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ORIGINAL RESEARCH

Network Pharmacology Approach to Unveiling the Mechanism of Wolfberry Mulberry Raspberry Decoction in the Treatment of Sepsis-Induced Myocardial Dysfunction

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Objective: To investigate the mechanisms by which the Wolfberry Mulberry Raspberry Decoction (WMRD) affects Sepsis-Induced Myocardial Dysfunction (SIMD) using network pharmacology and experimental validation.

Methods: We explored the TCM Systems Pharmacology Database to gather biological data for WMRD compounds. The GeneCards, PharmGkb, Therapeutic Target Database (TTD), and Online Mendelian Inheritance in Man (OMIM) databases were utilized to identify target proteins associated with SIMD. Overlapping elements between SIMD and drug targets were analyzed. This data was integrated into the STRING platform to visualize protein interactions. Cytoscape software was then used to construct a network diagram illustrating relationships between drug components and their corresponding targets. Gene Ontology enrichment and Kyoto Encyclopedia of Genes and Genomes pathways analyses were conducted using a database for annotation and visualization. Predictive pathways were validated through experimental studies on cellular and animal models.

Results: Network pharmacology analysis identified 58 active compounds of WMRD and revealed that WMRD partially ameliorated SIMD by modulating apoptosis, TNF signaling pathway and IL-17 signaling pathway. Quercetin, one of the main components of WMRD, suppresses apoptosis and oxidative stress in H9C2 cell via regulating the MMP9, TNF-α, IL-1β and BCL/BAX axis. Quercetin increased BCL-2 expression and decreased MMP9, TNF-α, IL-1β, Bax, and Caspase-3 protein expression in H9C2 cells treated with LPS. Moreover, Quercetin attenuated LPS-Induced myocardial injury and apoptosis in SIMD mice model. Therefore, this study suggests that Wolfberry Mulberry Raspberry decoction may be a potential drug for the treatment of septic myocardial injury, in which Quercetin may play an important role.

Conclusion: Quercetin, a key component of WMRD, suppressed H9C2 cell apoptosis by dysregulating MMP9, TNF-α, IL-1β, and BCL/BAX axis, highlighting its therapeutic potential in SIMD.

Keywords: sepsis-induced myocardial dysfunction, H9C2 cells, quercetin, network pharmacology, wolfberry mulberry raspberry decoction

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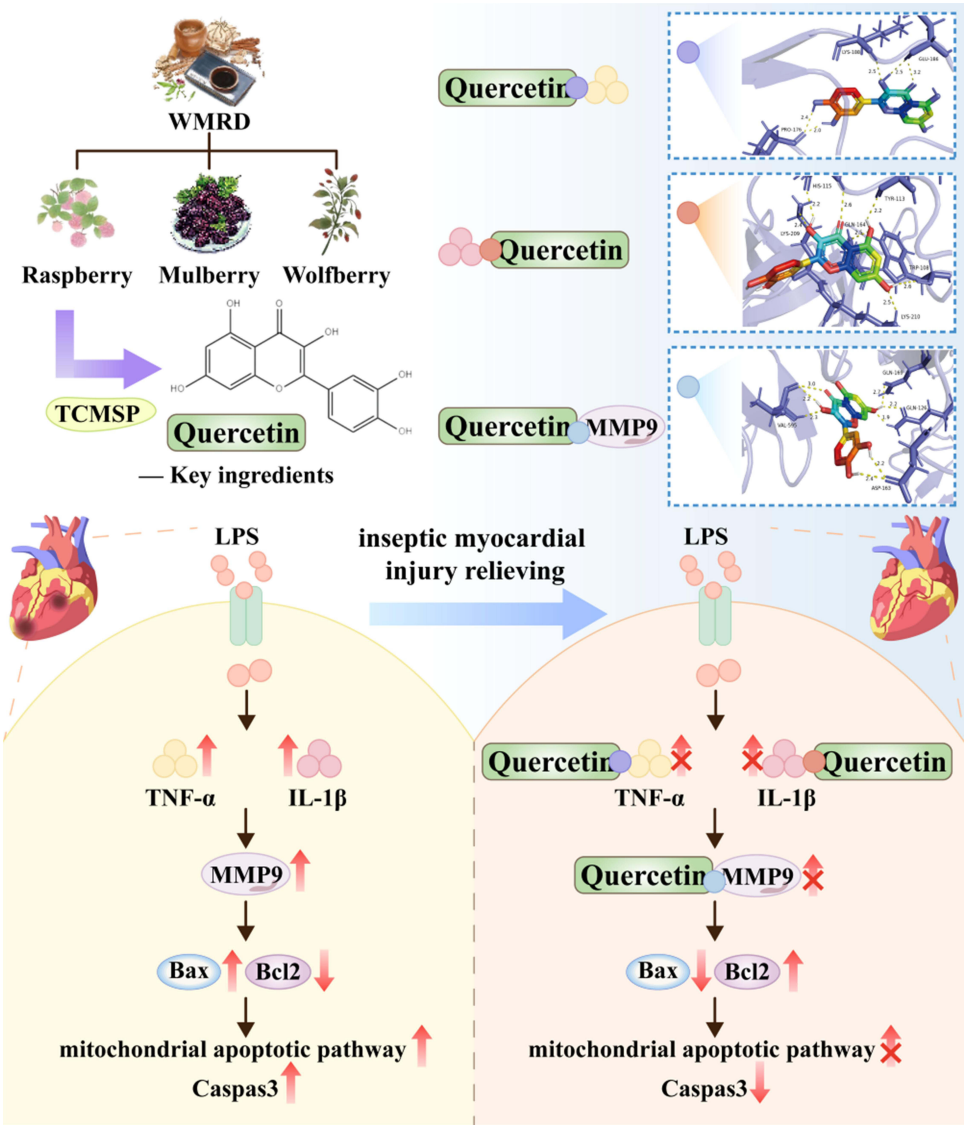
Graphical Abstract



Introduction

Sepsis-induced myocardial dysfunction (SIMD) is a severe complication that affects the prognosis of sepsis patients globally.[1] Epidemiological data shows that approximately 40% to 60% of patients with severe sepsis develop myocardial injury, characterized by decreased cardiac output, left ventricular systolic dysfunction, and arrhythmias.[2] Patients often present with symptoms such as hypotension, tachycardia, elevated cardiac enzymes, and dysfunction of other organs. The pathogenesis of sepsis-induced myocardial injury is complex and involves multiple factors, including the massive release of inflammatory mediators, oxidative stress, mitochondrial dysfunction, and immune dysregulation.[3] Important risk factors for its occurrence include age, underlying cardiovascular diseases, severity of sepsis, and type of infectious source.[4] Exploring these risk factors is crucial for developing prevention and treatment strategies and improving patient prognosis.

The Wolfberry Mulberry Raspberry Decoction (WMRD) is a traditional Chinese medicine formula mainly composed of wolfberry, mulberry, and raspberry, widely used for nourishing the liver and kidneys, replenishing essence and blood, and anti-aging treatments. Wolfberry are rich in polysaccharides, carotenoids, and flavonoids, exhibiting antioxidant,

immune-regulating, and anti-inflammatory effects.[5] Mulberry are rich in various vitamins, minerals, and bioactive substances, capable of improving blood circulation, lowering blood lipids, and protecting the cardiovascular system.[6] Raspberry contains various phenolic compounds with antioxidant and anti-inflammatory properties, enhancing the body's immune system. These pharmacological properties make the WMRD clinically used in treating various age-related diseases such as hypertension, diabetes, and atherosclerosis. Recent studies have suggested that this decoction may have potential therapeutic effects on sepsis-induced myocardial injury. Its possible mechanisms include reducing oxidative stress and inflammatory responses, improving myocardial cell metabolism, protecting mitochondrial function, and regulating immune responses, thereby alleviating sepsis-induced myocardial injury.[7,8] In addition, the polysaccharide components in goji berries and sangberries may exert cardioprotective effects by activating antioxidant enzymes and inhibiting the release of inflammatory mediators.[9]

Network pharmacology is a novel approach to comprehending the effects of drugs that contain multiple components.[10] Li[11] introduced the concept of "network target", which broadens the idea of a drug target from individual molecules to encompass their systematic influence on biological networks. This notion has been useful in studying herbal formulas, which are composed of numerous compounds. The utilization of network targets as a fundamental principle in TCM network pharmacology presents an encouraging research strategy for investigating the underlying biology of herbal formulas and facilitating identification of active ingredients within them. TCM network pharmacology theory and methods have already demonstrated successful applications in analyzing various herb formulas such as Lushi Runzao Decoction, Sijunzi Decoction, and Moluodan.[12–14] Additionally, this continuously evolving theory has achieved significant breakthroughs across diverse fields including intelligent prescription recommendations for TCM and early detection of gastric cancer cells.[15]

To explore the underlying mechanism of how WMRD improves SIMD, we employed a comprehensive approach that combined network pharmacology analysis with experimental validation. We successfully predicted the targets of the compounds in WMRD with a high level of accuracy. Additionally, we constructed a herb-biological function network for WMRD to elucidate its therapeutic mechanism in treating SIMD. Experimental verification showed that Quercetin, a key component of WMRD, could suppress H9C2 cell apoptosis and oxidative stress by regulating the TNF and IL-17 signaling pathways. This study provides a promising strategy to explore the mechanisms of action underlying the therapeutic effects of herbal formulas such as WMRD.

