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Mechanism study of naringenin in treating sepsis-induced kidney injury based on network pharmacology

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Abstract: Objective The purpose of this investigation was to identify and confirm the molecular mechanisms through which naringenin exerts its therapeutic effects in sepsis-induced acute kidney injury (AKI), employing network pharmacology methodologies. Methods An integrative bioinformatics pipeline was deployed across multiple databases and analytical platforms to identify molecular targets, map protein interactome networks and assess functional annotation clusters. Molecular docking studies were executed to verify the findings. The efficacy was validated using a cecal ligation and puncture-induced AKI mouse model. Histopathological changes were assessed through hematoxylin-eosin staining. Biochemical parameters, including blood urea nitrogen (BUN) and creatinine (Cr), were quantified. Pro-inflammatory mediators (IL-1 and TNF-α) were evaluated via ELISA, while Nrf2 and HO-1 protein expression was determined through Western blot analysis. Results The network pharmacology analysis revealed 3,449 potential therapeutic targets of naringenin in AKI treatment. Target analysis demonstrated significant associations with oxidative stress response and apoptotic signaling cascades. KEGG pathway analysis highlighted the involvement of the Nrf2/HO-1 signaling axis in renal injury. Experimental results showed that naringenin improved pathological changes in AKI mice, down regulated serum BUN and Cr levels, reduced inflammatory factors IL-1 and TNF-α levels and decreased the expression of Nrf2 and HO-1 proteins in sepsis-related AKI. Conclusion The therapeutic efficacy of naringin in AKI is mediated through pleiotropic effects on multiple targets and signaling cascades, with its renoprotective mechanism primarily involving the regulation of Nrf2/HO-1 pathway-dependent oxidative stress reduction.

Keywords: network pharmacology; naringenin; sepsis-related acute kidney injury; Nrf2/HO-1 signaling pathway

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INTRODUCTION

Acute kidney injury (AKI) manifests as a rapid deterioration in renal function attributed to multiple etiological factors. Among the various precipitating causes, infectious processes remain predominant, with sepsis representing the most severe infectious complication (Ronco *et al.*, 2019). The systemic inflammatory cascade triggered by sepsis commonly results in AKI, which remains a predominant factor in ICU patient mortality (Reerapornratana *et al.*, 2019). Consequently, the prevention and management of AKI, coupled with reducing sepsis-associated morbidity and mortality, have emerged as crucial therapeutic objectives in clinical practice.

The intricate pathophysiological mechanisms underlying sepsis-induced AKI present substantial therapeutic challenges. Recent studies have demonstrated that oxidative stress mechanisms and inflammatory cascades play pivotal roles in both the development and evolution of acute renal dysfunction (Zarbock *et al.*, 2014; Yang *et al.*, 2020; Rashid *et al.*, 2023).

Naringenin, a naturally occurring bioflavonoid predominantly found in citrus fruits, with particular abundance in grapefruit species (Shilpa *et al.*, 2023), has garnered significant scientific interest. Recent investigations have demonstrated its diverse biological properties, encompassing anti-inflammatory and antioxidant capabilities (Mahmoud *et al.*, 2019; Amini *et al.*, 2022; Xu *et al.*, 2021). Furthermore, substantial evidence supports its efficacy in ameliorating obesity and metabolic syndrome manifestations (Lu *et al.*, 2023).

Given the documented therapeutic properties of naringenin, we postulated its potential therapeutic efficacy in sepsis-induced AKI. To evaluate this hypothesis, we designed a comprehensive investigation utilizing network pharmacology methodologies to elucidate the underlying mechanisms of naringenin in AKI treatment, followed by experimental validation through *in vivo* models. This investigation aims to establish a theoretical framework for naringenin's clinical application in AKI management and provide a foundation for subsequent detailed investigations.

