jcp.22724
35. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, Flores E, Garcia-Ropero A, Sanz J, Hajjar RJ, Fuster V. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. Journal of the American College of Cardiology. 2019 Apr 23;73(15):1931-44. https://doi.org/10.1016/j.jacc.2019.01.056
36. Pan M, Liu J, Huang D, Guo Y, Luo K, Yang M, Gao W, Xu Q, Zhang W, Mai K. FoxO3 modulates LPS-activated hepatic inflammation in turbot (Scophthalmus maximus L.). Frontiers in immunology. 2021 Jul 1;12:679704. https://doi.org/10.3389/fimmu.2021.679704
37. Liu J, Li S, Xiong D, Shang W, Zhan T, Zhu X, He S, Wang Y, Zhang Q, Hu Y. Screening of potential core genes in peripheral blood of adult patients with sepsis based on transcription regulation function. Shock. 2023 Mar 1;59(3):385-92. https://doi.org/10.1097/SHK.0000000000002072
38. Yildiz IE, Topcu A, Bahceci I, Arpa M, Tumkaya L, Mercantepe T, Batcik S, Yildiz Y. The protective role of fosfomycin in lung injury due to oxidative stress and inflammation caused by sepsis. Life Sciences. 2021 Aug 15;279:119662. https://doi.org/10.1016/j.lfs.2021.119662
39. Majid Z, Muhammad-Baqir B, Al-Shimerty DF, Hadi NR. The possible cardioprotective effect of ghrelin during experimental endotoxemia in mice. Journal of Medicine and Life. 2024 May;17(5):486.