Materials and Methods

Network Pharmacology

Active Ingredient and Predicted Target Collection of WMRD

Using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) platform(https://old.tcmsp-e.com/tcmsp.php),[16] we searched for the three herbs in the Wolfberry Mulberry Raspberry Decoction using the keywords "gouqi", "sangshen", and "fupenzi" to obtain preliminary chemical composition data. Since the WMRD is an oral formula, active chemical ingredients were determined based on oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 as screening conditions. Then, corresponding target information was obtained by searching the TCMSP database. The target names were standardized by limiting the species to "Homo sapiens" in the protein database (https://www.uniprot.org/).[17] This study was approved by the Ethics Committee of Sichuan Provincial People's Hospital and Sichuan Academy of Medical Sciences (2024–486).

Screening of Target Genes Related to SIMD

Using "Sepsis-induced myocardial dysfunction" as the keyword, target genes related to sepsis-induced myocardial injury were searched in the GeneCards database (https://www.genecards.org/),[18] OMIM database (https://www.omim.org/),[19] TTD database (https://db.idrblab.net/ttd/)[20] and PharmGkb database (https://www.pharmgkb.org/)[21] to obtain potential targets for sepsis-induced myocardial injury.

Construction of Interaction Networks Based on Intersection Targets

The obtained effective ingredients and common targets for sepsis-induced myocardial injury were imported into STRING 11.0 (https://cn.string-db.org/),[22] setting the species as "Homo sapiens", to construct a protein-protein interaction (PPI)

network for the treatment of sepsis-induced myocardial injury by the WMRD. Additionally, visualization analysis was conducted on the interaction relationships among the intersection targets.

Selection of Core Clusters and Key Targets

Import the network data into Cytoscape 3.10.2 for visualization and topological analysis, and calculate the hub genes using three algorithms: Maximal Clique Centrality (MCC), Degree Centrality (DC), and Closeness Centrality (CC).

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment Analysis of Intersection Genes

The gene targets that were commonly identified underwent conversion into gene IDs using the DAVID 6.8 database for online ID conversion. The common targets were subjected to analysis of GO annotations for BP, CC, and MF as well as KEGG pathway enrichment analysis. To determine the biological processes and signaling pathways involved in treating sepsis-induced myocardial injury with WMRD, a criterion of corrected P-value less than 0.05 was used for analysis.

Molecular Docking

The molecular structure of Quercetin (CID: 5280343) was obtained from the PubChem database. The protein structures of MMP9 (PDBID: 1GKC), TNF (PDBID: 1A8M), and IL1β (PDBID: 1HIB) were acquired from the PDB database. Molecular docking was performed using AutoDock 1.5.6 software by hydrogenating and assigning charges to the active compounds and target proteins. The Lamarckian Genetic Algorithm (LGA) was used to search for optimal binding conformations, and binding affinities were evaluated based on the calculated binding energy (kcal/mol). The lowest binding energy conformation was selected for further analysis. Visualization and presentation of docking results were conducted using PyMOL software. Additionally, docking reliability was assessed by redocking co-crystallized ligands into their respective protein binding pockets, ensuring that the predicted docking pose was consistent with known binding modes.

Cell Studies

Cell Culture

The H9C2 rat cardiomyocytes were purchased from the cell bank of the Chinese Academy of Sciences (SCSP-5211). They cultured in a constant temperature incubator at 37°C and 5% CO_2, using DMEM medium supplemented with 10% fetal bovine serum and 1 % penicillin/streptomycin. Passage was performed once the cell fusion rate exceeded 90%. For subsequent experiments, only well-conditioned cardiomyocytes in the logarithmic growth phase were utilized. The study consisted of three groups: a normal control group, an LPS group (LPS, MCE, HY-D1056), and an LPS (100 ng/mL)[23]+ Quercetin group (with concentrations of 30 μg/mL, 90 μg/mL, and 150 μg/mL respectively)(Quercetin, MCE, HY-18085) /WMRD group for 24h.

CCK-8 Assay for Cell Proliferation

The logarithmically growing cells were distributed into 96-well plates with 10^6/well. Following a 24-hour incubation, each well received 10 μL of CCK-8 solution and was further cultured for an additional hour in the chamber. The microplate reader was utilized to measure the OD value of the cell groups.

Western Blot

Cells and tissues were collected from the mentioned groups and total protein was extracted using RIPA buffer with PMSF. Western blotting was conducted to determine the levels of MMP9, TNF-α, IL1β, BAX, BCL2, Caspase3 proteins. GAPDH served as an internal reference and Image J software was utilized to calculate the grayscale values representing the relative expression levels of the target proteins.

Detection of Inflammatory Factors

ELISA Kits were employed to identify the presence of various cytokines in H9C2 cells (Rat ELISA Kit, ThermoFish, BMS629). After centrifugation, the manufacturer's protocols were followed to measure cytokine concentrations in the supernatants. The quantification of data was performed using a microplate reader.

Cell Survival Analysis

The membrane integrity and cell viability of H9C2 cells were analyzed by propyl iodide (PI) staining. After treatment, the cells were harvested, washed with PBS, then suspended in Binding Buffer diluted 1:4 with deionized water at a concentration of 1×10^6 cells/mL. The suspension with a volume of 100 μL was mixed with 5 μL Annexin V-FITC and incubated at room temperature (20–25°C) for 10 minutes in a dark room. Before detection, 10 μL PI was added and the samples were diluted with 400 μL PBS.

Animal Studies

Construction of the Sepsis-Induced Myocardial Dysfunction (SIMD) Model

The animal studies was approved by the Ethics Committee of Sichuan Provincial People's Hospital and Sichuan Academy of Medical Sciences (2024–486). ICR mice were purchased by Cyagen company, which is named Ldlr KO (em) Mice. The genetic background of mice is C57BL/6JCya. The male ICR mice were kept in an environment with an ambient temperature of approximately 22°C, a relative humidity ranging from 50% to 60%, and a light/dark cycle of 12 hours. They were provided with unrestricted access to both food and water. Following one week of acclimation, the male ICR mice were randomly assigned into three groups (Control group, LPS group, and LPS+ Quercetin group) using a random number table method. Each group consisted of six mice. The sepsis-induced myocardial dysfunction (SIMD) model was established in the LPS group based on previously reported literature.[23] Briefly, the Control group was administered an intraperitoneal injection of an equal volume of physiological saline. The LPS group received an intraperitoneal injection of lipopolysaccharide (LPS) at a dose of 10 mg/kg to induce the SIMD model. The Quercetin group was pre-treated with an intraperitoneal injection of Quercetin at a dose of 2.5 mg/kg two hours prior to LPS injection. 24 hours following the LPS injection, echocardiography was performed to evaluate cardiac function in all experimental mice. After completing cardiac function assessments, plasma was collected, and the mice were euthanized under deep anesthesia with 1% sodium pentobarbital (30 mg/kg, i.p). The hearts were perfused with pre-chilled sterile PBS to remove blood and subsequently snap-frozen at −80 °C for further analyses. All experiments complied with the ethical standards for the humane use and care of experimental animals, ensuring minimal animal suffering and employing measures to reduce the number of animals used. The study protocol and procedures align with international guidelines for animal research and include steps to ensure scientific rigor and reproducibility in the SIMD modeling process.

HE Staining

Mice myocardial tissues were initially fixed in a 10% paraformaldehyde solution to preserve cellular structures. Later, the tissues were dehydrated with ethanol and xylene, embedded in paraffin, allowing for the formation of solid blocks suitable for sectioning. These blocks were then sliced into thin sections, typically ranging from 5 to 10 micrometers in thickness, using a microtome. Following dewaxing, the sections were flushed with gradient alcohol and distilled water for 5 min, dyed with hematoxylin for 5 min, rinsed in running water for 3 s, washed with 1% hydrochloric acid ethanol for 3 s, and stained with 5% eosin for 3 min. After dehydration, the slices were cleaned, and a light microscope was used to observe the histological changes in the myocardial tissues.

TUNEL Staining

The myocardial tissues of mice were fixed with 4% paraformaldehyde for 24 h, followed by paraffin embedding and sectioning. The sections were subjected to TUNEL detection according to the kit's manual to label apoptotic cells. The samples were observed under a light microscope, and images were taken. Cells with brownish-yellow granules in the nuclei were identified and marked as apoptotic cells.

Quantitative Real-Time PCR (qPCR)

Myocardial tissues were processed as previously described. Briefly, tissues were preserved in RNAprotect® Tissue Reagent (QIAGEN) to maintain RNA stability. Homogenization was performed using a disperser, after which 1 mL of Trizol was added for cell lysis. Subsequently, 0.2 mL of chloroform was introduced, and the mixture was centrifuged at 14,000×g for 25 minutes to achieve phase separation. RNA was then purified from the aqueous phase using the RNeasy Mini Kit (QIAGEN) following the manufacturer's instructions. Reverse transcription of the isolated RNA to cDNA was

performed using a high-capacity cDNA synthesis kit. qPCR was conducted using SYBR Green detection and specific primers for serum amyloid A (Saa) and CRP (Crp). Gapdh was employed as a reference gene to standardize target gene expression levels. The relative expression of the target genes was analyzed using the ΔΔCt method, with PCR efficiency correction performed using Rotor-Gene Q (Qiagen). Ct (cycle threshold) values for each sample were adjusted relative to Gapdh and compared to those of the control group.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 8.0. The mean ± standard deviation was used to express all quantitative data. Prior to statistical testing, normality of the data was assessed using the Shapiro–Wilk test. To compare two groups, the Student's *t*-test was employed, while for comparison among multiple groups, ANOVA was utilized, followed by post hoc analysis using the Tukey's test to control for multiple comparisons. A significance level of $P < 0.05$ indicated statistical significance.

