

Investigating the Therapeutic Mechanisms of Honeysuckle (China) in Sepsis Through Network Pharmacology and Experimental Validation

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Background: Sepsis is a critical condition characterized by an atypical immune response to infection, resulting in systemic inflammatory response syndrome. Honeysuckle, a traditional Chinese medicinal plant with anti-inflammatory, anti-tumor, and anti-oxidant characteristics, shows promise in mitigating sepsis-related inflammatory responses. The precise mechanism by which honeysuckle confers protection against sepsis remains uncertain. This research utilized network pharmacology to explore the mechanisms through which honeysuckle mitigates sepsis.

Methods: Bioactive compounds of honeysuckle were sourced from the Traditional Chinese Medicine System Pharmacology database, and their corresponding targets were identified. Sepsis-associated genes were gathered from the GeneCards and Online Mendelian Inheritance in Man databases. The regulatory network depicting “active ingredients-target” relationships was constructed utilizing Cytoscape 3.9.1 software. Target genes affected by honeysuckle in sepsis were analyzed utilizing the String database to create a protein-protein interaction network. Kyoto Encyclopedia of Genes and Genomes and Gene Ontology analyses were performed through the Database for Annotation, Visualization, and Integrated Discovery platform, aiming to identify pathways associated with these pivotal targets. Subsequently, molecular docking confirmed the binding capacity of these bioactive ingredients to pivotal targets. Subsequent in vitro experiments were conducted for additional validation. Network pharmacology analysis employed R software for extensive data processing. A Student's *T*-test compared the mean values of the two groups in the in vitro experimental data. Statistical analysis for multiple group comparisons was carried out utilizing one-way ANOVA, with Tukey's post hoc test applied for further analysis.

Results: The screening process identified 23 active ingredients in honeysuckle, which are linked to 291 targets. Molecular docking demonstrated strong binding affinities of kaempferol, luteolin, and quercetin to the target proteins TP53, TLR4, and MYD88. In vitro experiments demonstrated that honeysuckle and its active components mitigate sepsis by inhibiting the TLR4/MYD88 signaling pathways, thereby reducing proinflammatory cytokine production.

Conclusion: These findings indicate that honeysuckle may be an effective treatment for sepsis by modulating key proteins such as TP53, TLR4, and MYD88.

Keywords: network pharmacology, sepsis, molecular docking, traditional Chinese medicine, inflammatory response syndrome

Introduction

Sepsis, a critical systemic inflammatory reaction to microbial invasion, is notably triggered by lipopolysaccharide (LPS).¹ It is a systemic inflammatory response syndrome that may progress to septic shock, marked by significant mortality, morbidity, and treatment expenses.² When the infection triggers widespread systemic symptoms like fever, increased heart rate, or elevated respiratory rate, it is identified as sepsis. If the systemic response escalates and leads to organ

dysfunction remote from the infection site, the condition is classified as severe sepsis. Septic shock, on the other hand, is characterized by severe organ dysfunction accompanied by persistent hypotension or hypoperfusion that does not improve with initial fluid resuscitation.^{3,4} Sepsis is a prevalent, life-threatening condition in clinical practice and a leading cause of death in ICU patients. Annually, sepsis impacts approximately 31.5 million individuals worldwide, resulting in 5.3 million deaths.⁵ In China, sepsis patients have a mortality rate of 35.5%, with severe cases experiencing rates over 50%.⁶ The management of sepsis primarily involves fluid resuscitation, antibiotics administration, anticoagulation therapy, glucocorticoid usage, and renal replacement therapy;^{3,7–9} however, recurrent infections and multi-drug resistance pose significant challenges in clinical treatment.^{10–12} Recently, the utilization of Chinese herbal medicine in the management of sepsis has progressively emerged as a pivotal and efficacious therapeutic approach, significantly reducing sepsis-related mortality rates.^{13–15} Sepsis falls within the domain of heat disorders in traditional Chinese medicine, where the Inner Canon advocates for “treating heat with coldness”, thus predominantly emphasizing the selection of drugs that possess heat-clearing and detoxifying properties.^{16,17}

Honeysuckle (*Lonicera japonica* Thunb.), a widely recognized traditional Chinese medicinal herb, has a rich history of therapeutic use. The first recorded mention appears in the Miscellaneous Records of Famous Physicians (Ming Yi Bie Lu). Ethnobotanically, honeysuckle is valued for its ability to clear heat, detoxify, expel wind, and eliminate dampness.^{18,19} According to the Chinese Pharmacopoeia (2020 edition), honeysuckle is described as sweet in taste and cooling properties, primarily acting on the stomach and lung meridians.^{20,21} Its clinical applications include the treatment of febrile diseases, sore throats, dysentery, heat toxicity, and wind-heat colds. Morphologically, honeysuckle is a perennial, twining vine with opposite leaves and fragrant, tubular flowers that transition from white to yellow as they age. It is distributed across East Asia, including China, Japan, and Korea, thriving in temperate and subtropical climates. Recent pharmacological research indicates that honeysuckle exhibits anti-inflammatory, antiviral, antioxidative, antibacterial, and hepatoprotective properties.^{22–24} Recent research indicates that honeysuckle improves the prognosis and complications of sepsis by exerting anti-inflammatory, improving endothelial function, improving renal injury, improving myocardial injury, and regulating gastrointestinal function.^{25–27} However, the key components and specific mechanisms of honeysuckle in sepsis therapy are still unclear.

Sepsis pathogenesis involves complex genetic and molecular changes, making it challenging for single-target therapies to achieve optimal outcomes.^{28–30} Network pharmacology is extensively applied in traditional Chinese medicine research to clarify drug molecular mechanisms and aid in predicting individual drugs or compounds.^{31,32} It can examine the overarching relationship between drugs and diseases. This study employs molecular docking and network pharmacology to identify the bioactive ingredients, relevant targets, and signaling pathways of honeysuckle in sepsis therapy, aiming to elucidate its mechanism of action and offer insights for clinical application and research.

Methods

Identification of Bioactive Compounds in Honeysuckle

The active ingredients of honeysuckle were screened through the use of the Traditional Chinese Medicine System Pharmacology (TCMSP) database and analysis platform (<https://old.tcmsp-e.com/tcmsp.php>). The TCMSP platform is an integrated database designed to analyze the pharmacokinetic properties of compounds in Chinese herbal medicine. It facilitates the identification of bioactive components and their potential targets through criteria such as drug-likeness (DL) and oral bioavailability (OB). To identify the active ingredients, the term “honeysuckle” was searched within the TCMSP database. OB and DL were chosen as evaluation indicators due to their roles in the human body’s metabolism, distribution, absorption, and excretion processes. OB denotes the proportion of a drug’s effective concentration that reaches systemic circulation following oral administration. A higher OB indicates that the compound can be efficiently absorbed through the gastrointestinal tract and retain significant concentrations even after first-pass metabolism in the liver. Compounds with OB $\geq 30\%$ generally ensure sufficient biological efficacy without requiring high doses, which is crucial for reducing toxicity and improving patient compliance. If OB is insufficient, alternative administration methods like injection or structural modifications might be required, leading to increased development costs and time. This assessment is grounded in the chemical properties of approved medications to determine if a compound adheres to druggability criteria, such as Lipinski’s Rule of Five and Veber’s Rule. Statistical analyses suggest that compounds with a

DL value ≥ 0.18 are more structurally and chemically similar to known drugs. Conversely, compounds with a DL below 0.18 may fall outside the chemical space of drugs and require extensive optimization to meet drug development requirements. Selecting compounds with DL ≥ 0.18 enhances the accuracy of druggability predictions, avoiding excessive resource allocation to potential failures during early screening. Compounds with OB $\geq 30\%$ and DL ≥ 0.18 are likely to possess favorable ADME properties and align with the chemical space criteria for drug development.