MATERIALS AND METHODS

Experimental Animals Male C57BL/6 mice (8 weeks of age, body mass 22-26 g) were obtained from Changzhou Cavens Laboratory Animal Co., Ltd. (License No. SCXK (Su) 2021-0013). The mice were housed in a specific-pathogen-free environment with unrestricted availability

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of regular diet and drinking water during the study. The experimental protocols were reviewed and endorsed by the Institutional Animal Care and Use Committee of Wuxi Higher Health Vocational Technology School (Protocol No. 2023006).

Pharmaceuticals and Analytical Reagents The following materials were utilized: Naringenin (Batch No. 20230323, Xi'an Natural Field Bio-Technology Co., Ltd); Creatinine Detection Kit (Cat. No. D799853-0096, Sangon Biotech); Urea Nitrogen Quantification Kit (Cat. No. D799850-0100, Sangon Biotech); Hematoxylin and Eosin Staining Solution (Cat. No. G1005, Wuhan Servicebio Technology Co., Ltd); Mouse IL-1 ELISA Kit (Cat. No. EK301A, MultiSciences); Mouse TNF-α High-Sensitivity ELISA Kit (Cat. No. EK382HS, MultiSciences); Anti-Nrf2 antibody (Cat. No. AF0639, Affinity); Anti-HO-1 antibody (Cat. No. AF5393, Affinity); and Anti-GAPDH antibody (Cat. No. AF7021, Affinity).

Instrumentation and Software The experimental apparatus comprised: OLYMPUS IX53 Inverted Microscope (Japan); Leica RM2016 Rotary Microtome (Germany); Nikon Eclipse C1 Upright Fluorescence Microscope (Japan); Bio-Rad BE6085 Electrophoresis Transfer System (USA). GraphPad Prism version 7.0 was utilized for data analysis (GraphPad Software Inc., San Diego, CA, USA) and ImageJ densitometry software.

Network Pharmacology Study

Target Identification for Naringenin A comprehensive screening of naringenin's molecular targets was conducted utilizing multiple databases, including Traditional Chinese Medicine Systems Pharmacology (TCMSP) (https://old.tcmsp-e.com/index.Hypertext Preprocessor), PubChem's bioassay repository (https://pubchem.ncbi.nlm.nih.gov/), and the Swiss Target Prediction platform (https://swisstargetprediction.ch/).

Identification of Naringenin-AKI Associated Targets The investigation of AKI related genes was performed through extensive mining of the GeneCards databases (https://genecards.org/) and Online Mendelian Inheritance in Man (OMIM) database (https://www.omim.org/). For GeneCards-derived targets, a threshold-based selection was implemented, wherein targets exceeding the median relevance score were designated as potential therapeutic candidates. The therapeutic targets were determined by identifying the overlapping elements between naringenin-associated and AKI-related targets.

Construction of naringenin-target-AKI network The “disease-drug-pathway-target” relationships were summarized and organized. Network visualization and analysis were performed using the Cytoscape platform (version 3.9). The network analysis function in the toolbar was utilized to analyze the network, and key components were screened based on degree values.

The identified overlapping targets were uploaded to STRING database v11.0 (https://string-db.org/) to establish a molecular interaction map, with Homo sapiens selected as the organism. Network analysis was subsequently performed using Cytoscape software version 3.9, and the eight most significant hub proteins were identified through degree centrality ranking.

Functional enrichment and pathway analyses were performed using the Metascape analytical platform (https://metascape.org/). The identified naringenin targets associated with AKI treatment were subjected to Gene Ontology (GO) term enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway mapping, with Homo sapiens selected as the reference organism. The enrichment outcomes were visualized in clustered formats.