Results

Network Pharmacology

Screening of Therapeutic Targets for WMRD

The WMRD was queried in the Traditional Chinese Medicine Systems Pharmacology Database. With the screening criteria of "Oral Bioavailability (OB) ≥ 30% and Drug-Likeness (DL) ≥ 0.18", a total of 45 components from Wolfberry, 6 components from Mulberry, and 7 components from Raspberry were collected. Through queries of Gene Cards, OMIM, PharmGkb and TTD, 463 target genes related to septic myocardial injury were retrieved. Intersection analysis was performed to identify 53 therapeutic targets for the prevention and treatment of septic myocardial injury by WMRD.

Analysis of the "Active Ingredients-Septic Myocardial Injury" Network Diagram

The drugs, molecular active ingredients, and 53 common targets were imported into Cytoscape 3.8.0 software to construct the "Active Ingredients-Septic Myocardial Injury" visual network (Figure 1A). The sectors represent screened active molecular components, while the rectangles represent the targets. An analysis of the overall characteristics of the visualized network revealed that among active ingredients, some corresponded to multiple target proteins, and some corresponded to the same target protein, indicating that WMRD possesses the characteristics of multi-active ingredients and multi-target effects.

GO Analysis and KEGG Database Enrichment Analysis

GO enrichment analysis of the interaction target genes between WMRD and SIMD was conducted using R language. A total of 2328 enriched terms were identified, including 2152 related to Biological Processes (BP), 141 to Molecular Functions (MF), and 35 to Cellular Components (CC). To ensure statistical significance, a threshold criterion of $P < 0.05$ was applied for filtering the results. The top 10 terms for BP, MF, and CC were ranked based on ascending *P* values and presented in bar charts (Figure 1B). The results revealed that the WMRD targets involved in the prevention and treatment of SIMD were primarily enriched in biological processes such as response to lipopolysaccharide, response to molecules of bacterial origin and biotic stimulus.

KEGG pathway enrichment analysis of the overlapping genes between WMRD and SIMD was also performed using R software. A total of 146 signaling pathways related to the prevention and treatment of SIMD by WMRD were identified. Applying a threshold of $P < 0.05$, the top 30 KEGG pathways were selected and represented in bar charts (Figure 1C). These pathways predominantly included the AGE-RAGE signaling pathway, fluid shear stress, lipid metabolism pathways, TNF signaling pathway, and IL-17 signaling pathway. This analysis underscores the potential mechanisms of WMRD in mitigating SIMD through the regulation of multiple biological pathways and processes.

Construction of the WMRD-SIMD Protein-Protein Interaction (PPI) Network

A total of 53 therapeutic targets related to the prevention and treatment of SIMD by WMRD were obtained from the String database. Using Cytoscape 3.8.0 for network topology analysis, the PPI network was found to consisted of 53 nodes and 864 edges (Figure 2A).

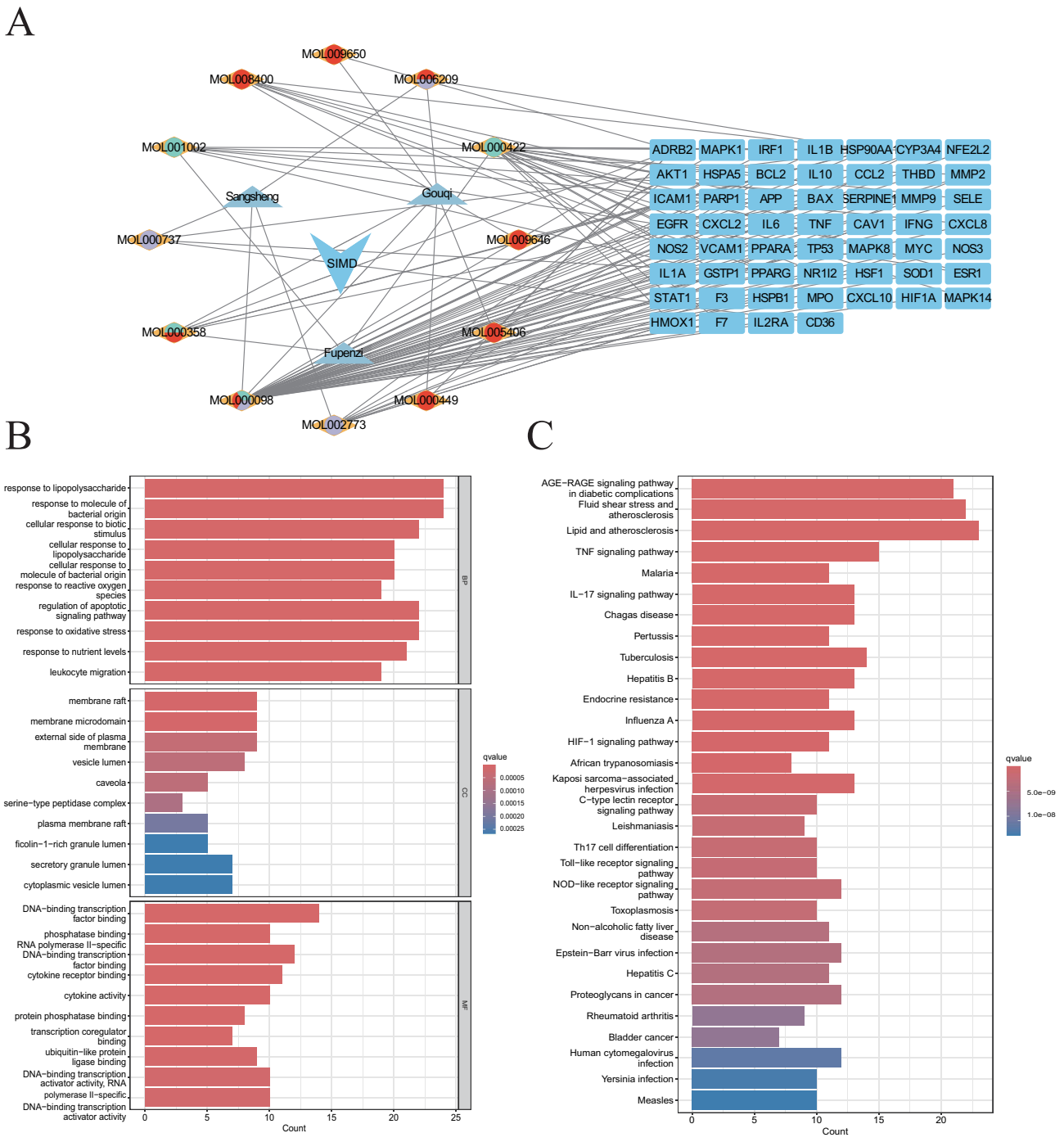


Figure 1 Pharmacological targets of WMRD in sepsis myocardial injury. (**A**) Network diagram of interaction of target proteins overlapping between sepsis myocardial injury and the WMRD. The Green part represents Raspberry, purple part represents Mulberry, red part represents Wolfberry. (**B**) GO enrichment analysis of WMRD and sepsis myocardial injury. (**C**) KEGG enrichment analysis of WMRD and sepsis myocardial injury.
Abbreviations: GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Based on key network parameters, including Degree Centrality (DC), Closeness Centrality (CC), and Maximum Clique Centrality (MCC), 10 core targets were identified. Among these, key targets such as MMP9, TNF, IL1β, and IL6 were prominently involved. These targets play critical roles in the PPI network, highlighting their significance as potential therapeutic targets for SIMD (Figure 2B–D).

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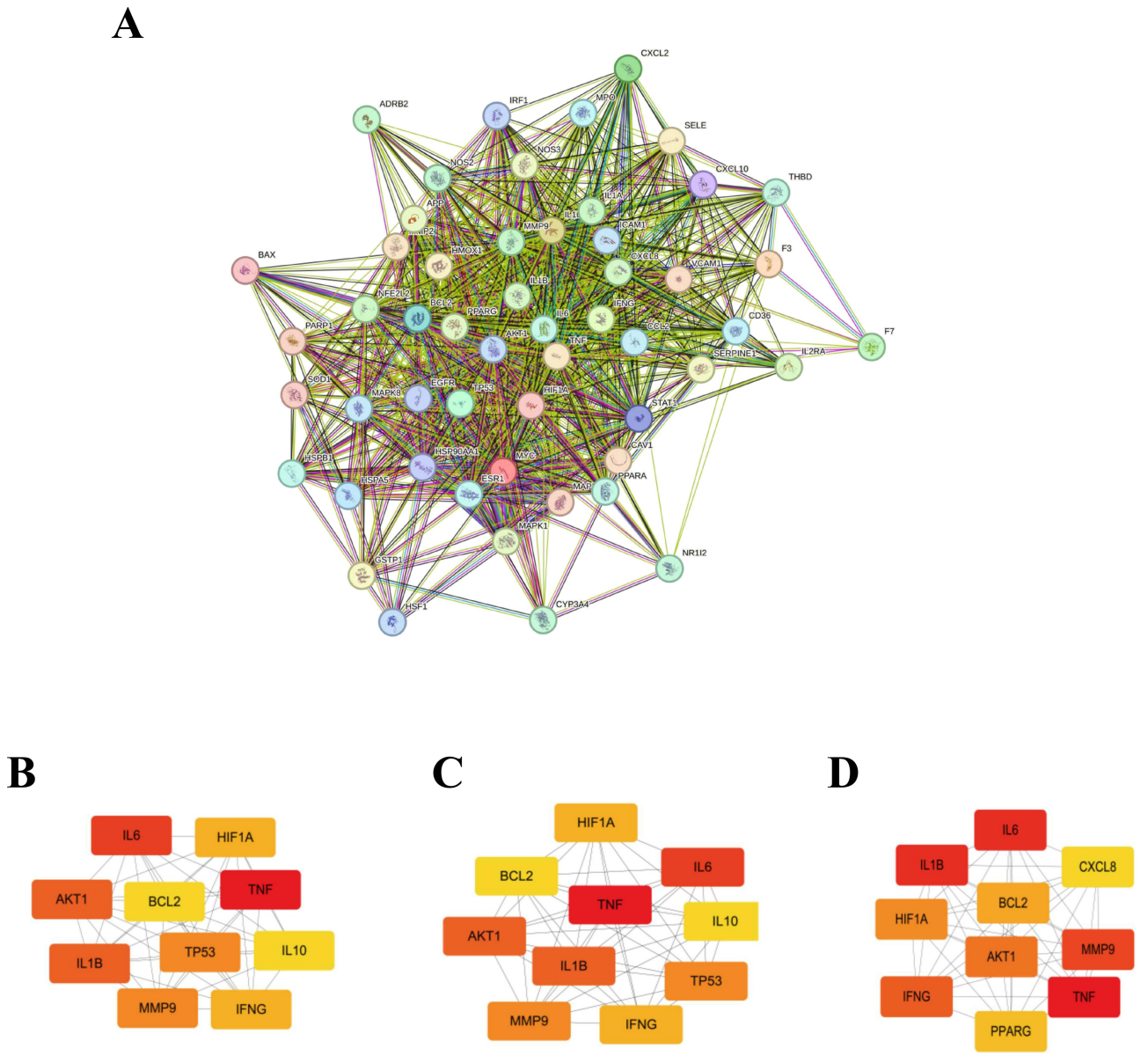