Screening Targets of Honeysuckle

The TCMSP was utilized to predict the targets of honeysuckle, which were then uploaded to the UniProt database for search, selecting *Homo sapiens* as the target species. The 2D structures of these active components saved in SDF format were obtained from a PubChem search for honeysuckle. The PharmMapper platform was employed to predict honeysuckle-related targets through reverse pharmacophore matching, which was also uploaded to the UniProt database for screening against human targets. Finally, the BATMAN-TCM database was used to predict high-relevance targets of honeysuckle by uploading its PubChem ID. The integration of these three methods facilitated the elimination of redundant, non-human, and unqualified targets, thereby identifying honeysuckle-related targets.

Identification of Sepsis-Related Targets

The databases GeneCards (<https://www.genecards.org>) and OMIM (<https://www.omim.org>) were searched using the keyword “Sepsis” to find target genes related to sepsis. Then, Excel software was used to summarize and analyze the relevant target genes corresponding to the disease, and duplicate genes were deleted to build the target database of sepsis. To determine the crucial intersection between honeysuckle and sepsis, the Venn website (<http://bioinformatics.psb.ugent.be/webtools/Venn/>) was employed.

Construction of Active Ingredient-Target Network

To identify common targets between honeysuckle and sepsis, we employed the online Venn diagram tool for visualization. The study identified common targets between sepsis and honeysuckle’s active ingredient by intersecting their respective targets and visualizing the overlap using Venn diagrams. These overlapping genes indicate potential targets of honeysuckle in the therapy of sepsis. Additionally, we predicted the target genes related to active components and sepsis and standardized their nomenclature into gene names. To build a network diagram of active components and targets, sepsis-related targets were brought into Cytoscape 3.9.1.

Construction of the Protein-Protein Interaction (PPI) Network

To establish the PPI network, we first identified the intersection of targets related to honeysuckle and sepsis. These targets were submitted to the STRING database (version 12.0), with the species restricted to “*Homo sapiens*” to ensure the results are specific to human biology. The STRING database calculates interactions based on experimental data, curated databases, and computational predictions, assigning confidence scores to indicate interaction reliability. To improve data reliability, we employed “*Homo sapiens*” PPI data with a minimum confidence score of 0.7, prioritizing the largest connected component in the PPI network. The network created by STRING was brought into Cytoscape 3.9.1 for additional analysis. Using the CytoHubba plugin in Cytoscape, we applied topological algorithms (Betweenness, Degree, and Closeness) to analyze the network’s structure and identify key targets. These algorithms evaluate node significance in a network by: 1) Degree, which counts a node’s direct connections to indicate centrality; 2) Betweenness, which gauges a node’s presence on shortest paths between others to reflect its connectivity role; and 3) Closeness, which measures a node’s communication efficiency with all other nodes. The value of these parameters indicates the importance of a node among all targets, with higher values indicating greater significance. Targets surpassing average parameters were chosen, and the CytoHubba plugin was employed to determine the leading 10 nodes according to their ranking, as previously outlined. This systematic approach ensures the identification of significant targets that are most likely to influence the pathophysiology of sepsis and the therapeutic effects of honeysuckle.

Functional Enrichment Analysis

The intersection of honeysuckle- and sepsis-related key targets were input into the DAVID database (<http://david.ncifcrf.gov/>), with the parameters set to human (*Homo sapiens*). An analysis was conducted on key targets to determine their enrichment in biological processes from Gene Ontology (GO) and pathways from KEGG. The GO biological enrichment analysis included molecular function (MF), cellular component (CC), and biological process (BP). Genes that had a P-value under 0.05 were identified, with the leading 10 from GO analysis and the leading 20 from KEGG pathway analysis chosen for more detailed exploration.

Molecular Docking of Active Ingredients with Primary Targets

A 3D structure of the active ingredient was created from its 2D structure, which was sourced from PubChem, utilizing Chem3D software version 14.0. The target protein's crystal structure was retrieved from the PDB database (<https://www.rcsb.org/>) and processed in PyMOL software (version 2.5) to delete water molecules. Subsequently, AutoDock Tools software was utilized to process the target protein by adding hydrogens, charges, etc. The 2D structure of honeysuckle's active compounds was imported into ChemBio3D software and saved in mol2 format to obtain its 3D structure. Both the target protein and original ligand were set in pdbqt format recognized by AutoDock Tools software with the original ligand's position serving as an active pocket on the target protein. Molecular docking analysis between honeysuckle's active ingredients and the target proteins was conducted to evaluate their affinity. The binding energy serves as a crucial indicator for assessing effective binding between ligand and receptor molecules; lower values indicate better binding performance.

Cell Culture and Reagents

The key active compounds of honeysuckle (Kaempferol, Quercetin, and Luteolin) were investigated in this research. Kaempferol (CAS No. 520–18-3), Luteolin (CAS No. 491–70-3), and Quercetin (CAS No. 117–39-5) were acquired from Shanghai Haoyuan Medchemexpress Co., Ltd, China. Sigma-Aldrich in St. Louis, MO, USA, supplied LPS (L2880). The RAW264.7 murine macrophages were sourced from the Stem Cell Bank of the Chinese Academy of Sciences in Shanghai, China, and obtained from ATCC. The culture medium for the cells was DMEM with 100 µg/mL streptomycin, 2 mM L-glutamine, 50 U/mL penicillin, and 10% FBS (GIBCO), and incubated at 37°C with 5% CO₂. The EZ-PCR Mycoplasma Test Kit (Beijing Novo Biotechnology Co., LTD) confirmed the absence of mycoplasma contamination. Cells were pretreated with PBS or a 160 µM solution of kaempferol, luteolin, and quercetin for 2 hours, then incubated with 100 ng/mL LPS for 6 hours. Cells and supernatants were subsequently collected for enzyme-linked immunosorbent assay (ELISA) and quantitative real-time PCR (qRT-PCR).

ELISA

An ELISA Kit from ExCell Bio in Shanghai, China, was used to measure IL-1β and IL-6 concentrations in the supernatant, following the instructions provided by the manufacturer.

qRT-PCR

The isolation of total RNA from RAW264.7 cells was carried out using TRIzol reagent (Solarbio, China) following the manufacturer's instructions. RNA purity and concentration were assessed using ultraviolet spectrophotometry. Following extraction, the RNA was reverse-transcribed to generate complementary DNA. An RT-qPCR detection system and SYBR Premix Ex Taq II were employed for RT-qPCR assays. Normalization of mRNA expression levels was performed with β-actin as the internal control, and the $2^{-\Delta\Delta C_t}$ method was used to determine relative expression levels. Table 1 presents the RT-qPCR primer sequences for IL-6, IL-1β, TP53, TLR4, and MYD88.

MTT Assay

MTT (CAS 298–93-1) from Sigma-Aldrich was dissolved in PBS at pH 7.2 to create a stock solution with a concentration of 5 mg/mL. A final concentration of 0.5 mg/mL was obtained by diluting the stock solution with RPMI 1640 medium, creating the MTT working solution. Samples were applied at different concentrations to RAW264.7 cells (5×10^4) seeded in 96-well plates for a duration of 6.5 hours. Following treatment, wells were rinsed with PBS and then 100 µL of MTT solution was added. To dissolve the formazan crystals, 100 µL of dimethyl sulfoxide was added to each well after a 4-hour incubation at 37 °C. Next, the

Table 1 qRT-PCR Primer Sequences

Gene	Forward	Reverse
TP53	5'-CCAGTGGTAATCTACTGGGACG-3'	5'-CTGACGCACACCTATTGCAAGC-3'
TLR4	5'-GACTCTGATCCCAGCCATGG-3'	5'-AGGAACCACCTCCACGCA-3'
MYD88	5'-ATGTCTGCGGGAGACCCCGCGTG-3'	5'-TCAGGGCAGGGACAAGCCTTGG-3'
IL-6	5'-ATGAACCTCTTCTCCACAAGCGC-3'	5'-GAAGAGCCCTCAGGCTGGACTG-3'
IL-1 β	5'-ATGGCAGAAGTACCTAAGCTCGC-3'	5'-ACACAAATTGCATGGTGAAGTCAGTT-3'
β -actin	5'-CATGGATGATGATATCGCCGCG-3'	5'-CCTAAGGTGTGCACTTTTATTCAAC-3'

plates underwent incubation for a further 10 minutes at 37 °C. To assess cell viability, absorbance was measured at 580 nm utilizing a Tecan Infinite® M1000 Microplate Reader (Tecan, Männedorf, Switzerland). To calculate cell viability percentage, the formula was applied: (%) = $[100 \times (\text{sample absorbance}) / (\text{control absorbance})]$.

