

Original Research Article

Anti-inflammatory and antioxidant effects of taxifolin against sepsis-induced renal injury in mice

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Abstract

Purpose: To investigate the effect of taxifolin in sepsis-induced renal injury.

Methods: A total of 24 adult male Swiss albino mice were randomly and equally assigned to 4 groups ($n = 6$). Group 1 was the control (exposed to abdominal laparotomy without cecal ligation and puncture (CLP) procedure), group 2 underwent CLP with no treatment, and groups 3 and 4 received intraperitoneal DMSO and taxifolin (10 mg/kg), respectively, 1 h before the CLP procedure. Renal function, NF- κ B, MDA levels, Nrf2 expression, and caspase-3 activity were evaluated.

Results: Sepsis induced by CLP led to significant deterioration of renal function, characterized by higher serum creatinine and renal KIM-1, including severe histopathological kidney damage. Sepsis induced by CLP increased NF- κ B and MDA levels, downregulated Nrf2 expression, and elevated caspase-3 activity. Taxifolin administration significantly mitigated these alterations, enhanced renal function and histological architecture, suppressed oxidative damage and the inflammatory response, and restored Nrf2 signaling.

Conclusion: Taxifolin conferred a substantial renoprotective effect against acute kidney impairment induced by sepsis by reducing inflammatory responses, oxidative stress, and preserving tubular structural integrity.

Keywords: Cecal ligation and puncture, Inflammation, Oxidative stress, Sepsis, Taxifolin

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INTRODUCTION

The definition of sepsis has changed over the past few decades, with the current definition highlighting the presence of organ failure [1]. Sepsis significantly contributes to morbidity and mortality globally, despite advancements in medical management and rising awareness [2]. Approximately 11 million deaths and 48.9 million sepsis cases were recorded globally in 2017, representing 20 % of worldwide fatalities [3]. Global hypoperfusion, affecting multiple organs, results from an immunological response that

triggers significant macro- and microcirculatory dysfunction. Irrespective of the location of infection, people with sepsis may exhibit dysfunction in nearly every system. The hematologic system, central nervous system, and organs like the heart, liver, lungs, and kidneys are the most frequently affected [4]. Studies indicated that acute kidney injury (AKI) is prevalent among sepsis patients within the intensive care unit, with mortality rates of up to 60 % [5]. Complex and heterogeneous mechanisms lead to AKI and originate directly from infection and the corresponding immune

response. Furthermore, sepsis and its management may result in secondary effects involving systemic and renal inflammatory responses, mitochondrial dysfunction, metabolic disturbances, and impairments in both the microcirculatory and macrocirculatory systems [6]. Sepsis and sepsis-associated acute kidney injury (SA-AKI) are characterized by the activation of multiple pro-inflammatory pathways, resulting in the excessive production of reactive oxygen species (ROS), chemokines, and pro-inflammatory cytokines. During the cytokine storm, pattern recognition receptors, particularly toll-like receptors (TLRs), recognize microbial-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs), thereby amplifying the inflammatory response [7]. Oxidative damage is a significant factor in renal injury during sepsis. Increased ROS production, primarily from activated immune cells and damaged mitochondria, reduces nitric oxide bioavailability, impairs vasoregulation, and initiates lipid peroxidation within tubular epithelial cells. Also, mitochondrial-derived DAMPs further activate innate immune responses, linking metabolic dysfunction with inflammation and kidney tubular damage in SA-AKI [8]. Mitochondrial ROS also act as danger signals that activate inflammasomes, initiating inflammation and cell death. The resultant oxidative cascade promotes diverse forms of programmed cell death, including apoptosis. An essential step in cell death, caspase-3 activation, follows both intrinsic (mitochondrial) and extrinsic (death receptor) pathways, leading to cleavage of cellular substrates, DNA fragmentation, and apoptotic body formation in renal tubular cells [9].