The crystallographic coordinates of target proteins were sourced from the RCSB PDB repository (https://www1.rcsb.org/). Prior to docking simulations, crystallographic water molecules and heteroatoms were eliminated utilizing PyMOL visualization system. Bioactive compound structures were acquired from the TCMSP database in mol2 format and subsequently transformed to PDB format through PyMOL interface. In silico molecular docking experiments were executed employing AutoDock 1.5.7 in conjunction with AutoDock Vina. The interaction strength between protein-ligand complexes was evaluated based on calculated binding energy parameters

Animal experiment verification

After a 3-day acclimation period, Male C57BL/6 mice were randomly assigned to three experimental groups: regular control institution, version organization (AKI group), and remedy institution, with 8 mice in every organization. The sepsis model become established by cecal ligation and puncture (CLP) surgery. Drug administration began 12 hours after surgery, with the treatment group receiving daily tail vein injections of naringenin (50 mg/kg), while the model group and normal control group received equal volumes of saline. The treatment lasted for 3 weeks. Animal conditions were closely monitored during the administration period, and survival rates were recorded. At the conclusion of the study, animals were euthanized using ether anesthesia for tissue collection.

Renal morphological analysis was performed on mouse kidney specimens fixed in 4% paraformaldehyde (24h), processed through standard dehydration protocols, embedded in paraffin, and sectioned at 4 μm. Following H&E staining, histopathological evaluation was conducted using light microscopy to assess tubular damage, glomerular architecture, and inflammatory infiltrates.

After three weeks of treatment, orbital sinus blood was extracted and subjected to centrifugation (3,000×g, 15 min) for serum isolation. The obtained serum specimens were analyzed for creatinine and urea nitrogen concentrations. Quantification of serum IL-1 and TNF-α levels in mice was performed utilizing sandwich ELISA methodology. All reagent preparation and washing procedures were executed in accordance with the manufacturer's specifications. The experimental protocol encompassed sequential steps of sample dilution, specimen application, prescribed incubation periods, and antibody introduction. Spectrophotometric measurements were conducted at λ = 450 nm, followed by standard curve construction to derive the inflammatory marker concentrations for each experimental group.

To perform Western blotting, proteins were extracted from kidney cortical specimens using an isolation kit, followed by BCA-based concentration determination. Equivalent protein loads were electrophoresed on 10% SDS-PAGE gels and electroblotted to nitrocellulose/PVDF membranes. Immunoblots were exposed to specific primary antibodies (4°C, overnight), then appropriate secondary antibodies (1h, room temperature). Following TBST washing procedures, protein bands were revealed by chemiluminescence detection and subjected to densitometric evaluation using Image J software.

Data analysis and visualization were conducted with GraphPad Prism 8.0 software. Records have been expressed as $x \pm s$. One-way ANOVA evaluates whether the population means of several independent groups differ significantly. Multiple comparisons between means were performed using Tukey's test. Statistical significance was established at $p<0.05$.

RESULTS

Target prediction for sepsis-induced acute kidney injury and screening of common targets

Through searching the GenCards database, 2,786 sepsis-induced acute kidney injury-related targets were obtained, while 1,673 related targets were found in the DisGeNet database. After merging and removing duplicates, a total of 3,512 sepsis-induced acute kidney injury-related targets were obtained. The TCMSP database was used to screen potential targets of naringenin. Using the jvenn tool to draw a Venn diagram (fig. 1A), 63 intersecting targets were identified as potential targets for naringenin in treating sepsis-induced acute kidney injury.

PPI network analysis and core target prediction

A protein-protein interaction network was generated in STRING database using the 63 overlapping targets (fig. 1B). Using the cytoHubba plugin of CytoScape software, 8 core genes were identified for naringenin's action on sepsis-induced acute kidney injury: BCL2, APP, AKT1, PTGS2, SRC, PPARG, ESR1 and CASP3 (fig. 1C and 1D). These core genes may play crucial roles in naringenin's treatment of sepsis-induced acute kidney injury.

GO enrichment analysis and KEGG pathway analysis

Gene Ontology (GO) enrichment analysis revealed significant enrichment in multiple biological processes (BP), predominantly in the regulation of apoptotic cascade, nitric oxide biosynthesis modulation, xenobiotic response mechanisms, and peptidyl-serine phosphorylation pathways (fig. 2A). These findings indicate naringenin's multifaceted regulatory roles in cellular homeostasis and signal transduction networks.