Statistical Analyses

Network pharmacology analysis involved comprehensive data processing using R software. In vitro experimental data were statistically analyzed with the help of GraphPad Prism 8.0.1 (GraphPad Software Inc., San Diego, CA, USA). A Student's *T*-test compared mean values between two groups, and One-way ANOVA with Tukey's post hoc test enabled multiple comparisons. Statistical significance is represented by a *p*-value of less than 0.05.

Results

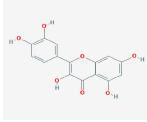
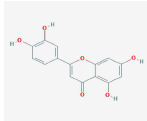
Identification of Active Compounds in Honeysuckle and their Primary Target Genes

Active compounds in honeysuckle were identified using the TCMSP database. Applying the criteria of $DL \geq 0.18$ and $OB \geq 30\%$, 23 bioactive compounds were identified (Table 2). The TCMSP database was then utilized to identify the targets linked to these active compounds, resulting in 291 unique targets after deduplication and summarization.

Acquisition of Target Genes Related to Sepsis

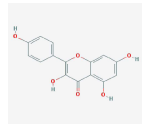
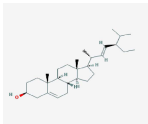
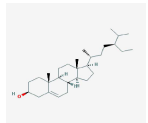
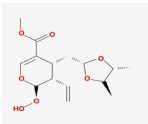
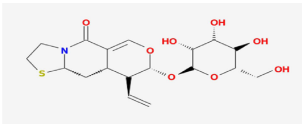
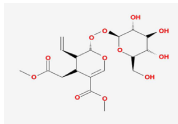
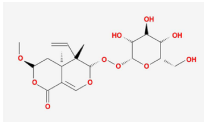
A total of 947 potential target genes associated with sepsis were identified by screening and removing redundant entries using the GeneCards, OMIM, DrugBank, and TTD databases. The intersection between these 947 sepsis-related targets and the 291 active ingredients-related targets yielded 78 key targets as depicted in Figure 1.

Table 2 Active Compounds in Honeysuckle

Serial Number	CAS	Active Ingredients	Chemical Structure
MOL000098	73,123–10-1	Quercetin	
MOL000006	491–70-3	Luteolin	

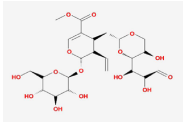
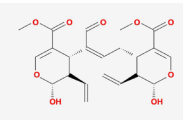
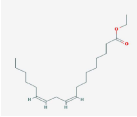
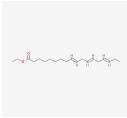
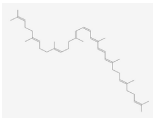
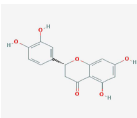
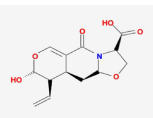
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Table 2 (Continued).

Serial Number	CAS	Active Ingredients	Chemical Structure
MOL000422	520-18-3	Kaempferol	
MOL000449	83-48-7	Stigmasterol	
MOL000358	83-46-5	Beta-sitosterol	
MOL003117	Na	Ioniceracetalides B qt	
MOL003124	74,518-57-3	XYLOSTOSIDINE	
MOL003128	25,488-59-9	Dinethylsecologanoside	
MOL003101	Na	7-epi-Vogeloside	

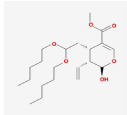
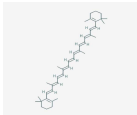
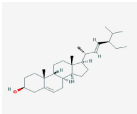
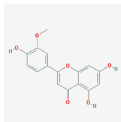
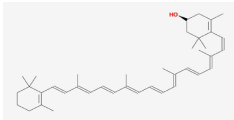
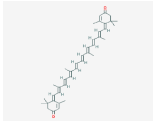
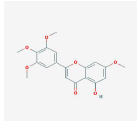
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Table 2 (Continued).

Serial Number	CAS	Active Ingredients	Chemical Structure
MOL003108	Na	Caeruloside C	
MOL003111	Na	Centauroside_qt	
MOL001494	544-35-4	Mandenol	
MOL001495	1191-41-9, 34,079-45-3	Ethyl linolenate	
MOL002707	540-05-6	Phytofluene	
MOL002914	4049-38-1	Eriodyctiol (flavanone)	
MOL003006	Na	(-)-(3R,8S,9R,9aS,10aS)-9-ethenyl-8-(beta-D-glucopyranosyloxy)-2,3,9,9a,10,10a-hexahydro-5-oxo-5H,8H-pyrano[4,3-d]oxazolo[3,2-a]pyridine-3-carboxylic acid_qt	

(Continued)

Table 2 (Continued).

Serial Number	CAS	Active Ingredients	Chemical Structure
MOL003014	Na	Secologanic dibutylacetal_qt	
MOL002773	7235–40-7	Beta-carotene	
MOL003036	19,716–26-8	ZINC03978781	
MOL003044	491–71-4	Chryseriol	
MOL003059	472–70-8	Kryptoxanthin	
MOL003062	116–30-3	4,5'-Retro-.beta.,.beta.-Carotene-3,3'-dione, 4',5'-didehydro-	
MOL003095	18,103–41-8	5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone	

Construction of the PPI Networks

The STRINC11.0 database received 78 potential target genes, with Homo sapiens set as the species, for the purpose of constructing a PPI network. The network was subsequently analyzed using Cytoscape 3.9.1 software. The network analysis

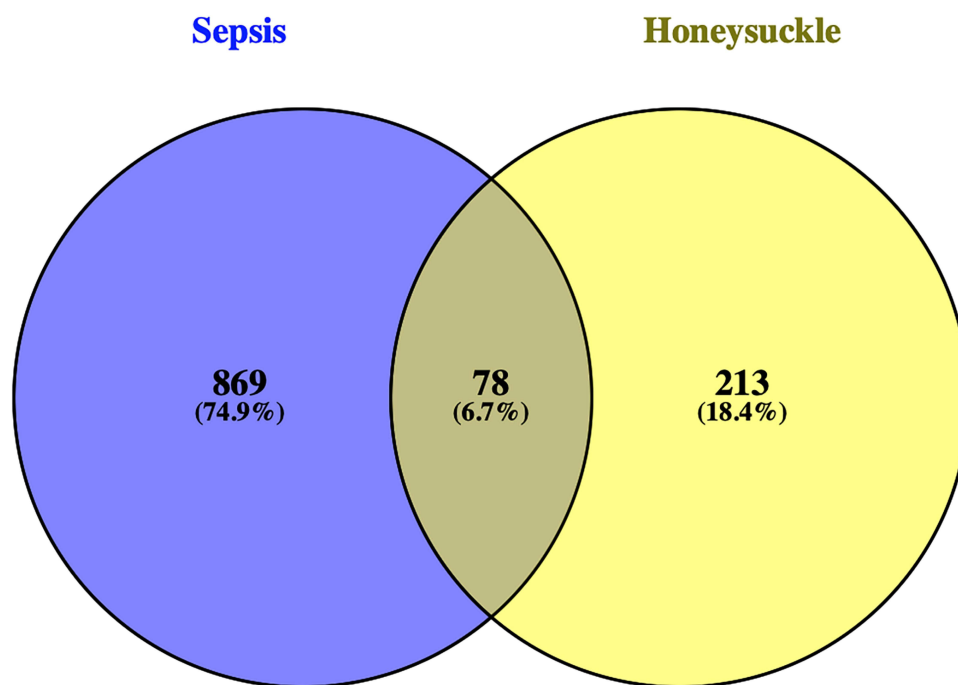


Figure 1 Venn diagram of honeysuckle's active ingredients and sepsis-related target genes.