The nuclear factor κ B (NF- κ B) and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, which are involved at the molecular level, play pivotal yet opposing roles in SA-AKI. The NF- κ B acts as a central pro-inflammatory transcription factor that, when activated by sepsis-induced oxidative stress and DAMPs, upregulates cytokines and chemokines that exacerbate renal inflammation and tubular injury. Conversely, Nrf2 acts as a principal antioxidant defense regulator. Following oxidative stress, Nrf2 undergoes nuclear translocation and induces expression of cytoprotective genes such as HO-1, GPX4, and other antioxidant enzymes. Upregulation of the Nrf2 pathway reduces ROS accumulation, attenuates downstream NF- κ B signaling, and limits inflammatory cytokine release, thereby protecting tubular cells from oxidative and inflammatory injury [10]. Modulation of this Nrf2/NF- κ B balance is a promising molecular strategy for mitigating SA-AKI [11]. Medicinal plants contain bioactive substances in their

leaves, roots, or flowers that are used in the treatment of various conditions. Flavonoids, which are recognized as active components of many medicinal plants, exhibit diverse phenolic structures. Flavonoids are essential components in various pharmacological, medical, and cosmetic applications due to their cardioprotective, anticancer, anti-inflammatory, and antioxidant properties [12]. Taxifolin (dihydroquercetin) is a naturally occurring bioactive flavonoid. It possesses potent antioxidant properties and has demonstrated powerful inhibitory effects on inflammation, cancer, microbial infections, oxidative stress, cardiovascular disorders, and hepatic diseases [13]. However, the benefit of taxifolin in AKI induced by sepsis remains unknown. Therefore, this study investigated the renoprotective effects of taxifolin in CLP-induced sepsis by evaluating renal function, histopathological alterations, oxidative stress (MDA), inflammation (NF- κ B), apoptosis (caspase-3), and Nrf2 signaling.

EXPERIMENTAL

Animals

A total of 24 adult male Swiss albino mice (6 – 8 weeks, 25 – 35 g) were obtained from Kufa University College of Science animal house. The animals were kept under standard laboratory conditions (12 h dark/light cycle, relative humidity of 50 – 70 %, 25 ± 1 °C) with unrestricted access to feed and water.

Ethical approval

It was obtained from the Institutional Animal Care and Use Committee (IACUC), University of Kufa (approval no. 2329), and complied with the guidelines for the use and care of laboratory animals [14].

Preparation of sample

Taxifolin (Cat. No. T1738, TargetMol, USA) was freshly prepared for administration by dissolving it in dimethyl sulfoxide (DMSO; Cat. No. T0341, TargetMol, USA) and subsequently diluting it with normal saline.

Study design

The animals were randomly and equally assigned to four groups (n = 6 each). Group 1 was the control (exposed to abdominal laparotomy without cecal ligation and puncture (CLP) procedure), group 2 underwent CLP with no treatment, and groups 3 and 4 received

intraperitoneal DMSO and taxifolin (10 mg/kg), respectively, 1 h before the CLP procedure [15].

Sepsis model

A sepsis model was established using the CLP procedure [16]. After anesthesia with intraperitoneal ketamine (100 mg/kg) and xylazine (10 mg/kg), the cecum was exposed by a midline abdominal incision (1 - 2 cm) and ligated with a 6.0 silk suture at 50 - 75 % of its length. Then dual punctures were conducted with a 22-gauge needle. Gentle pressure was applied to extract a small quantity of fecal content, and the cecum was returned to its location in the abdominal area [17]. The abdomen was sutured, and 1 mL of normal saline was given for resuscitation [18].

Sample collection

Direct cardiac puncture was employed to obtain blood samples. Approximately 0.8 mL of blood was collected from each mouse under anesthesia. A total of 5 mL of blood was collected per group (pooled from 6 mice) and the blood was left to coagulate. Samples were centrifuged at 2000 - 3000 rpm for 20 min to obtain serum.