Figure 2 Identification of hub genes of Wolfberry Mulberry Raspberry Decoction. (**A**) Protein-protein interaction network of Wolfberry Mulberry Raspberry Decoction and Sepsis-Induced Myocardial Dysfunction. (**B**) Potential important nodes obtained by CC. (**C**) Potential important nodes obtained by DC. (**D**) Potential important nodes obtained by MCC.

Molecular Docking

To further investigate the interaction between major active components of WMRD and key target proteins, molecular docking analysis was performed, focusing on Quercetin, a primary bioactive compound in WMRD. The docking results demonstrated that Quercetin exhibited strong binding affinity within the docking pockets of the key target proteins. A series of potential target proteins were subsequently examined through experimental studies (Figure 3A–C).

Interaction network analysis revealed that MMP9, IL1β, and TNF-α were highly connected nodes within the network and may play crucial roles in the action of Quercetin in SIMD. Molecular docking confirmed that Quercetin could bind to these proteins with high affinity, with docking scores of −4.53, −3.55, and −3.36 for MMP9, IL1β, and TNF-α, respectively. These results suggest that Quercetin may influence the function of these proteins by competitively binding to their receptor pockets, potentially inhibiting their activity.

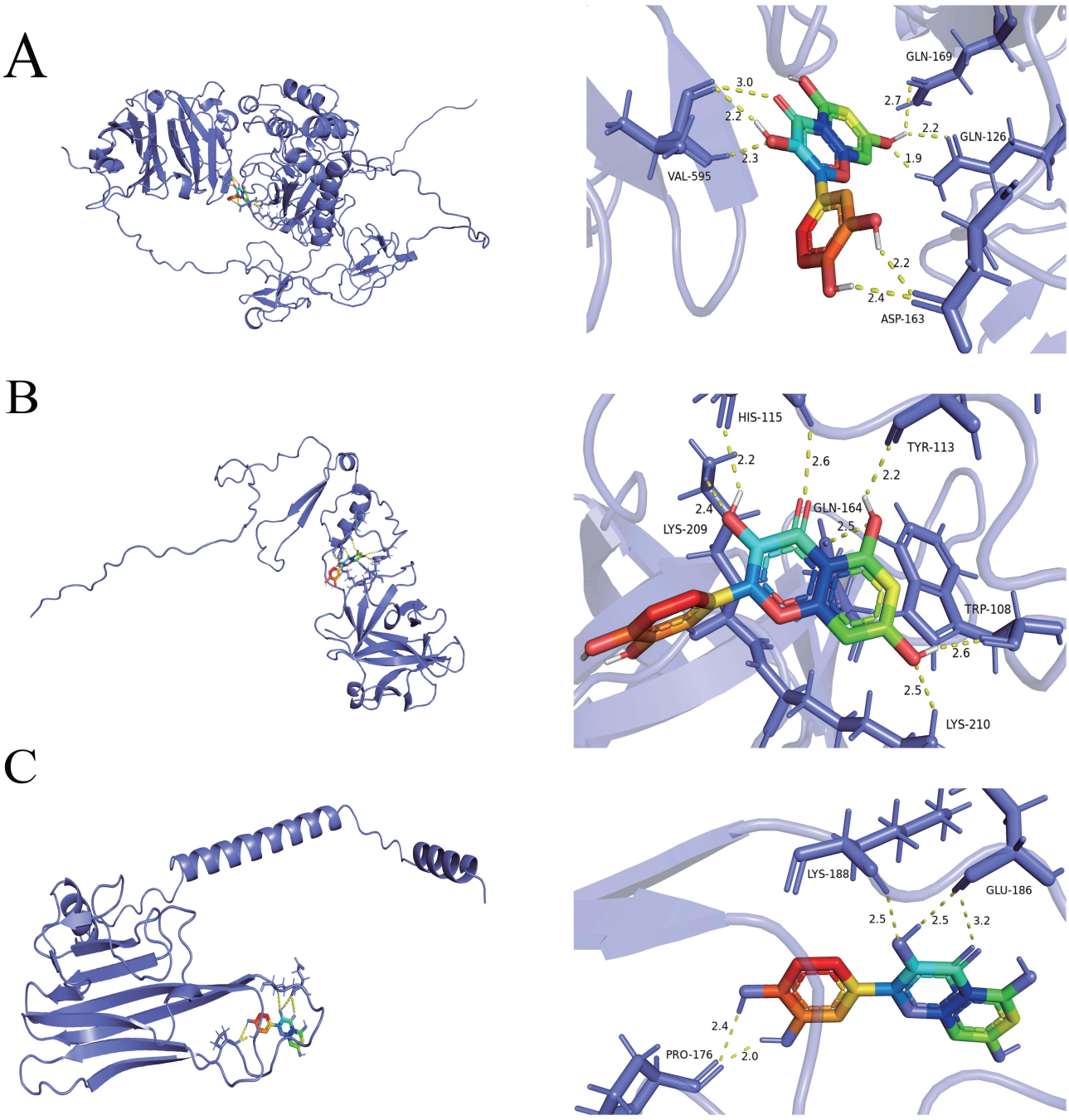

Figure 3 Molecular models of Quercetin binding to its predicted protein targets. (**A**) 3D model of MMP9 (PDBID: 1GKC) crystal structure docking. (**B**) 3D model of IL1β (PDBID: 1HIB) crystal structure docking. (**C**) 3D model of TNF (PDBID: 1A8M) crystal structure docking.

In conclusion, these findings indicate that Quercetin, through its interaction with key targets in the SIMD network, holds promise as a therapeutic agent for the treatment of septic myocardial injury. This underscores the multi-target nature of WMRD in the prevention and treatment of SIMD and highlights the potential of Quercetin as a key active ingredient.

Cell Studies

Effect of Quercetin on the Proliferation of LPS-Induced H9C2 Cells

The effect of Quercetin on the proliferation of lipopolysaccharide (LPS)-induced H9C2 cells was evaluated using the CCK-8 assay. The results showed that, compared to the control group, cell proliferation decreased in the LPS-treated

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group. However, treatment with 90 μg/mL of Quercetin, a primary active ingredient of WMRD, similarly and significantly enhanced cell proliferation compared to the LPS-treated group. (Figure 4A). These findings suggest that WMRD exerts its proliferative effects on H9C2 cells predominantly through Quercetin, highlighting its crucial role in promoting cell proliferation in the context of SIMD.

Quercetin Alleviated the LPS-Induced Apoptosis and Inflammatory Response in H9C2 Cells

Annexin V/PI staining revealed that LPS treatment exacerbated myocardial cell necrosis, whereas treatment with Quercetin and WMRD significantly alleviated myocardial injury (Figure 4B). Subsequently, ELISA was performed to evaluate the effect of Quercetin on the inflammatory response in H9C2 cells. The results showed that LPS stimulation increased the production of pro-inflammatory factors, such as IL-1β and TNF-α, while significantly reducing the expression of the anti-inflammatory factor IL-10. This trend was subsequently reversed by treatment with WMRD and Quercetin (Figure 4C). Notably, both WMRD and Quercetin treatments significantly suppressed the expression of IL-1β and TNF-α. This finding aligns with the competitive binding interactions observed in the previous molecular docking analysis. Moreover, no significant difference was observed between the therapeutic effects of WMRD and Quercetin, suggesting that WMRD exerts its therapeutic effects primarily through Quercetin.

Quercetin Inhibits SIMD by Inhibiting the p38MAPK/NF-κB Signaling Pathway

Western blot analysis revealed that in response to LPS treatment, the expression levels of pro-inflammatory factors IL-1β, TNF-α, and MMP9 were significantly elevated, while the expression of the anti-apoptotic protein Bcl-2 was reduced. In contrast, the expression levels of pro-apoptotic proteins BAX and Caspase3 were markedly increased compared to the control group. However, treatment with Quercetin significantly reversed these changes, reducing the expression of IL-1β, TNF-α, and MMP9, increasing Bcl-2 levels, and decreasing the expression of BAX and Caspase3 (Figure 5A and B). These findings suggest that LPS stimulation induces a pronounced pro-inflammatory and pro-apoptotic response in H9C2 cells, as evidenced by the upregulation of inflammatory mediators (IL-1β, TNF-α, and MMP9) and the activation of apoptosis-related proteins (BAX and Caspase3). The observed reduction in Bcl-2 expression indicates that the balance between pro- and anti-apoptotic signals is shifted toward apoptosis under LPS stimulation, contributing to myocardial cell injury associated with SIMD.