employed degree, betweenness, and closeness as primary criteria for node selection. Nodes were selected if their degree exceeded twice the network nodes' median degree, their betweenness surpassed the median degree, and their closeness was greater than the median degree. The results were visualized using Cytoscape 3.9.1, as depicted in [Figure 2A](#). There are 867 nodes and 893 edges in the network, which has an average node degree of 2.06 and a local clustering coefficient of 0.980. Using Cytoscape 3.9.1 and the NetworkAnalyzer plug-in, a PPI network diagram ([Figure 2B](#)) was created from the imported network data, focusing on node density values. A node's size and color intensity increase with its degree. The higher the interaction score between proteins, the thicker the line connecting the nodes, and the deeper the color. The proteins TP53, TLR4, EP300, MYD88, IL1- β , FN1, CTNN1, JUN, AKT1, and CXCR4 ranked highest in degree centrality measures, including Degree, Betweenness, and Closeness ([Figure 2C](#)). TP53, TLR4, and MYD88 were pinpointed at the intersection of targets identified by the three methods used ([Figure 3](#) and [Table 3](#)). These target proteins are likely to be an important part of the pivotal targets for honeysuckle in sepsis therapy.

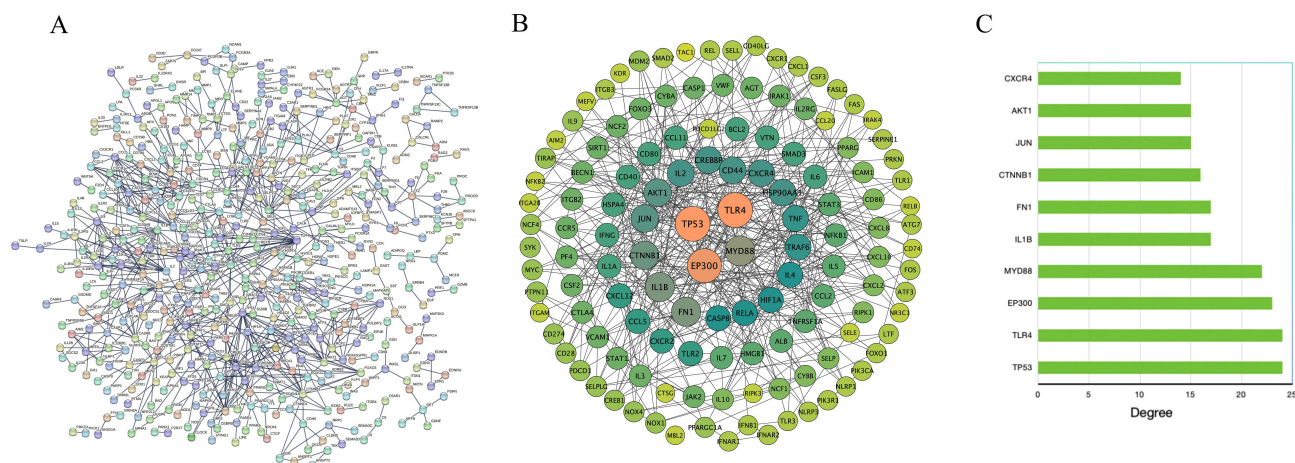


Figure 2 The protein-protein interaction (PPI) network of honeysuckle and sepsis targets. **(A)** PPI network created using STRING. **(B)** PPI network visualized with Cytoscape 3.9.1. Nodes signify proteins, with colors ranging from pink to red indicating the degree of binding between proteins. Edges represent protein-protein associations. **(C)** Histograms displaying the top 10 target genes based on their degree values within the PPI network.

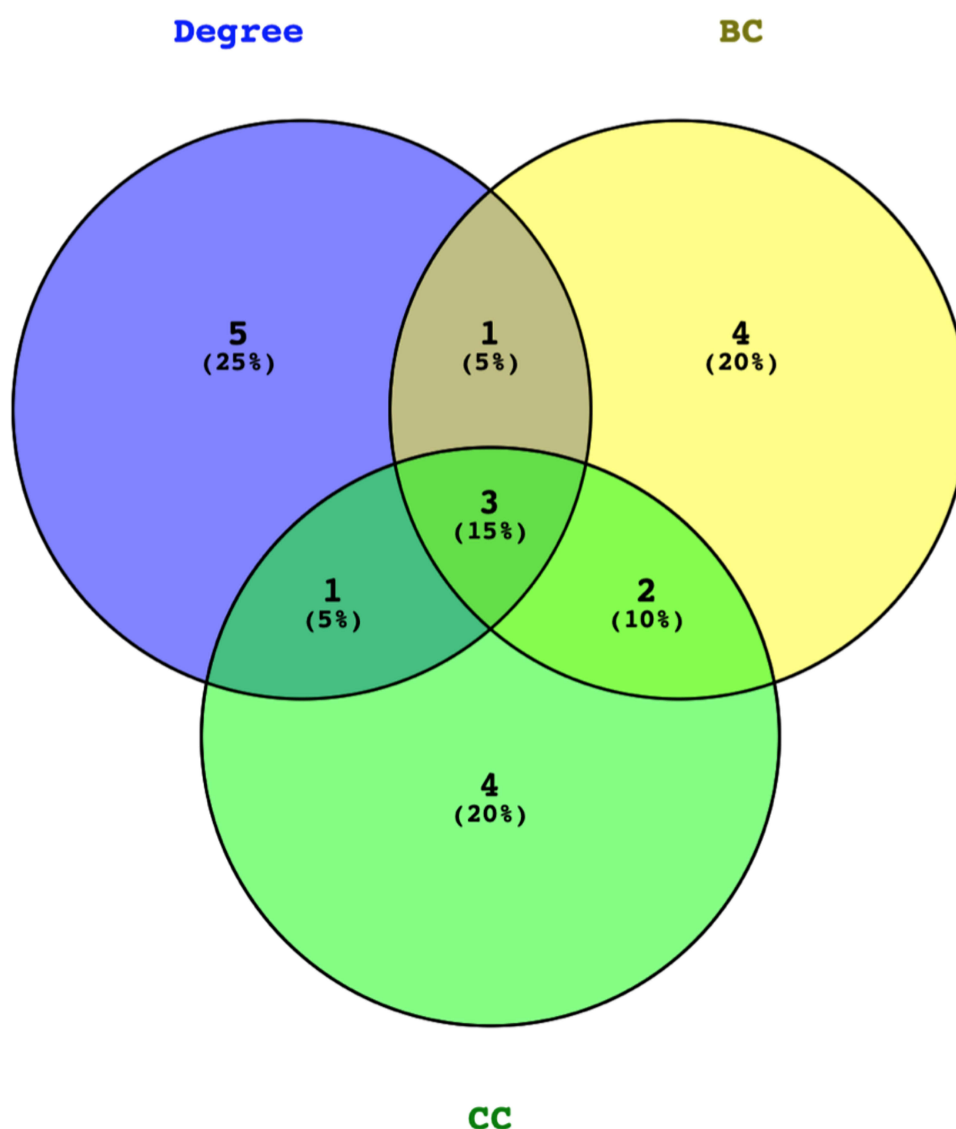


Figure 3 Selection of key target genes. Key targets identified by intersecting centrality measures (Degree, Closeness, and Betweenness).