Evaluation of parameters/indices

Serum creatinine levels

Creatinine level was determined using a colorimetric method, and absorbance was read at 510 nm with a UV-visible spectrophotometer.

Kidney homogenate markers

After blood sample collection, the kidney was taken and cut into two parts. The first part was weighed and put in a ratio of 1:9 with phosphate-buffered saline and homogenized using an ultrasonic processor. The homogenate was centrifuged at 12,000 rpm and 4 °C for 15 min to obtain a supernatant which was used to determine levels of kidney injury molecule-1 (KIM-1; cat. No. SL0339Mo), NF- κ B (cat. No. SL0723Mo), malondialdehyde (MDA; cat. No. SL0370Mo), caspase-3 (cat. No. SL0679Mo), and Nrf2 (cat. No. SL1027Mo) by enzyme-linked immunosorbent assay (ELISA).

Histological evaluation

Kidney tissues were fixed in 10% formalin, embedded in paraffin, and cut into 5 μ m sections. The sections were then stained with hematoxylin and eosin (H&E). The slides were

examined by a pathologist blindly, and a semiquantitative scoring system was used to grade the level of kidney damage. Scores of 0, 1, 2, 3, and 4 indicated no damage, < 25, 25 - 50, 50 - 75, > 75 %, respectively.

Statistical analysis

Data were analyzed using GraphPad Prism 10.6 software (GraphPad Software, San Diego, CA, USA). Data normality was assessed using the Shapiro-Wilk test and homogeneity of variance was evaluated using the Brown-Forsythe test. Data were expressed as mean $\pm$ standard error of the mean (SEM) and compared using one-way analysis of variance (ANOVA), followed by the Bonferroni test. Kruskal-Wallis test followed by Dunn's multiple comparison test was used to compare histological data. $P < 0.05$ was considered statistically significant.

RESULTS

Effect on renal function

Serum creatinine (Scr; Figure 1 A) and renal KIM-1 (Figure 1 B) levels were significantly higher following the CLP procedure compared to control ($P < 0.0001$). However, Scr was significantly reduced following taxifolin treatment compared to groups 2 and 3 ($P < 0.01$).

Effect on inflammation

Levels of NF- κ B in renal tissue were significantly higher following the CLP procedure compared to control ($****P < 0.0001$). However, NF- κ B was significantly reduced following treatment with taxifolin compared to groups 2 and 3 ($P < 0.0001$; Figure 2).

Effect on oxidative stress

Renal MDA levels (Figure 3 A) were significantly higher, and Nrf2 (Figure 3 B) was suppressed following the CLP procedure compared to control ($P < 0.01$). However, MDA levels were significantly reduced and Nrf2 levels increased following treatment with taxifolin compared to groups 2 and 3 ($P < 0.05$; Figure 3).

Effect on apoptosis

There was a significant increase in caspase-3 level following the CLP procedure compared to control ($P < 0.001$). However, treatment with taxifolin significantly decreased caspase-3 level compared to groups 2 and 3 ($*P < 0.05$; Figure 4).