The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis identified significant enrichment in oncogenic pathways, lipid metabolism and atherosclerosis signaling, and VEGF-mediated signaling cascades (fig. 2B). The results suggest that naringenin's therapeutic effects in sepsis-induced acute kidney injury may be attributed to its pleiotropic regulation of these molecular pathways.

Effects of naringenin on renal cortex pathology in AKI mice

HE staining results (fig. 3) showed that in the control group, the renal cortical epithelial cells were arranged regularly and uniformly, with normal glomerular size and morphology, and clear boundaries. The kidney tissue of the model group mice showed significant pathological changes, including glomerular necrosis and hypertrophy. After naringenin treatment, these pathological changes were significantly improved. This indicates that naringenin can improve the renal pathological condition in mice with sepsis-related acute kidney injury.

Effects of naringenin on serum Cr, BUN, and inflammatory factors IL-1 and TNF-α levels in AKI mice

Biochemical analysis revealed that mice in the model group exhibited markedly elevated serum levels of Cr and BUN, accompanied by significant upregulation of pro-inflammatory cytokines including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) compared to the control group ($P<0.05$ *and* $P<0.01$, respectively). Administration of naringenin substantially attenuated these alterations, as evidenced by the significant reduction in Cr, BUN, IL-1 and TNF-α levels ($P<0.05$) in AKI mice, as depicted in fig. 4A-4D. These findings suggest that naringenin exhibits renoprotective effects through modulation of renal function parameters and suppression of inflammatory mediators in the AKI mouse model.

Effects of naringenin on the Nrf2/HO-1 pathway in AKI mice

Western blot examination demonstrated that Nrf2 and HO-1 protein levels were substantially elevated in kidney tissues of the model cohort relative to the control group (*P*