These findings highlight the dual inflammatory and apoptotic mechanisms underlying LPS-induced cardiovascular dysfunction in the context of SIMD. LPS treatment activates the p38MAPK/NF-κB signaling pathway, as evidenced by increased levels of inflammatory mediators (IL-1β, TNF-α, and MMP9) and a shift in the balance of apoptotic regulatory proteins, favoring apoptosis (downregulation of Bcl-2 and upregulation of BAX and Caspase3). These changes collectively contribute to increased myocardial inflammation and apoptosis, exacerbating myocardial injury during sepsis. The ability of Quercetin to reverse these changes demonstrates its anti-inflammatory and anti-apoptotic actions, which are likely mediated by inhibition of the p38MAPK/NF-κB signaling pathway. By restoring the balance between pro-apoptotic and anti-apoptotic signaling and reducing the inflammatory response.

In vivo Studies

Quercetin and WMRD were found to alleviate LPS-induced myocardial injury in SIMD mice. Histological examination of myocardial tissue revealed that the control group exhibited well-organized myocardial fibers, while the LPS group exhibited disorganized myocardial fibers and widened interstitial spaces. In contrast, both the Quercetin and WMRD treatment group showed a reduced disdegree of myocardial fibers compared to the LPS group. TUNEL staining further demonstrated that while the apoptosis rate of myocardial cells in the Quercetin and WMRD groups were higher than that in the Control group, it remained lower than that observed in the LPS group (Figure 6A). Additionally, LPS treatment significantly increased the expression of inflammatory markers such as CRP and SAA, which were markedly reduced by Quercetin and WMRD treatment (Figure 6B). A power analysis confirmed that the sample size of six mice per group was sufficient to meet the experimental requirements (Figure 6C).

Western blot analysis revealed that the expression levels of pro-inflammatory factors (IL-1β, TNF-α, MMP9), pro-apoptotic proteins (BAX and Caspase3), and the anti-apoptotic protein BCL2 were dysregulated in the LPS group, with

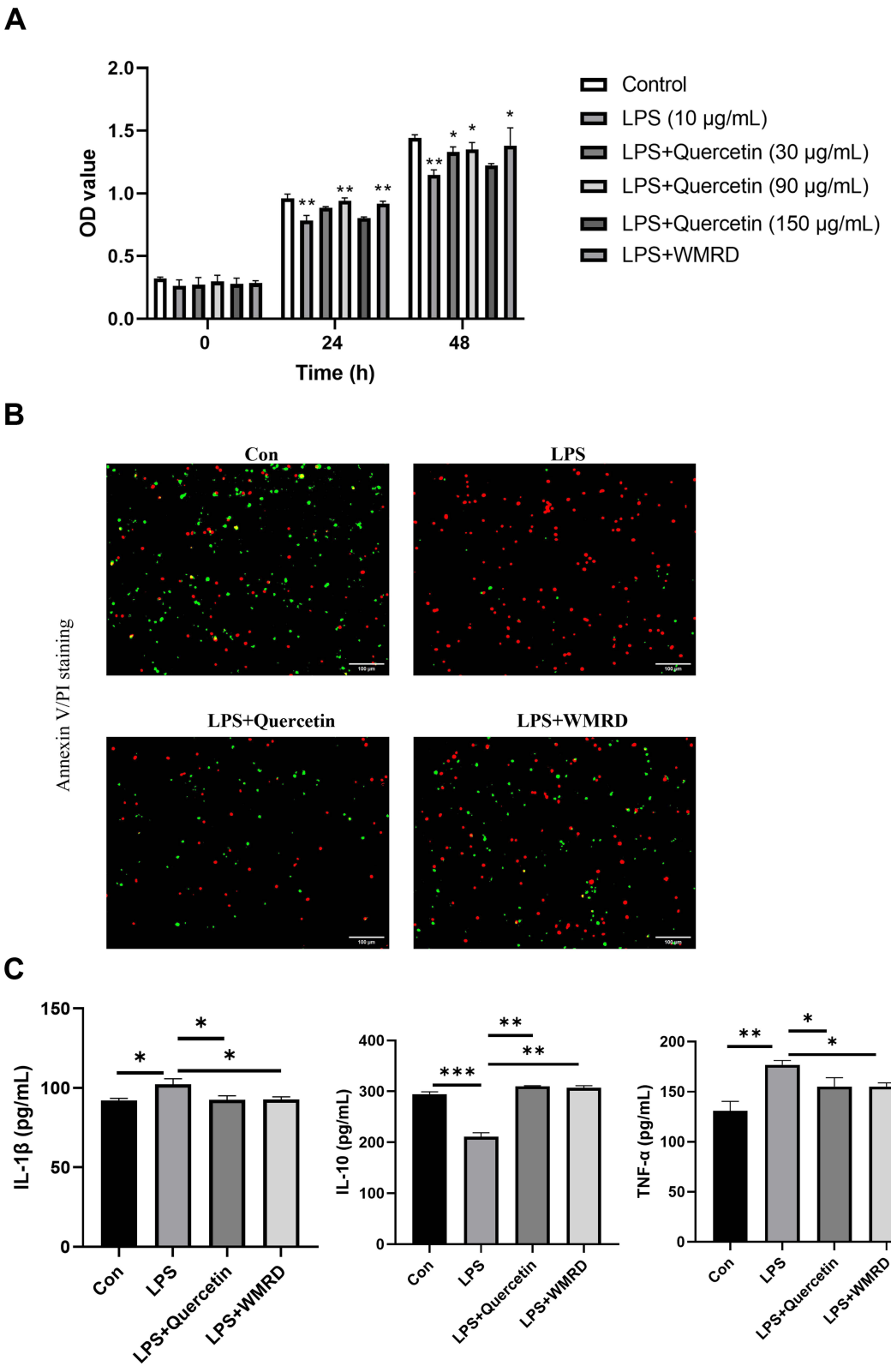

Figure 4 Quercetin as the principal active component of WMRD exhibits prominent effects in ameliorating H9C2 cell injury. (**A**) The therapeutic effects of different concentrations of Quercetin and WMRD on the proliferation of LPS-induced injured H9C2 cells. (**B**) Annexin V/PI staining of H9C2 cells induced by LPS in each group (×20). Scale bar: 20 μm. (**C**) The effect of Quercetin on the expression of IL-1β, IL-10 and TNF-α proteins in LPS-induced H9C2 cells,(n = 6, and data are presented as mean ± SD) **P* < 0.05, ***P* < 0.01.****P* < 0.001. **Abbreviations**: PI staining, Propidium Iodide staining; IL-1β, Interleukin-1beta; IL-10, Interleukin-10; TNF-α, tumor necrosis factor-α; LPS, Lipopolysaccharide.

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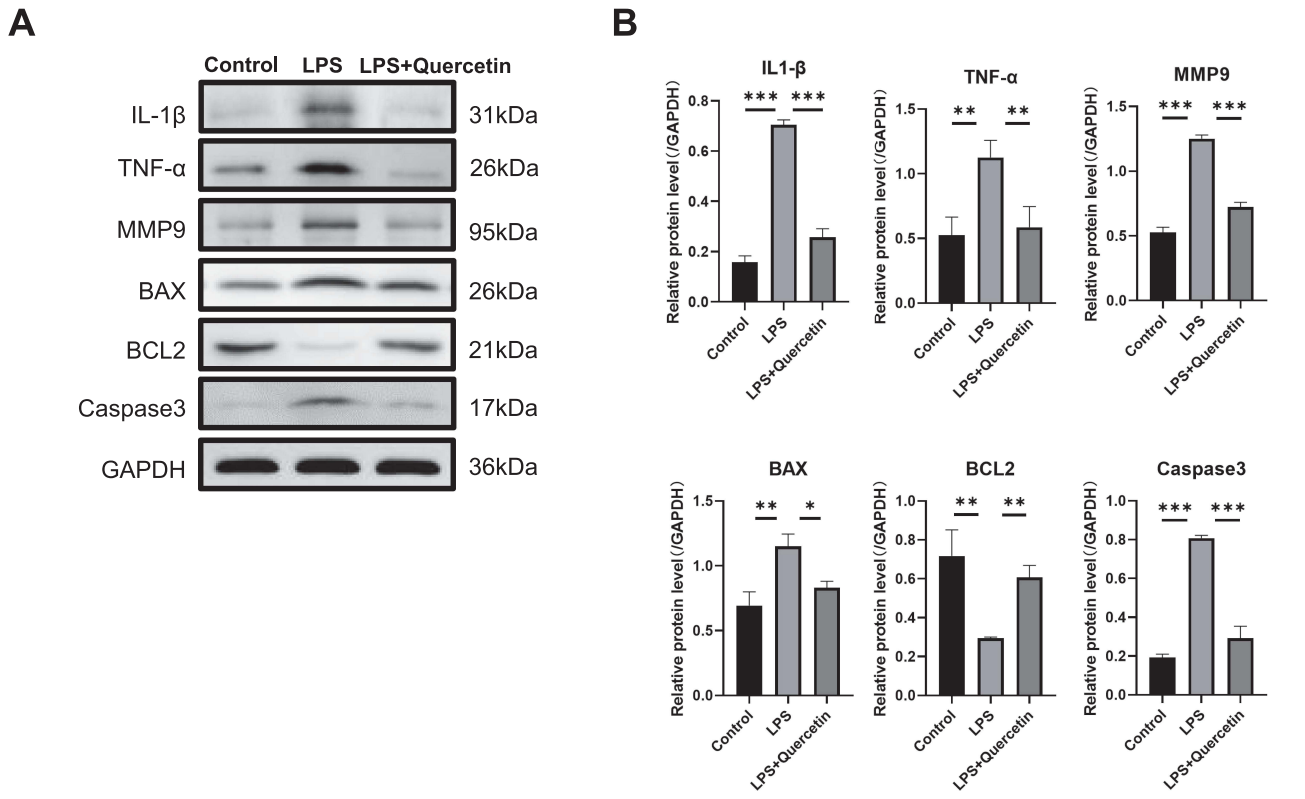