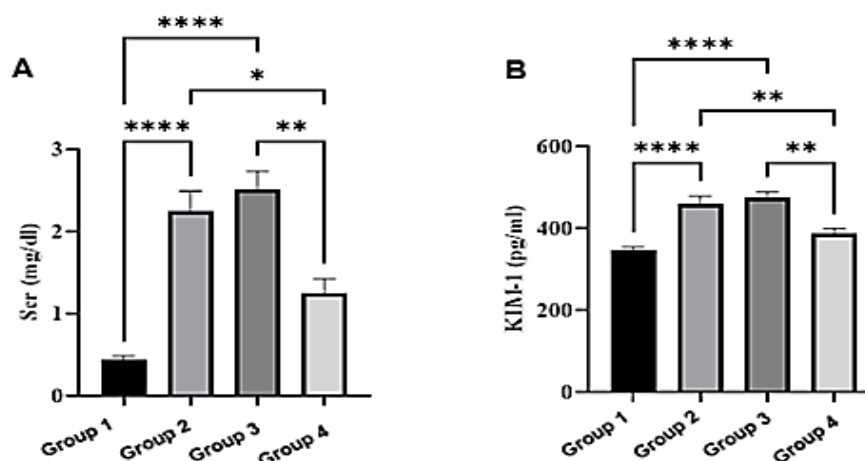


Figure 1: Effect of taxifolin on serum creatinine (A) and KIM-1 (B) levels. Data presented as mean $\pm$ SEM. Group 1 (control), group 2 (CLP with no treatment), group 3 (CLP + DMSO), group 4 (CLP + 10 mg/kg taxifolin) 1 h before the CLP procedure. * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$

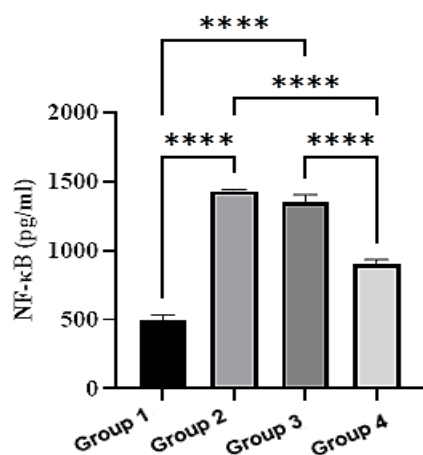


Figure 2: Effect of taxifolin on renal NF-κB levels. Data presented as mean $\pm$ SEM. Group 1 (control), group 2 (CLP with no treatment), group 3 (CLP + DMSO), group 4 (CLP + 10 mg/kg taxifolin) 1 h before the CLP procedure. **** $P < 0.0001$

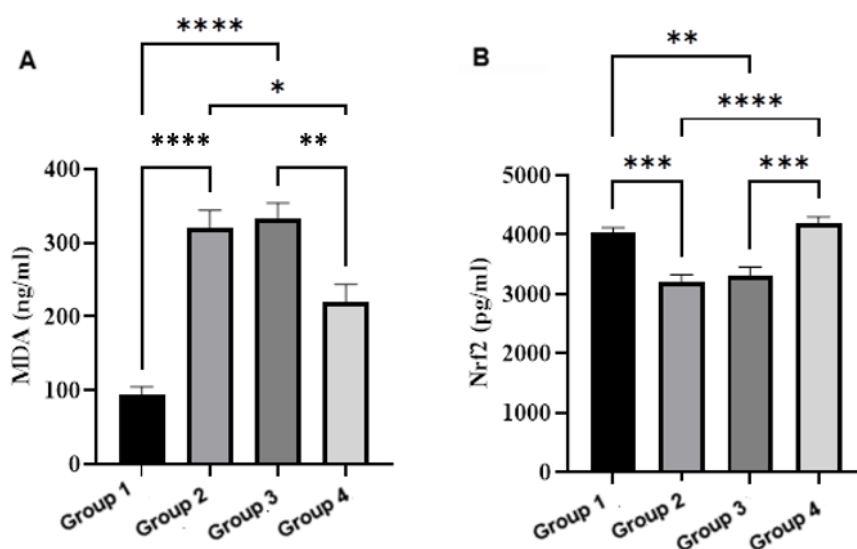


Figure 3: Effect of taxifolin on MDA (A) and Nrf2 (B). Data presented as mean $\pm$ SEM. Group 1 (control), group 2 (CLP with no treatment), group 3 (CLP + DMSO), group 4 (CLP + 10 mg/kg taxifolin) 1 h before the CLP procedure. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