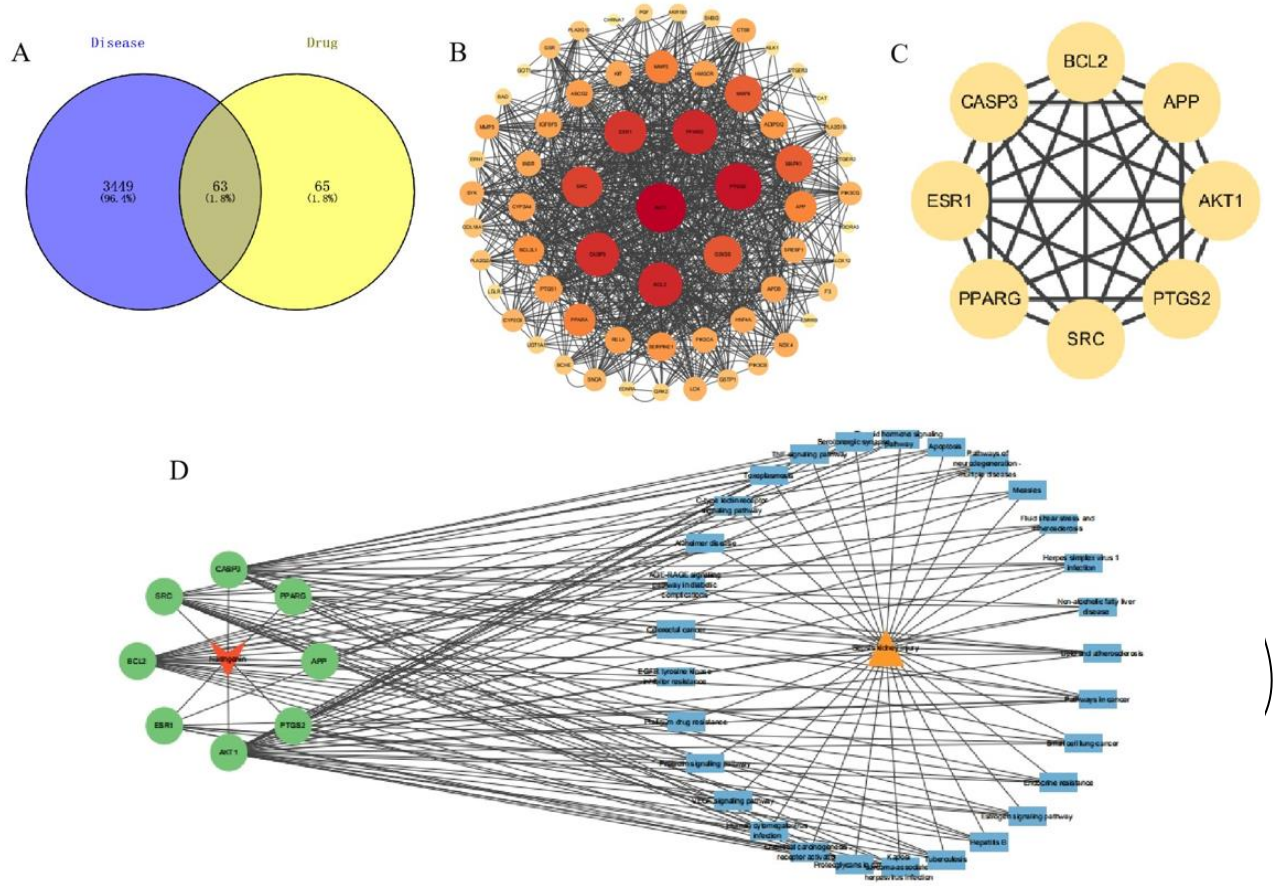

Fig. 1: Target prediction for naringenin in treating sepsis-induced acute kidney injury Note: A: Venn diagram of intersecting targets between naringenin and sepsis-induced acute kidney injury-related genes; B: "Disease-drug-pathway-target" network for naringenin in treating sepsis-induced kidney injury; C: PPI network of potential targets for naringenin in treating sepsis-induced kidney injury; D: Core targets of naringenin in treating sepsis-induced kidney injury.

<0.01), indicating an adaptive mechanism against oxidative stress. The administration of naringenin effectively reduced these heightened protein expressions in AKI mice (*P<0.01*), as illustrated in fig. 4E. The data suggests that the protective mechanisms of naringenin may operate through regulation of the Nrf2/HO-1 signaling cascade.

DISCUSSION

As a prominent dihydroflavone constituent prevalent in Rutaceae species, naringenin has emerged as a focal point of scientific investigation due to its diverse nephroprotective properties. Experimental investigations have demonstrated that naringenin mitigates ischemia-reperfusion-induced AKI in rodent models through the suppression of inflammatory cascades and oxidative stress mechanisms. These protective effects appear to be mediated through multiple pathways. Khalid Alhazzani's study showed that naringenin mitigated the upregulation of pro-inflammatory cytokines (TNF-α, NF-κB and IL-6) induced by dasatinib (DASA), indicating an anti-inflammatory effect (Alhazzani *et al.*, 2025). Naringenin protects IR-AKI by alleviating inflammation, and its mechanism is related to increasing BCL3 and thereby inhibiting the NF-κB pathway (Dai *et al.*, 2021). Furthermore, naringenin exhibits therapeutic potential in diabetic nephropathy through 20-HETE modulation (Ding *et al.*, 2019) and demonstrates protective effects against cyclophosphamide (CP)-induced nephrotoxicity in rat models (Rehman *et al.*, 2012). Nevertheless, the precise molecular mechanisms underlying naringenin's therapeutic effects in sepsis-induced acute kidney injury remain to be fully elucidated.