Figure 5 The inhibitory effect of Quercetin on LPS-mediated the inflammation and apoptosis of H9C2 cells. (**A**) Western blot analysis showing protein expression levels of IL-1β, TNF-α, MMP9, Caspase3, BAX, and BCL2 in LPS-induced H9C2 cells. (**B**) Quantification of protein expression levels of IL-1β, TNF-α, MMP9, Caspase3, BAX, and BCL2 (n = 6, and data are presented as mean ± SD) *$P < 0.05$, **$P < 0.01$.***$P < 0.001$.

increased pro-inflammatory and pro-apoptotic markers and decreased BCL2 expression. These changes were effectively reversed by Quercetin treatment, WMRD's main active component (Figure 6D and E).

Discussion

Understanding the underlying mechanisms of WMRD in treating SIMD is crucial for developing novel, effective therapeutic strategies and promoting clinical translation. In this study, a network pharmacology approach was combined with in vitro and in vivo experiments to explore the therapeutic potential of WMRD for SIMD. The findings provide compelling evidence of WMRD's multi-target effects and highlight its potential for clinical applications for SIMD. Network pharmacology analysis identified 58 active compounds in WMRD that collectively target 58 proteins related to SIMD. This characteristic of multi-component, multi-target characteristic is a hallmark of TCM, enabling a comprehensive approach to disease management. The compounds in WMRD interact with various signaling pathways, demonstrating its broad therapeutic potential.

For the selection of core genes, three approaches—DC, CC, and MCC—were used, each with its own strengths and limitations. DC is advantageous for identifying critical nodes that mediate interactions between different signaling pathways, thus highlighting potential cross-talk hubs. However, it may overlook nodes that are essential within individual pathways but lack extensive interactions.[24] CC measures the average shortest path distance of a node to all others, making it suitable for identifying globally influential nodes that are central to overall signaling regulation.[25] However, it may underestimate nodes with localized importance in highly complex subnetworks. MCC focuses on nodes associated with densely connected clusters or modules, emphasizing their roles in localized signaling hubs, such as functional pathways or protein complexes.[26] Its limitation lies in potentially neglecting nodes with broader regulatory influence across the network. These findings collectively illustrate the multitarget and systems-level therapeutic potential of WMRD, providing insights into its role in SIMD treatment and laying the groundwork for further clinical application.

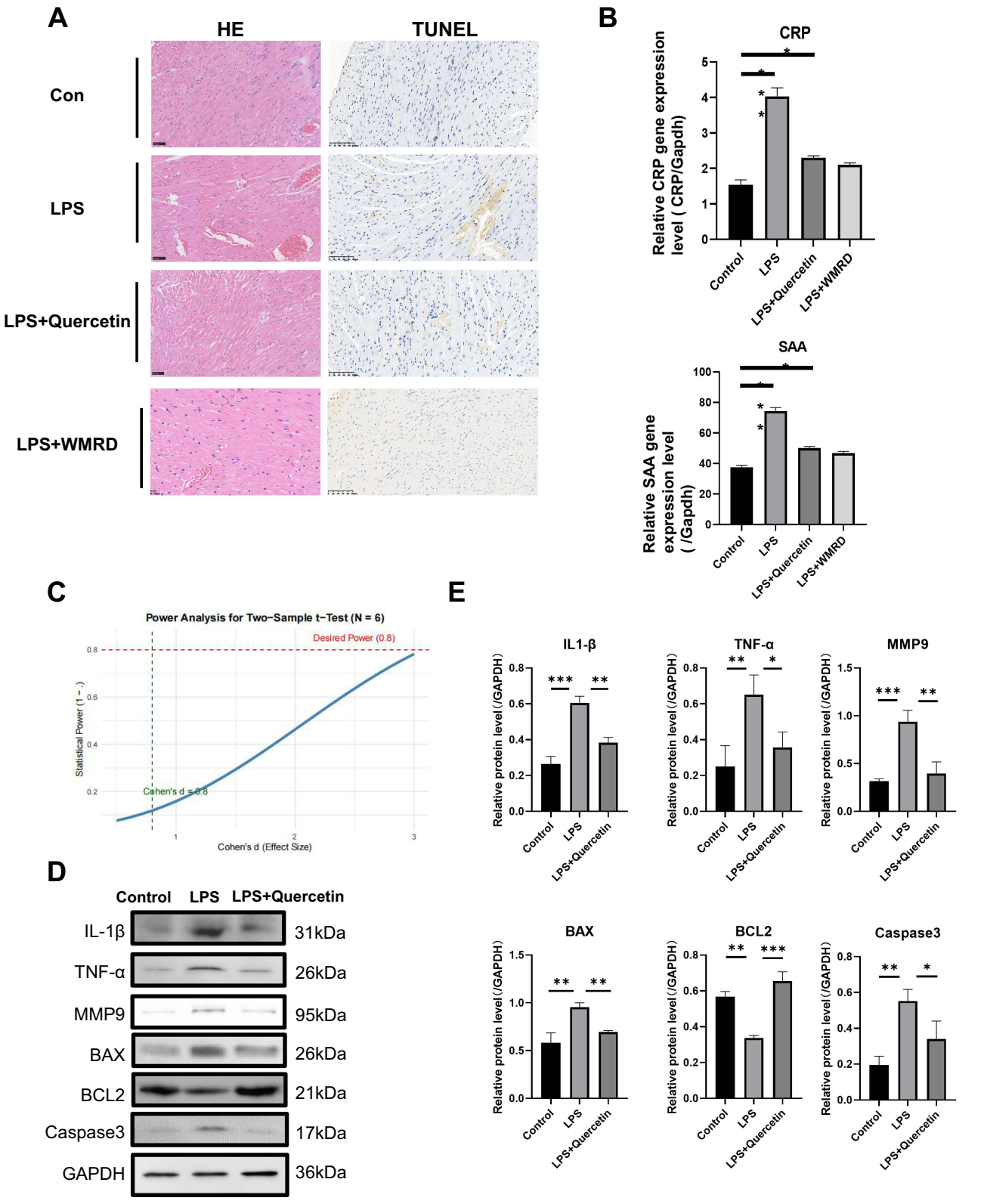

Figure 6 The protective effect of the active component Quercetin in WMRD on septic myocardial dysfunction in mice. (**A**) HE and TUNEL staining of myocardial tissues in each group (HE, TUNEL staining: ×20). Scale bar: 20 μm. (**B**) qPCR analysis showing the gene expression levels of inflammatory biomarkers CRP and SAA in myocardial tissues of each group. (**C**) Power analysis for a two-sample *t*-test (N = 6). (**D**) Western blot analysis showing protein expression levels of IL-1β, TNF-α, MMP9, Caspase3, BAX, and BCL2. (**E**) Quantification of protein expression levels of IL-1β, TNF-α, MMP9, Caspase3, BAX, and BCL2 in each group. (n = 6, and data are presented as mean ± SD) **P* < 0.05, ***P* < 0.01. ****P* < 0.001.

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This study demonstrated that Quercetin, one of the key components of WMRD, regulates apoptotic pathways by increasing the expression of the anti-apoptotic protein Bcl-2 and reducing the levels of pro-apoptotic proteins such as Bax and Caspase-3. GO and KEGG enrichment analyses revealed that pathways enriched in the interaction between WMRD and SIMD are predominantly inflammation-related, such as the TNF signaling pathway. Among all active components of WMRD, Quercetin has been extensively documented in the literature for its significant anti-inflammatory properties.[27–29] Therefore, we selected Quercetin—the bioactive component of WMRD—as the primary therapeutic element for further validation. In vitro and in vivo functional experiments confirmed that the therapeutic effects of WMRD are comparable to those of Quercetin alone, providing strong evidence that WMRD exerts its therapeutic effects primarily through Quercetin.