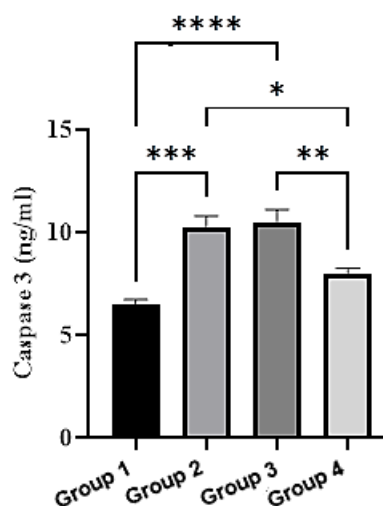


Figure 4: Impact of taxifolin on renal caspase-3 level. Data presented as mean $\pm$ SEM. Group 1 (control), group 2 (CLP with no treatment), group 3 (CLP + DMSO), group 4 (CLP + 10 mg/kg taxifolin) 1 h before the CLP procedure. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

Histological findings

Histopathological injury score

The histopathological score was significantly lower following taxifolin treatment compared to groups 2 and 3 ($P < 0.05$; Figure 5).

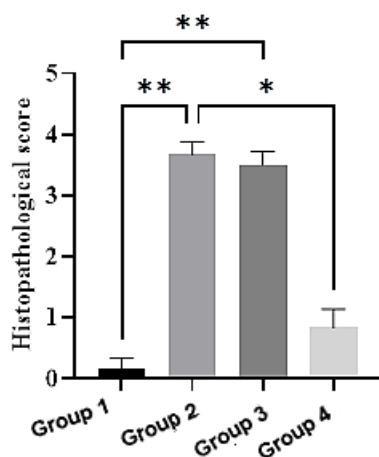


Figure 5: Effect of taxifolin on renal histopathological injury score. Data presented as mean $\pm$ SEM. Group 1 (control), group 2 (CLP with no treatment), group 3 (CLP + DMSO), group 4 (CLP + 10 mg/kg taxifolin) 1 h before the CLP procedure. The Kruskal–Wallis test was implemented and followed by Dunn's multiple comparison test to analyze nonparametric data. * $P < 0.05$, ** $P < 0.01$

Renal histoarchitecture

Examination of kidney sections obtained from the control group showed normal renal tissue

appearance, with well-preserved glomerular and tubular structures (A). The CLP procedure induced significant kidney injury characterized by vascular congestion and inflammatory cell infiltration within renal tubules (B). Group 3 (C) exhibited similar histological abnormalities to group 2, including inflammatory lymphocyte infiltration and vascular congestion. Taxifolin treatment (D) showed mild changes compared to group 2 (Figure 6).

DISCUSSION

Sepsis-induced AKI has a high morbidity and mortality rate. It is therefore important to identify therapeutic strategies effective in the treatment of sepsis-induced AKI [19]. The nephroprotective role of taxifolin was investigated due to its potent anti-inflammatory and antioxidant properties [20] and hence its potential to ameliorate kidney damage in CLP-associated AKI. To investigate the protective efficacy of taxifolin, a sepsis-induced AKI mouse model group was established through the CLP procedure. The CLP model is regarded as the gold standard due to its marked similarity to the development of human sepsis [21]. This study revealed that serum creatinine was significantly increased following the CLP procedure, indicating that a sepsis-induced AKI model had been established. Taxifolin treatment resulted in significantly lower Scr levels compared to group 2 (CLP-induced group only). The observed reduction in serum creatinine by taxifolin aligns with previous findings where taxifolin mitigated renal impairment in diabetic nephropathy models [22].

Biochemical evidence of renal injury was corroborated by histopathological evaluation following renal injury caused by CLP. The absence of tissue injury was confirmed by the normal architecture of kidney sections from the control group, which included intact glomeruli and well-preserved tubular structures. However, groups 2 and 3 (CLP and CLP + DMSO, respectively) demonstrated significant renal injury, characterized by vascular congestion and inflammatory cell infiltration within the renal parenchyma. This indicated a severe inflammatory process and tissue disruption induced by sepsis. Treatment with taxifolin significantly reduced these histological abnormalities, characterized by decreased congestion and inflammatory infiltration, suggesting partial preservation of renal architecture.