This investigation employed an integrated approach combining network pharmacology analysis with experimental validation to delineate the molecular mechanisms through which naringenin ameliorates sepsis-associated AKI. The findings suggest that naringenin's therapeutic efficacy may be attributed to its pleiotropic effects across multiple molecular targets and signaling cascades, with particular emphasis on the modulation of the Nrf2/HO-1 pathway as a central mechanism of action. Mechanistic investigation through network pharmacology unveiled diverse molecular targets and signaling cascades

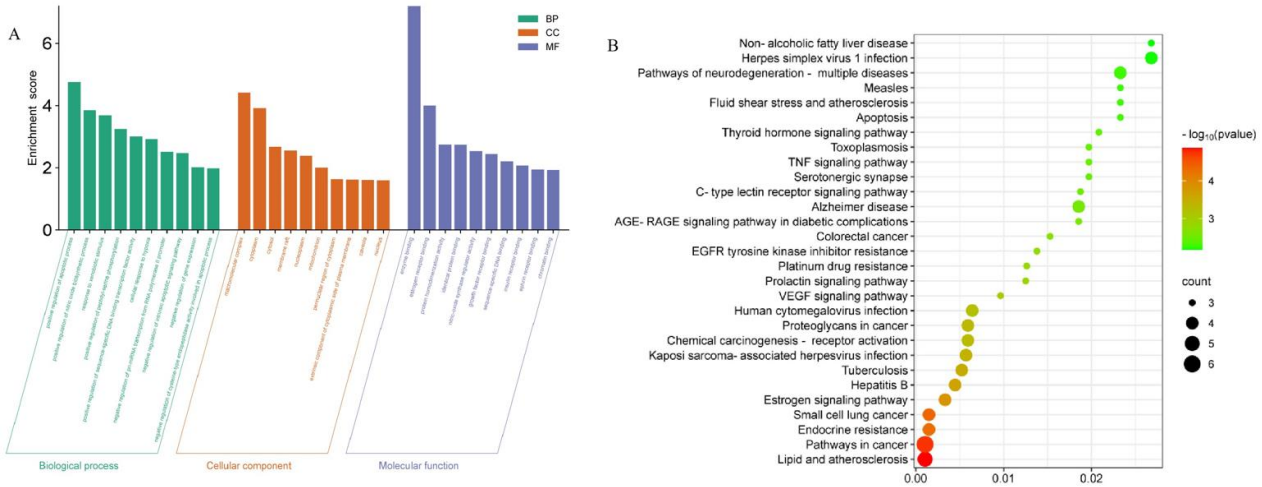

Fig. 2: GO functional enrichment analysis bar chart (2A) and KEGG pathway enrichment analysis bubble plot (2B) of core targets for naringenin in treating sepsis-induced acute kidney injury.

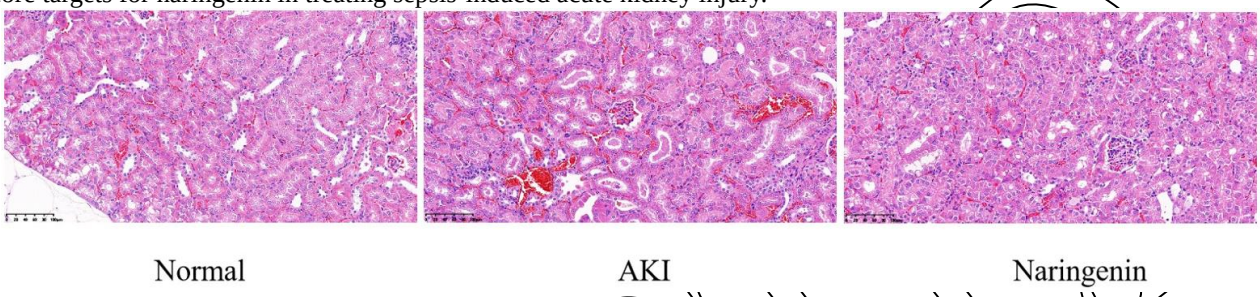

Fig. 3: Naringenin improves histological progression in sepsis-induced kidney injury mice (×200).

of naringenin in treating sepsis-related AKI. We identified BCL2, APP, AKT1, PTGS2, SRC, PPARG, ESR1 and CASP3 as core genes, which serves as a critical mediator in cell growth, division, and inhibition of apoptosis and autophagy and are considered important factors and prognostic indicators for chronic kidney disease (Poston *et al.*, 2019). The results mirror recent advances in our knowledge of sepsis-induced renal dysfunction, highlighting the critical roles of programmed cell death, inflammatory signaling networks, and reactive oxygen species (Wu *et al.*, 2022).