Results of GO Biological Enrichment Analysis

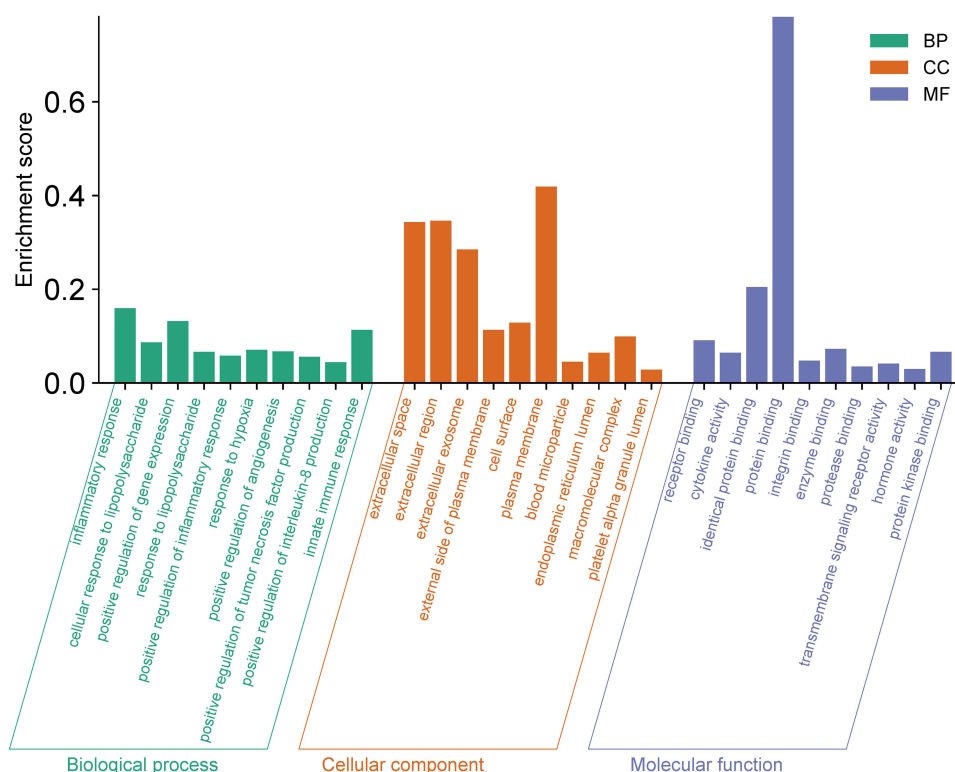
Using the DAVID database for GO enrichment analysis, the key targets of honeysuckle were primarily associated with 1600 biological processes (BP), 183 cellular components (CC), and 280 molecular functions (MF). **Figure 4** illustrates the leading 10 biological processes (BP), cellular components (CC), and molecular functions (MF) identified by a screening criterion of $P < 0.05$, ranked by target numbers. The BP included inflammatory and innate immune responses, cellular response to lipopolysaccharide, positive modulation of gene expression and angiogenesis, response to hypoxia, and production of tumor necrosis factor and interleukin-8. The CC included the extracellular space and region, extracellular exosome, plasma membrane's external side, cell surface, blood microparticle, endoplasmic reticulum lumen, macromolecular complex, and platelet alpha granule lumen. The MF included receptor binding, cytokine and hormone activity, identical protein, integrin, enzyme, and protease binding, transmembrane signaling receptor activity, and protein kinase binding. The results of the GO enrichment analysis indicate that these crucial targets are mainly associated with the progression of sepsis, particularly in regulating the inflammatory response, though further experimental validation is required.

Table 3 Information on the Top 10 Key Targets for Honeysuckle in the Treatment of Sepsis

Top 10 in Network PPI Ranked by Degree			Top 10 in Network PPI Ranked by Betweenness Centrality			Top 10 in network PPI ranked by Closeness Centrality		
Rank	Name	Score	Rank	Name	Score	Rank	Name	Score
1	MYD88	26	1	TLR4	0.30490603	1	TLR4	0.3010279
2	TP53	24	2	FN1	0.23825175	2	MYD88	0.27424749
3	TLR4	24	3	TP53	0.13204362	3	HSP90AA1	0.27333333
3	EP300	23	4	MYD88	0.12701142	3	HSPA4	0.27296937
3	IL1B	17	5	HSP90AA1	0.12585132	5	HMGB1	0.26797386
6	FN1	17	6	CD44	0.10872326	6	TRAF6	0.26797386
7	CTNNB1	16	7	CD40	0.08693913	7	IL1B	0.266061
7	JUN	15	8	VWF	0.08432187	8	TLR1	0.266061
9	AKT1	15	9	ALB	0.07720472	9	TP53	0.26131294
10	CXCR4	14	10	HMGB1	0.07711109	10	BECN1	0.26015228

Results of KEGG Pathway Enrichment Analysis

Through KEGG pathway enrichment analysis utilizing the DAVID database, 172 signaling pathways were found. We chose and displayed the top 20 signaling pathways by using a screening criterion of $P < 0.05$, focusing on target numbers (Figure 5). In the visualization, each bubble's size and darkness indicate the significance and abundance of enriched key targets within the pathway. The top 20 signaling pathways encompass those associated with cancer, atherosclerosis, lipid metabolism, PI3K-Akt, cytokine-cytokine receptor interaction, NF-kappa B, neutrophil extracellular trap formation, TNF, tuberculosis, human papillomavirus, NOD-like receptor, Kaposi sarcoma-associated herpesvirus, JAK-STAT, neurodegeneration, human cytomegalovirus, Epstein-Barr virus, neuroactive ligand-receptor interaction, MAPK, influenza A, Herpes simplex virus 1, and Toll-like receptor signaling. Using Cytoscape software, a “target-pathway” network diagram was generated to visually represent the primary pathways and their associated targets (Figure 6). The development of

**Figure 4** Analysis of GO enrichment.

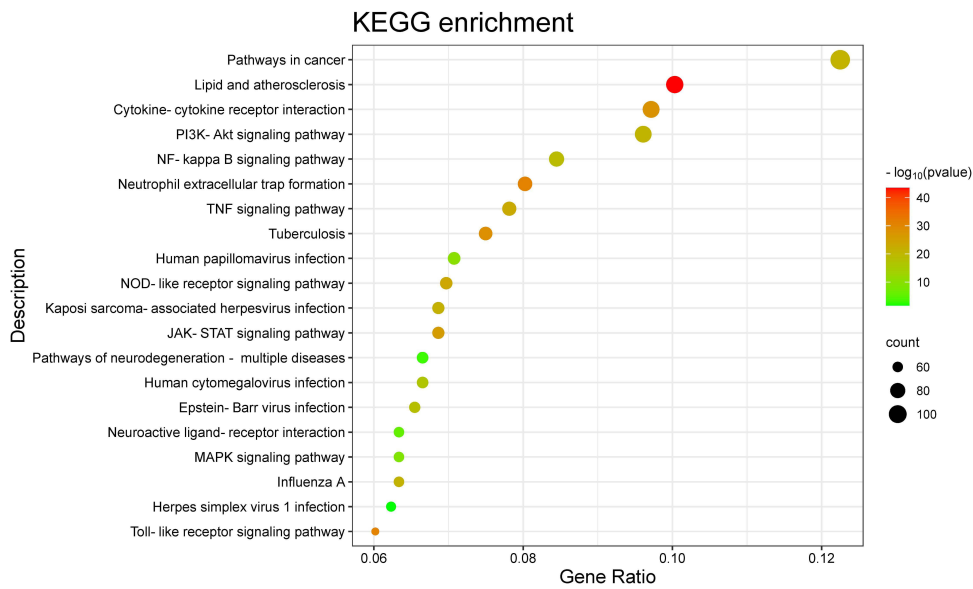


Figure 5 KEGG pathway enrichment analysis.