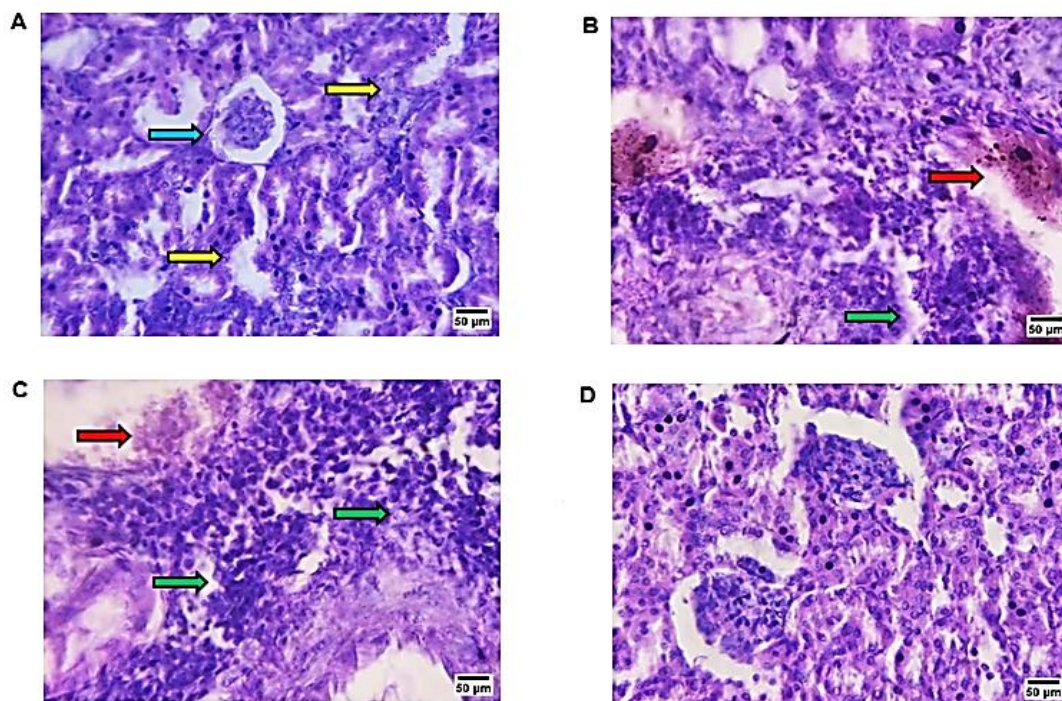


Figure 6: Changes in renal histoarchitecture (H & E), 400 $\times$. Scale bar = 50 μ m. Control group showed intact glomeruli (blue arrow) and distinct tubular structures (yellow arrows; A). Group 2 showed significant damage (score 3), characterized by vascular congestion (red arrow), widespread infiltration of inflammatory cells in the renal tubules and interstitial spaces (green arrow; B). Group 3 showed similar histological abnormalities to group 2, including inflammatory lymphocyte infiltration (green arrows) and vascular congestion (red arrow; C). Treatment with taxifolin significantly reduced CLP-induced renal damage and showed preserved renal glomeruli and tubules (score 1; D)

Following renal injury, oxidative stress and inflammatory reactions activate pathways such as NF- κ B, which enhance KIM-1 gene transcription. Also, cytokines and ROS promote tubular cell dedifferentiation and membrane shedding, resulting in elevated KIM-1 expression and release [23]. Kidney tissue levels of KIM-1 were significantly increased following the CLP procedure, which correlated with kidney damage. This was reversed following treatment with taxifolin, supporting the protective role of taxifolin in sepsis-associated AKI. This is in tandem with an earlier study which revealed that taxifolin decreased serum creatinine and KIM-1 levels following kidney injury induced by cisplatin [24]. The NF- κ B upregulates a variety of genes through both canonical and non-canonical pathways, resulting in nuclear translocation of NF- κ B dimers and transcription of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which drive persistent inflammation and tissue injury in sepsis [25]. This study showed that the CLP procedure significantly increased NF- κ B signaling, reflecting heightened inflammation. However, administration of taxifolin significantly diminished NF- κ B activation, emphasizing its anti-inflammatory properties. These findings are consistent with those reported by Alanezi et al. [26], who demonstrated that