Cardiomyocyte apoptosis is a key process in SIMD. WMRD has been demonstrated to help maintain cell viability and reduce myocardial damage. During sepsis, a severe inflammatory response occurs in the body, leading to the release of a large number of cytokines such as TNF-α, and IL-1β.[30] These inflammatory cytokines such as TNF-α and IL-1β.[23] These inflammatory cytokines induce cardiomyocyte apoptosis by activating multiple signaling pathways.[31] Specifically, cell apoptosis is mainly achieved through two pathways: endogenous and exogenous. The endogenous pathway mainly involves mitochondrial dysfunction.[32] Bcl2 and Bax are pivotal regulatory factors in mitochondrial-mediated apoptosis, directly influencing mitochondrial function and the balance between cell survival and death. Belonging to different subgroups of the Bcl-2 protein family, they exert anti-apoptotic and pro-apoptotic effects, respectively, and interact to regulate mitochondrial structure and function, particularly mitochondrial membrane permeability and the initiation of apoptosis.[33,34] Upon stimulation by pro-apoptotic signals, Bax translocates from the cytoplasm to the mitochondrial outer membrane, where it inserts into the membrane and forms oligomers, thereby increasing mitochondrial outer membrane permeability and forming pores. This oligomerization of Bax can lead to the loss of mitochondrial membrane potential and the release of pro-apoptotic factors from the mitochondrial cristae, such as cytochrome C and second mitochondria-derived activator of caspases. These factors further activate downstream caspase enzymes (eg, Caspase-3), driving the progression of programmed cell death.[35] The exogenous pathway mainly involves death receptor-mediated apoptosis. TNF-α activates the Fas/FasL signaling pathway via its receptor TNFR1, triggering a cascade reaction of Caspases.[36] In addition, signaling pathways such as TNF-α also play important roles in inflammatory cytokine-mediated apoptosis of myocardial cells.[37] Although WMRD is a multi-component formulation, this study focuses on its key bioactive component, Quercetin, which primarily exerts therapeutic effects. The roles of mulberry and raspberry in the treatment of SIMD remain inadequately explored. Future research will investigate their therapeutic potential in greater depth.

During sepsis, large amounts of pro-inflammatory cytokines such as TNF-α and IL-1β are released. These reactive molecules directly damage key cellular structures such as the cell membrane and mitochondria in myocardial cells, ultimately resulting in apoptosis and necrosis.[38] The TNF signaling pathway plays a crucial role in inflammatory mediators. TNF-α not only directly induces ROS production, which damages myocardial cells, but also enhances other pro-inflammatory pathways, such as the IL-17 signaling pathway, further intensifying the inflammatory response. The IL-17 signaling pathway exacerbates cellular damage during sepsis by regulating ROS production.[39] IL-17 induces a series of pro-inflammatory factors and oxidative stress responses, further amplifying the effects of the TNF signaling pathway, creating a vicious cycle of inflammation and oxidative stress.[40,41] This cycle aggravates myocardial apoptosis and necrosis while worsening the systemic inflammatory response. Under the state of sepsis, the mitochondrial function of myocardial cells is significantly affected. Mitochondria are the main energy production centers in cells and the main source of ROS. Sepsis-induced mitochondrial dysfunction leads to reduced efficiency of the electron transport chain, further increasing ROS production, while reducing ATP generation, leading to disrupted energy metabolism of myocardial cells. Oxidative stress not only damages mitochondrial DNA and proteins but also reduces mitochondrial membrane potential through the oxidative phosphorylation mechanism, ultimately leading to cell apoptosis or necrosis. Studies have shown that antioxidants and mitochondrial protectants have potential therapeutic effects in alleviating sepsis-induced myocardial injury, further emphasizing the central role of oxidative stress in the pathological process.[42] In conclusion, sepsis-induced myocardial injury is closely related to myocardial cell oxidative stress. Oxidative stress not only directly damages myocardial cells but also amplifies the inflammatory response and metabolic disorders through multiple mechanisms, leading to apoptosis and necrosis of myocardial cells. A deep understanding of the role of oxidative stress in sepsis-induced myocardial injury can help develop new treatment strategies and improve patient prognosis.

Quercetin seems to interact with the IL-17 signaling pathway in several important ways, especially in relation to inflammatory and autoimmune diseases. The IL-17 signaling pathway plays a pivotal role in inflammatory and autoimmune diseases, including sepsis. In the context of sepsis, IL-17 is predominantly produced by Th17 cells, along with contributions from γδ T cells, NK cells, NKT cells, and other immune cells.[43] These cells are particularly active in infection and inflammatory responses, making IL-17 a critical player in sepsis. IL-17 promotes the recruitment, activation, and survival of inflammatory cells, especially neutrophils and monocytes, by inducing the production of inflammatory cytokines such as IL-1β, IL-6, TNF-α, chemokines like CXCL1 and CXCL2, and pro-inflammatory mediators such as GM-CSF.[44] These factors intensify the inflammatory response by enhancing the recruitment and activation of inflammatory cells. While IL-17 exacerbates inflammation, it also forms part of the host defense mechanism, especially against bacterial and fungal infections, crucial in the sepsis context. It helps control infection and prevent pathogen over-proliferation. Additionally, IL-17 influences the function of other immune cells, affecting T cell differentiation and function, and modulating B cell antibody production.[45] This dual role complicates its function in sepsis, where it both aggravates inflammation and regulates immune responses to adapt to varying stages of infection and inflammation. Given the multifaceted role of IL-17 in sepsis, targeting the IL-17 pathway may offer therapeutic benefits. Interventions could include antibodies against IL-17 or its receptor to mitigate inflammation, or modulation of its signaling pathway to improve immune responses.[46,47] Understanding these mechanisms is vital for developing new therapeutic strategies and enhancing treatment outcomes for sepsis patients.

The multi-faceted pharmacological actions of WMRD offer a promising therapeutic strategy for SIMD. By targeting apoptosis, oxidative stress, and inflammation, WMRD can address the complex pathophysiology of SIMD more effectively than single-target therapies. This integrative approach aligns well with the principles of TCM, which emphasizes holistic and synergistic treatment modalities.

For future directions, one of the critical next steps is to investigate the potential of integrating WMRD with conventional sepsis treatments. Combining WMRD with standard care protocols could enhance therapeutic efficacy and improve patient outcomes. Clinical trials should be designed to evaluate the safety, efficacy, and optimal dosing regimens of such combined therapies in diverse patient populations. Moreover, while Quercetin was highlighted in this study, other active compounds in WMRD may also contribute to its therapeutic effects. Comprehensive studies using advanced techniques like metabolomics and proteomics can help identify and characterize these compounds. Understanding the interactions and synergistic effects among these compounds will provide deeper insights into the holistic benefits of WMRD. Further mechanistic studies should be conducted in various in vitro and in vitro models to confirm and expand upon the findings from H9C2 cells. Animal models, particularly those that closely mimic human sepsis conditions, are essential for validating the cardioprotective effects of WMRD and its individual components. Such studies will also help elucidate the detailed molecular mechanisms underlying WMRD's therapeutic actions.

Conclusion

This study provides substantial evidence supporting the use of WMRD in treating SIMD. The network pharmacology approach, combined with in vitro experiments, elucidated the underlying mechanisms of WMRD's therapeutic effects. Quercetin, a key component of WMRD, exerts significant cardioprotective effects by modulating apoptosis, oxidative stress, TNF signaling pathways and IL-17 signaling pathways. These findings underscore the potential of WMRD as a multifaceted therapeutic strategy for SIMD, warranting further clinical investigation and integration into sepsis management protocols. The study indicated the potential therapeutic effect of Quercetin in Wolfberry Mulberry Raspberry Decoction. Quercetin alleviates the complex pathophysiological processes of septic myocardial injury by regulating apoptosis, oxidative stress and inflammatory pathways, showing extensive therapeutic potential. Further clinical research and experimental verification will help to give full play to the advantages of Wolfberry Mulberry Raspberry Decoction as a comprehensive drug for the treatment of septic myocardial injury and provide an important reference for clinical transformation.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, [XC, YZ], upon reasonable request.

Ethics Approval

The study was approved by the Ethics Committee of Sichuan Provincial People's Hospital and Sichuan Academy of Medical Sciences (approval ID: 2024-486). All experimental techniques followed the guidelines for the Care and Use of Laboratory Animals and were conducted in compliance with the ARRIVE guidelines 2.0.

ARRIVE Guideline

The complete ARRIVE list has been uploaded as a supplementary document. This study followed the ARRIVE guidelines 2.0.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interests.