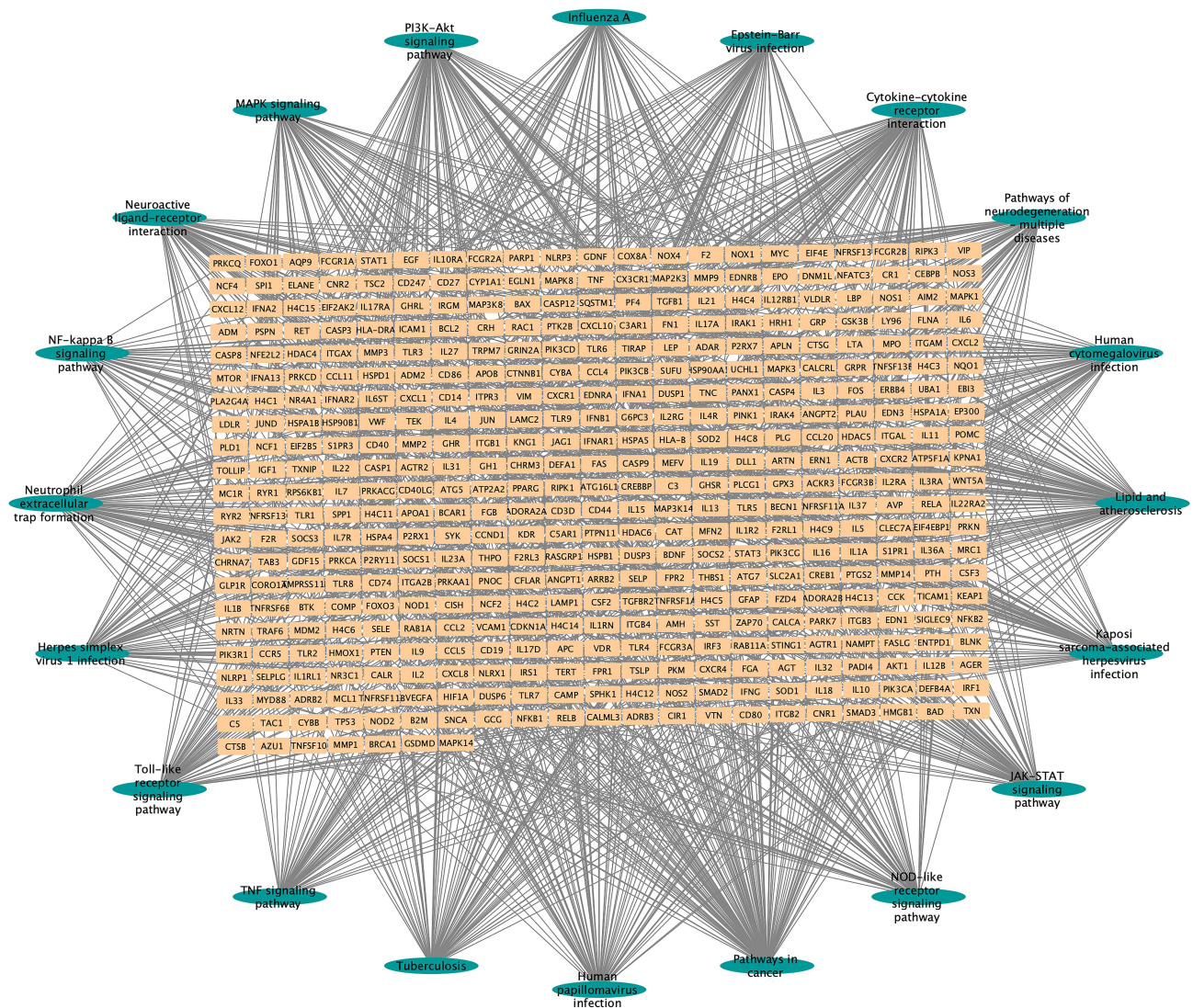
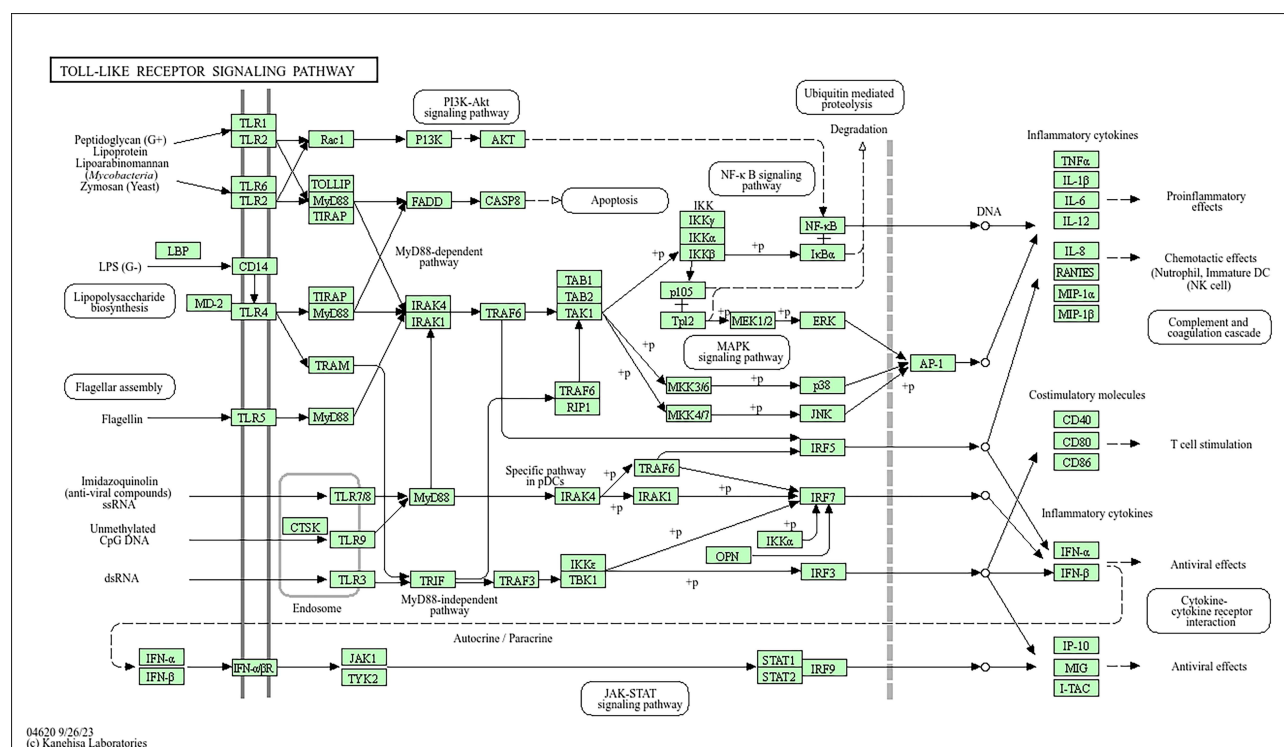


Figure 6 Figure 8 Diagram depicting the network connections between targets and signaling pathways.

sepsis heavily relies on the TLR signaling pathway, which is also significantly related to inflammatory infiltration. Figure 7 illustrates that TLR signaling pathways, influenced by honeysuckle's active ingredient targets, play a role in sepsis development, as evidenced by data integration from KEGG and the Genome Encyclopedia. The PI3k-Akt and NF-kappa B pathways play a role in creating an inflammatory microenvironment and are implicated in sepsis development. Overall, the findings indicate that honeysuckle primarily influences mechanisms related to the inflammatory response, offering potential treatment for sepsis.