GO enrichment analysis and KEGG pathway analysis further supported this view. The results showed that naringenin may exert its effects by regulating biological processes such as apoptosis, NO biosynthesis, and response to xenobiotic stimuli. These processes are closely related to the pathophysiological mechanisms of sepsis-induced AKI (Zhang *et al.*, 2022). KEGG pathway analysis revealed that naringenin may affect multiple signaling pathways, including cancer-related pathways, lipid metabolism and atherosclerosis, and VEGF signaling. These pathways play important roles in kidney injury and repair processes (Yang *et al.*, 2016).

Our experimental findings in the murine model demonstrated that naringenin administration resulted in marked amelioration of renal pathology in sepsis-induced AKI, accompanied by decreased serum creatinine and BUN levels, along with downregulation of pro-inflammatory cytokines IL-1 and TNF-α. These observations align with previous studies documenting naringenin's renoprotective properties in various kidney injury models (Amini *et al.*, 2022; Dai *et al.*, 2021), further confirming the therapeutic potential of naringenin in sepsis-induced AKI.

Our findings revealed that naringenin's protective mechanisms appear to be mediated through the Nrf2/HO-1 signaling pathway. Nrf2, a crucial transcription factor governing oxidative stress responses, regulates HO-1, its downstream target gene known for antioxidant and anti-inflammatory properties (Chen *et al.*, 2018). Our investigation demonstrated markedly elevated Nrf2 and HO-1 protein expression in renal tissues of mice with sepsis-induced AKI, likely representing a compensatory mechanism against oxidative stress. Naringenin administration resulted in significant downregulation of these proteins, indicating its potential to mitigate oxidative stress through Nrf2/HO-1 pathway modulation, thereby conferring renoprotective effects.

Nevertheless, this study has several limitations. Primarily, while our investigation centered on the Nrf2/HO-1 signaling axis, the therapeutic effects of naringenin likely involve multiple molecular pathways. Further investigations should examine alternative mechanisms, including the NF-κB and MAPK cascades (Amini *et al.*,