References

1. Shvilkina T, Shapiro N. Sepsis-induced myocardial dysfunction: heterogeneity of functional effects and clinical significance. *Front Cardiovasc Med*. 2023;10:1200441. doi:10.3389/fcvm.2023.1200441
2. Yang H, Zhang Z. Sepsis-induced myocardial dysfunction: the role of mitochondrial dysfunction. *Inflamm Res*. 2021;70(4):379–387. doi:10.1007/s00011-021-01447-0
3. Lin Y, Xu Y, Zhang Z. Sepsis-induced myocardial dysfunction (SIMD): the pathophysiological mechanisms and therapeutic strategies targeting mitochondria. *Inflammation*. 2020;43(4):1184–1200. doi:10.1007/s10753-020-01233-w
4. Rong J, Tao X, Lin Y, et al. Loss of hepatic angiotensinogen attenuates sepsis-induced myocardial dysfunction. *Circ Res*. 2021;129(5):547–564. doi:10.1161/CIRCRESAHA.120.318075
5. Li JS, Ji T, Su SL, et al. Mulberry leaves ameliorate diabetes via regulating metabolic profiling and AGEs/RAGE and p38 MAPK/NF-κB pathway. *J Ethnopharmacol*. 2022;283:114713. doi:10.1016/j.jep.2021.114713
6. Bowman R, Taylor J, Muggleton S, Davis D. Biophysical effects, safety and efficacy of raspberry leaf use in pregnancy: a systematic integrative review. *BMC Complement Med Ther*. 2021;21(1):56. doi:10.1186/s12906-021-03230-4
7. Zhao GZ, Guo YH, Li B, et al. Research progress of traditional Chinese medicine in prevention and treatment of sepsis. *Zhongguo Zhong Yao Za Zhi*. 2017;42(8):1423–1429. doi:10.19540/j.cnki.cjcmm.2017.0038
8. Zhang Y, Zhao Z, Tang E, Hu Y, Mao J. Additional traditional Chinese medicine on gastrointestinal dysfunction in patients with sepsis: a systematic review and meta-analysis. *Pak J Pharm Sci*. 2016;29(2 Suppl):663–669.
9. Li X, Wei S, Niu S, et al. Network pharmacology prediction and molecular docking-based strategy to explore the potential mechanism of Huanglian Jiedu decoction against sepsis. *Comput Biol Med*. 2022;144:105389. doi:10.1016/j.compbiomed.2022.105389
10. Zhang B, Wang X, Li S. An integrative platform of TCM network pharmacology and its application on a herbal formula, qing-luo-yin. *Evid Based Complement Alternat Med*. 2013;2013:456747. doi:10.1155/2013/456747
11. Li S, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chin J Nat Med*. 2013;11(2):110–120. doi:10.3724/SP.J.1009.2013.00110
12. Fengtao P, Kesong LI, Yi Z, Xiaopo T, Xinyao Z. Efficacy of Lushi Runzao decoction on ameliorating Sjogren's syndrome: a network pharmacology and experimental verification-based study. *J Tradit Chin Med*. 2023;43(4):751–759. doi:10.19852/j.cnki.jtcm.2023.04.004
13. Shang L, Wang Y, Li J, et al. Mechanism of Sijunzi Decoction in the treatment of colorectal cancer based on network pharmacology and experimental validation. *J Ethnopharmacol*. 2023;302(Pt A):115876. doi:10.1016/j.jep.2022.115876
14. Zhou W, Zhang H, Wang X, et al. Network pharmacology to unveil the mechanism of Moluodan in the treatment of chronic atrophic gastritis. *Phytomedicine*. 2022;95:153837. doi:10.1016/j.phymed.2021.153837
15. Zhou W, Yang K, Zeng J, et al. FordNet: recommending traditional Chinese medicine formula via deep neural network integrating phenotype and molecule. *Pharmacol Res*. 2021;173:105752. doi:10.1016/j.phrs.2021.105752
16. Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J Cheminform*. 2014;6(1):13. doi:10.1186/1758-2946-6-13

17. Bateman A, Martin M-J, Orchard S. UniProt: the universal protein knowledgebase in 2023. *Nucleic Acids Res*. 2023;51(D1):D523–d531. doi:10.1093/nar/gkac1052
18. Safran M, Dalah I, Alexander J, et al. GeneCards Version 3: the human gene integrator. *Database*. 2010;2010:baq020. doi:10.1093/database/baq020
19. Amberger JS, Hamosh A. Searching online mendelian inheritance in man (OMIM): a knowledgebase of human genes and genetic phenotypes. *Curr Protoc Bioinformatics*. 2017;58(1):1.2.1–1.2.12. doi:10.1002/cpbi.27
20. Zhou Y, Zhang Y, Zhao D, et al. TTD: therapeutic target database describing target druggability information. *Nucleic Acids Res*. 2024;52(D1): D1465–d1477. doi:10.1093/nar/gkad751
21. Thorn CF, Klein TE, Altman RB. PharmGKB: the pharmacogenomics knowledge base. *Methods Mol Biol*. 2013;1015:311–320.
22. Szklarczyk D, Kirsch R, Koutrouli M, et al. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res*. 2023;51(D1):D638–d646. doi:10.1093/nar/gkac1000
23. Fang D, Li Y, He B, et al. Gastrin attenuates sepsis-induced myocardial dysfunction by down-regulation of TLR4 expression in macrophages. *Acta Pharm Sin B*. 2023;13(9):3756–3769. doi:10.1016/j.apsb.2023.06.012
24. Oh KK, Gupta H, Min BH, et al. Elucidation of prebiotics, probiotics, postbiotics, and target from gut microbiota to alleviate obesity via network pharmacology study. *Cells*. 2022;11(18):2903. doi:10.3390/cells11182903
25. Li G, Li M, Wang J, Li Y, Pan Y. United neighborhood closeness centrality and orthology for predicting essential proteins. *IEEE/ACM Trans Comput Biol Bioinform*. 2020;17(4):1451–1458. doi:10.1109/TCBB.2018.2889978
26. Wu S, Liu M, Zhang M, et al. The gene expression of CALD1, CDH2, and POSTN in fibroblast are related to idiopathic pulmonary fibrosis. *Front Immunol*. 2024;15:1275064. doi:10.3389/fimmu.2024.1275064
27. Duan ZL, Wang YJ, Lu ZH, et al. Wumei Wan attenuates angiogenesis and inflammation by modulating RAGE signaling pathway in IBD: network pharmacology analysis and experimental evidence. *Phytomedicine*. 2023;111:154658. doi:10.1016/j.phymed.2023.154658
28. Li Y, Yao J, Han C, et al. Quercetin, Inflammation and Immunity. *Nutrients*. 2016;8(3):167. doi:10.3390/nu8030167
29. Islam MT, Tuday E, Allen S, et al. Senolytic drugs, dasatinib and quercetin, attenuate adipose tissue inflammation, and ameliorate metabolic function in old age. *Aging Cell*. 2023;22(2):e13767. doi:10.1111/acel.13767
30. Li N, Zhou H, Wu H, et al. STING-IRF3 contributes to lipopolysaccharide-induced cardiac dysfunction, inflammation, apoptosis and pyroptosis by activating NLRP3. *Redox Biol*. 2019;24:101215. doi:10.1016/j.redox.2019.101215
31. Wu B, Song H, Fan M, et al. Luteolin attenuates sepsis-induced myocardial injury by enhancing autophagy in mice. *Int J Mol Med*. 2020;45 (5):1477–1487. doi:10.3892/ijmm.2020.4536
32. Zou R, Tao J, Qiu J, et al. DNA-PKcs promotes sepsis-induced multiple organ failure by triggering mitochondrial dysfunction. *J Adv Res*. 2022;41:39–48. doi:10.1016/j.jare.2022.01.014
33. Peña-Blanco A, García-Sáez AJ. Bax, bak and beyond - mitochondrial performance in apoptosis. *Febs J*. 2018;285(3):416–431. doi:10.1111/ febs.14186
34. Ahsan N, Shariq M, Surolia A, Raj R, Khan MF, Kumar P. Multipronged regulation of autophagy and apoptosis: emerging role of TRIM proteins. *Cell Mol Biol Lett*. 2024;29(1):13. doi:10.1186/s11658-023-00528-8
35. Baines CP. The cardiac mitochondrion: nexus of stress. *Annu Rev Physiol*. 2010;72(1):61–80. doi:10.1146/annurev-physiol-021909-135929
36. Wang C, Yuan W, Hu A, et al. Dexmedetomidine alleviated sepsis-induced myocardial ferroptosis and septic heart injury. *Mol Med Rep*. 2020;22 (1):175–184. doi:10.3892/mmr.2020.11114
37. Xiong X, Lu L, Wang Z, et al. Irisin attenuates sepsis-induced cardiac dysfunction by attenuating inflammation-induced pyroptosis through a mitochondrial ubiquitin ligase-dependent mechanism. *Biomed Pharmacother*. 2022;152:113199. doi:10.1016/j.biopha.2022.113199
38. An R, Zhao L, Xu J, et al. Resveratrol alleviates sepsis-induced myocardial injury in rats by suppressing neutrophil accumulation, the induction of TNF-α and myocardial apoptosis via activation of Sirt1. *Mol Med Rep*. 2016;14(6):5297–5303. doi:10.3892/mmr.2016.5861
39. Ge Y, Huang M, Yao YM. Biology of interleukin-17 and its pathophysiological significance in sepsis. *Front Immunol*. 2020;11:1558. doi:10.3389/ fimmu.2020.01558
40. Paintlia MK, Paintlia AS, Singh AK, Singh I. Synergistic activity of interleukin-17 and tumor necrosis factor-α enhances oxidative stress-mediated oligodendrocyte apoptosis. *J Neurochem*. 2011;116(4):508–521. doi:10.1111/j.1471-4159.2010.07136.x
41. Csiszar A, Ungvari Z. Synergistic effects of vascular IL-17 and TNFalpha may promote coronary artery disease. *Med Hypotheses*. 2004;63 (4):696–698. doi:10.1016/j.mehy.2004.03.009
42. Xingyue L, Shuang L, Qiang W, Jinjuan F, Yongjian Y. Chrysin ameliorates sepsis-induced cardiac dysfunction through upregulating Nfr2/Heme oxygenase 1 pathway. *J Cardiovasc Pharmacol*. 2021;77(4):491–500. doi:10.1097/FJC.0000000000000989
43. Mills KHG. IL-17 and IL-17-producing cells in protection versus pathology. *Nat Rev Immunol*. 2023;23(1):38–54. doi:10.1038/s41577-022-00746-9
44. Griffin GK, Newton G, Tarrio ML, et al. IL-17 and TNF-α sustain neutrophil recruitment during inflammation through synergistic effects on endothelial activation. *J Immunol*. 2012;188(12):6287–6299. doi:10.4049/jimmunol.1200385
45. Li J, Casanova JL, Puel A. Mucocutaneous IL-17 immunity in mice and humans: host defense vs. excessive inflammation. *Mucosal Immunol*. 2018;11(3):581–589. doi:10.1038/mi.2017.97
46. Schinocca C, Rizzo C, Fasano S, et al. Role of the IL-23/IL-17 pathway in rheumatic diseases: an overview. *Front Immunol*. 2021;12:637829. doi:10.3389/fimmu.2021.637829
47. Zhao H, Wu L, Yan G, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. *Signal Transduct Target Ther*. 2021;6(1):263. doi:10.1038/s41392-021-00658-5