Results of Molecular Docking

The protein targets of honeysuckle's active compounds were connected to their respective genes using the UniProt protein database. Cytoscape 3.9.1 was used to create a network diagram depicting the interactions between honeysuckle, its active components, and target genes. As illustrated in Figure 8, this network comprises a total of 315 nodes (including 1 Traditional Chinese Medicine node, 23 nodes representing active ingredients, and 291 nodes representing corresponding target proteins). Notably, kaempferol, luteolin, and quercetin showed the highest degree of centrality and stronger binding to TP53, TLR4, and MYD88 (Figure 9). The main active compounds in honeysuckle demonstrated significant binding energies with the targets TLR4 (−4.39, −4.59, and −4.81 kcal/mol), TP53 (−6.31, −4.59, and −5.05 kcal/mol), and MYD88 (−5.6, −4.84, and −4.69 kcal/mol). These results indicate robust binding interactions between honeysuckle's main active ingredients and their target proteins. In molecular docking analyses (Figures 10–12), TP53 established hydrogen bonds with kaempferol through GLU-1575, GLU-1573, and PHE-1553 residues, whereas TLR4 interacted via the ALA-287 residue. MYD88 engaged with kaempferol through GLN-181, TRP-286, THR-287, and LYS-282 residues, forming multiple hydrogen bonding sites. Similarly, luteolin utilized GLN-181 and TYR-276 residues for binding to MYD88, while it binds to TP53 via MET1584, LEU-1547, and PHE-1553 residues, and binds to TLR4 by GLY-291, LYS-288, SER-286 residues. Quercetin interacted with TLR4 via ASN-260, LYS-288, and THR-259 residues, TP53 by GLU-1575 and SER-1554, and MYD88 through ASP-162, ARG-160, LEU-191, VAL-1, and CYS-203. These findings underscore the significant binding affinity between honeysuckle's active components and their respective protein targets.



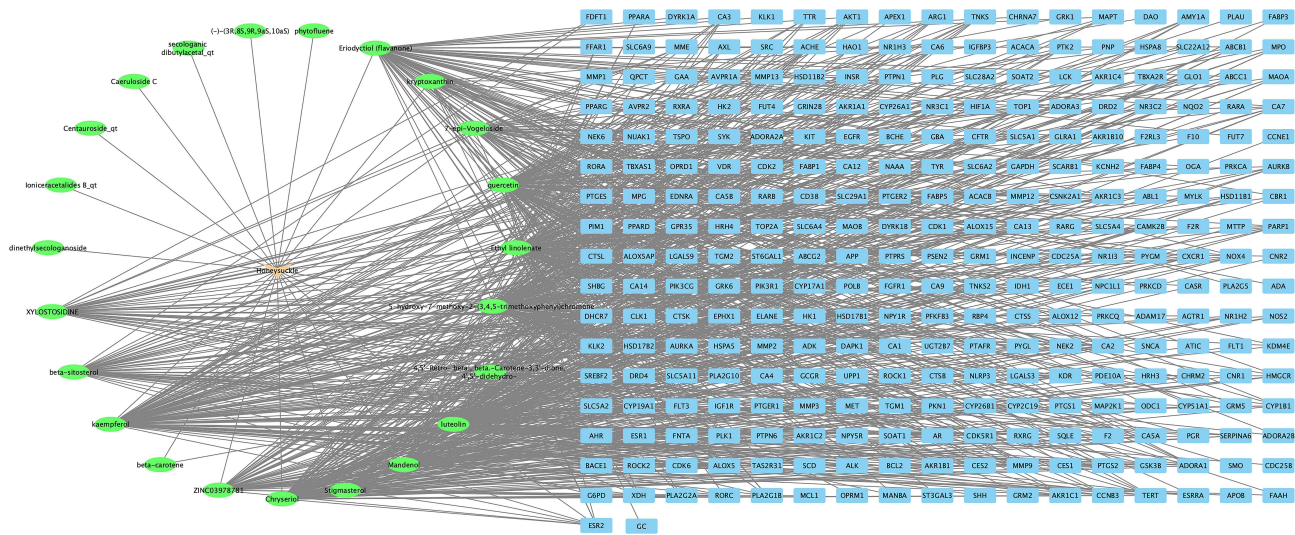


Figure 8 The active ingredient-target network diagram illustrating active ingredients and targets for honeysuckle in sepsis treatment. The green circular node signifies the active components of honeysuckle, whereas the other nodes denote their respective targets.

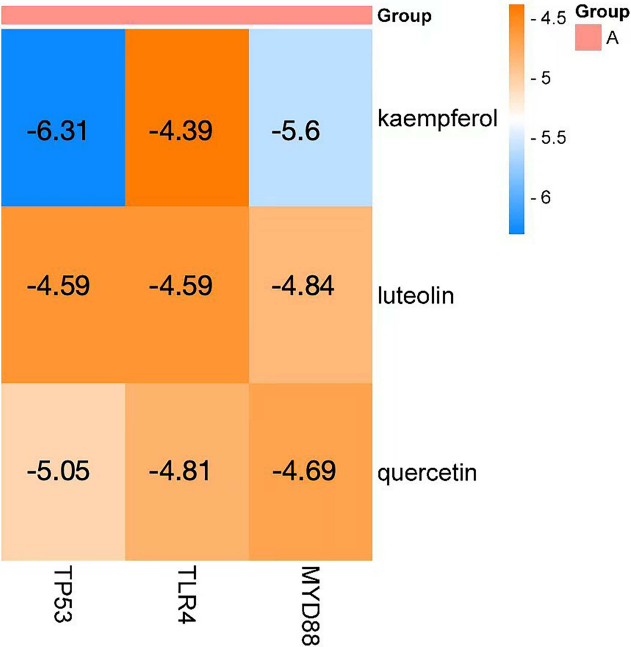


Figure 9 Heat map displaying binding affinities between active ingredients and selected key targets based on molecular docking results.

Honeysuckle Mitigates LPS-Induced Sepsis in Macrophages by Decreasing Proinflammatory Cytokine Production

Excessive proinflammatory cytokine production during infections can trigger a cytokine storm, which significantly increases mortality in sepsis syndrome.^{33,34} Macrophages are essential to innate immunity, initiating inflammatory responses against diverse pathogens. To investigate the impact of honeysuckle and its active constituents on sepsis, RAW 264.7 cells were subjected to different concentrations of honeysuckle and its active components, kaempferol, luteolin, and quercetin, to assess their effects on sepsis. The MTT assay indicated that 160 μ M concentrations of honeysuckle, kaempferol, luteolin, and quercetin were non-cytotoxic to RAW 264.7 cells (Figure 13A). Therefore,