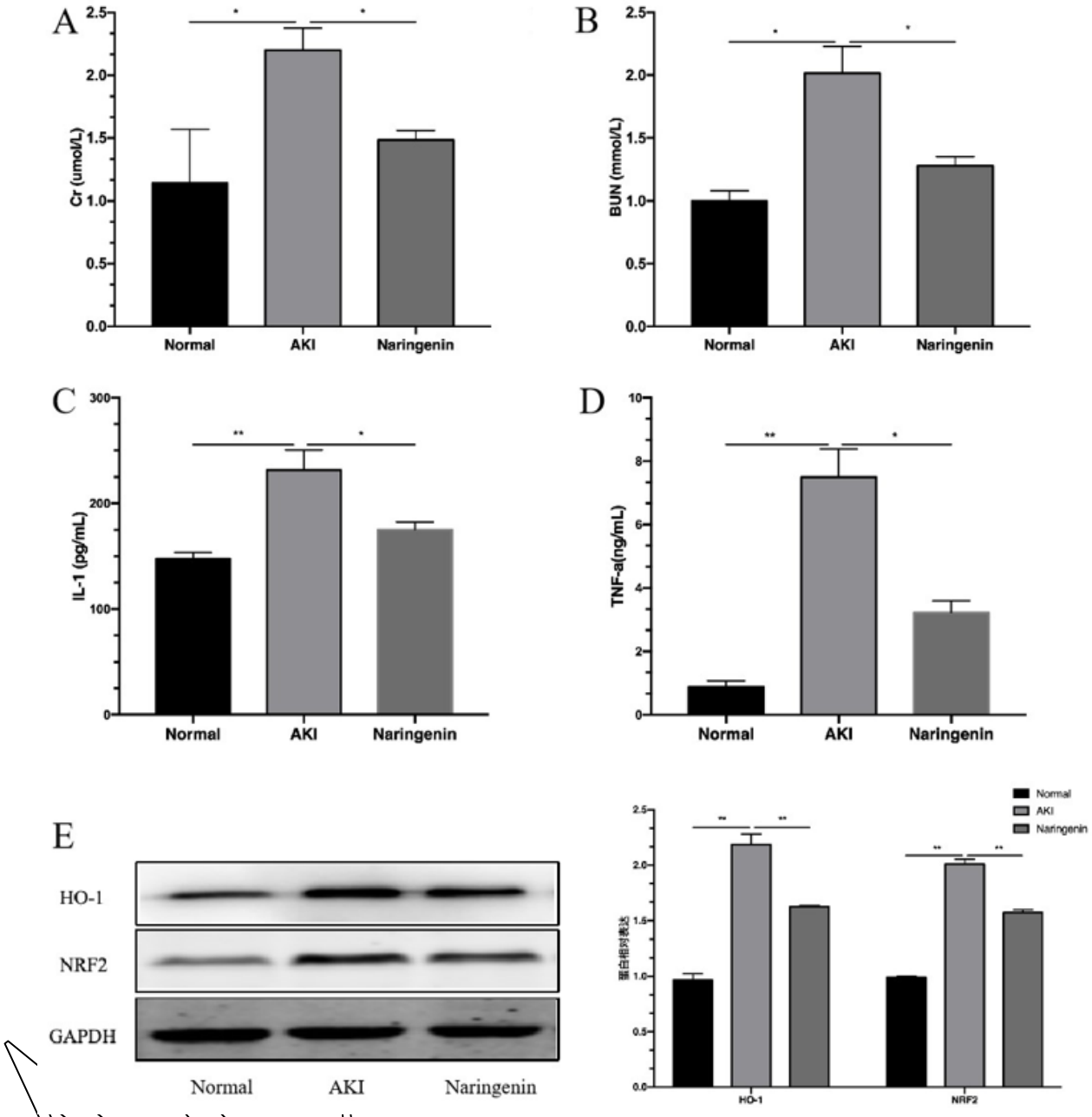

Fig. 4: Effects of naringenin on biochemical indicators, inflammatory factors and Nrf2/HO-1 pathway in sepsis-induced kidney injury mice Note: A-B: Effects of naringenin on Cr and BUN in AKI mice; C-D: Effects of naringenin on IL-1 and TNF-α in AKI mice; E: Effects of naringenin on Nrf2/HO-1 pathway in AKI mice; Compared with the model group, *$p \leq 0.05$ and **$p \leq 0.01$.

2022). Moreover, given that our findings are limited to preclinical models, human clinical trials are imperative to establish the therapeutic efficacy and safety parameters of naringenin. Furthermore, the delivery method and dosage optimization remain critical challenges. Recent advances suggest that nanoformulation approaches could significantly improve naringenin's bioavailability and targeted delivery (Elsori *et al.*, 2024). The exploration of innovative drug delivery systems may therefore be crucial for maximizing naringenin's therapeutic potential.

CONCLUSION

Through an integrated approach combining network pharmacology and experimental validation, this investigation revealed the underlying mechanisms by which naringenin ameliorates sepsis-induced acute kidney injury. The findings demonstrate that naringenin's renoprotective activity operates primarily through modulation of the Nrf2/HO-1 signaling cascade, resulting in the attenuation of inflammatory responses and

oxidative stress. These insights establish a scientific foundation for naringenin's therapeutic application in acute kidney injury and present novel directions for treatment strategy development. Future research should further explore other mechanisms of action of naringenin, optimize administration methods, and conduct clinical validation to promote its application in clinical practice.

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