taxifolin attenuated cisplatin-induced nephrotoxicity by inhibiting NF- κ B activation and suppressing the production of pro-inflammatory cytokines.

Excessive oxidative stress during sepsis leads to overproduction of ROS and exhaustion of endogenous antioxidant defenses, contributing to the development of AKI [27]. Malondialdehyde (MDA) serves as a reliable biomarker of lipid peroxidation and oxidative stress, formed as a reactive byproduct of polyunsaturated fatty acid oxidation. Elevated MDA levels reflect increased cellular membrane damage, correlating with pathological conditions linked to oxidative injury [28]. Severe lipid peroxidation and oxidative stress were observed following the CLP procedure, significantly raising MDA levels. However, treatment with taxifolin significantly reduced MDA concentrations compared to group 2, indicating its capacity to attenuate lipid peroxidation and oxidative stress under septic conditions. This effect is consistent with previous experimental studies in which taxifolin significantly reduced MDA levels in models of oxidative injury, including liver ischemia-reperfusion and cyclophosphamide-induced tissue damage [29,30].

The cellular antioxidant defense system is regulated by Nrf2, a critical transcription factor that induces antioxidant and cytoprotective genes [31]. Expression of Nrf2 within the kidney tissues was significantly increased by taxifolin treatment, suggesting a robust activation of the cellular antioxidant defense system. Previous studies demonstrated that taxifolin effectively upregulated Nrf2 expression in kidneys of rodents to counteract oxidative stress and preserve renal function [32]. Also, the observed increase in Nrf2 levels is in agreement with previous findings, which demonstrated that taxifolin restored renal Nrf2 protein levels in mice that had been exposed to drug-induced nephrotoxicity [33]. Apoptosis is a critical factor in the progression of sepsis-induced AKI, as it promotes loss of tubular cells and decline of renal function. Caspase-3 is a key effector enzyme in the apoptotic pathway that is activated downstream by intrinsic and extrinsic death pathways. Active caspase-3 cleaves cellular proteins, resulting in DNA fragmentation and irreversible cell demise [34].

The CLP procedure resulted in excessive oxidative stress and inflammation, leading to the activation of caspase-3, which in turn contributed to organ dysfunction and tissue injury. However, treatment with taxifolin significantly reduced the activation of caspase-3, as corroborated by findings from a previous experimental study [35]. Additional research is necessary to investigate additional mechanistic pathways and to ascertain the translational relevance of these discoveries in clinical environments. Collectively, targeting inflammation and oxidative stress may be a promising therapeutic approach for acute kidney injury associated with sepsis.

CONCLUSION

Taxifolin preserves renal function and maintains histological architecture, thereby effectively mitigating sepsis-induced AKI in the CLP model. The renoprotective properties of taxifolin are associated with the activation of antioxidant defense mechanisms, suppression of inflammatory signaling, and reduction of oxidative stress. These discoveries reinforce the potential of taxifolin as a promising therapeutic agent for the prevention and management of sepsis-associated acute renal injury.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

It was obtained from the Institutional Animal Care and Use Committee (IACUC), University of Kufa (approval no. 2329).

Use of Artificial intelligence/Large language models

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.

Availability of data and materials

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

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. AQA conducted the experiments, collected and analyzed the data, and prepared the initial draft of the manuscript. AMJ supervised the project, contributed to study design and data interpretation, and critically revised the manuscript.

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