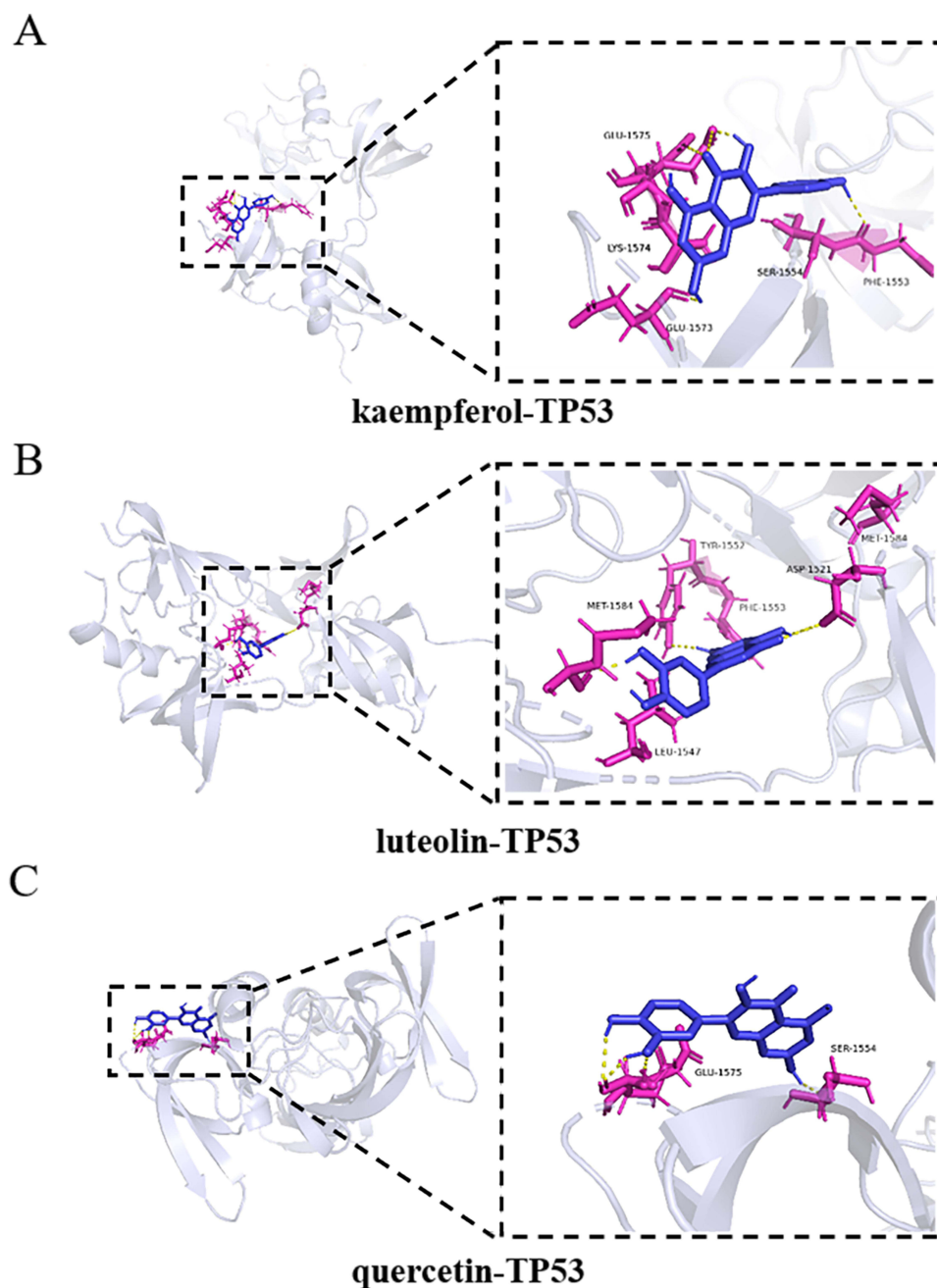


Figure 10 Molecular docking analysis of active compounds with TP53. **(A)** kaempferol-TP53; **(B)** luteolin-TP53; **(C)** quercetin-TP53.

subsequent experiments were conducted using a concentration of 160 μ M. We investigated the impact of honeysuckle and its active components on LPS-induced inflammation in RAW264.7 macrophages by assessing mRNA levels of proinflammatory cytokines. Our results demonstrated that honeysuckle and its active components significantly lowered the mRNA expression of IL-1 β and IL-6 induced by LPS in RAW264.7 cells (**Figure 13B–E**). ELISA assays demonstrated that honeysuckle and its active components reduced LPS-induced IL-1 β and IL-6 protein production in macrophages (**Figure 13F–I**). The results indicate that honeysuckle reduces LPS-induced inflammation by suppressing inflammatory cytokine production in both macrophages and mice.

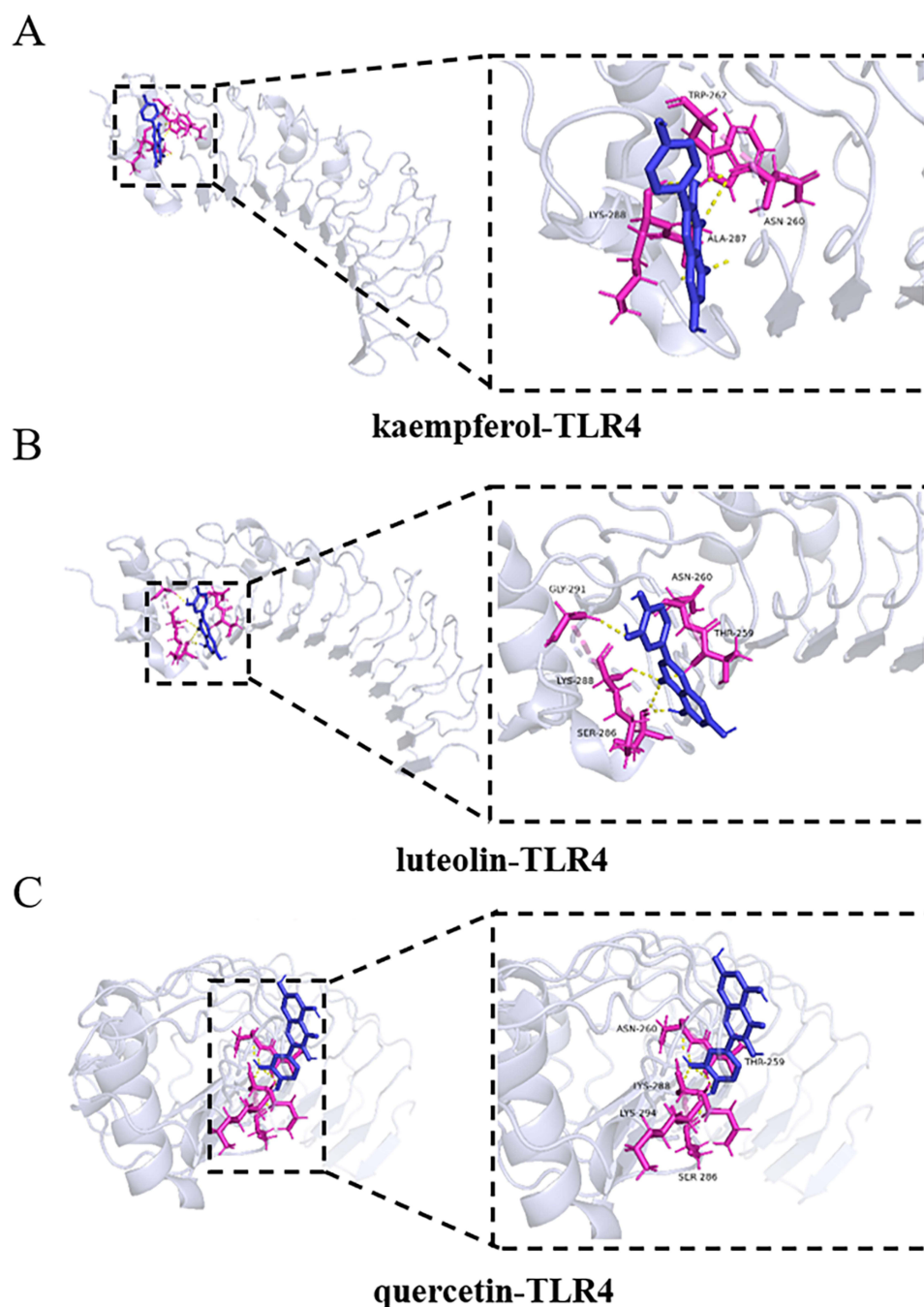


Figure 11 Molecular docking analysis of active compounds with TLR4. (A) kaempferol-TLR4; (B) luteolin-TLR4; (C) quercetin-TLR4.

Active Components of Honeysuckle Suppress LPS-Induced Activation of the TLR4/MYD88 Signaling Pathways

Molecular docking and network pharmacology experiments revealed a strong binding affinity between honeysuckle's active ingredient and the key target genes TLR4, TP53, and MYD88. The planar structures of kaempferol, luteolin, and quercetin in silico active compounds are shown in Figure 14A. Prior research has emphasized the crucial involvement of TLR4, TP53, and MYD88 in sepsis development.^{35–37} LPS, acting as a TLR4 agonist, primarily induces proinflammatory responses via the TLR4/MYD88 signaling pathway. To validate the impact of honeysuckle's active components on these core targets, qRT-PCR assays were conducted. The results indicated significant reductions in TLR4, TP53, and MYD88 expression levels following treatment with honeysuckle, kaempferol, luteolin, and quercetin (Figure 14B–D).

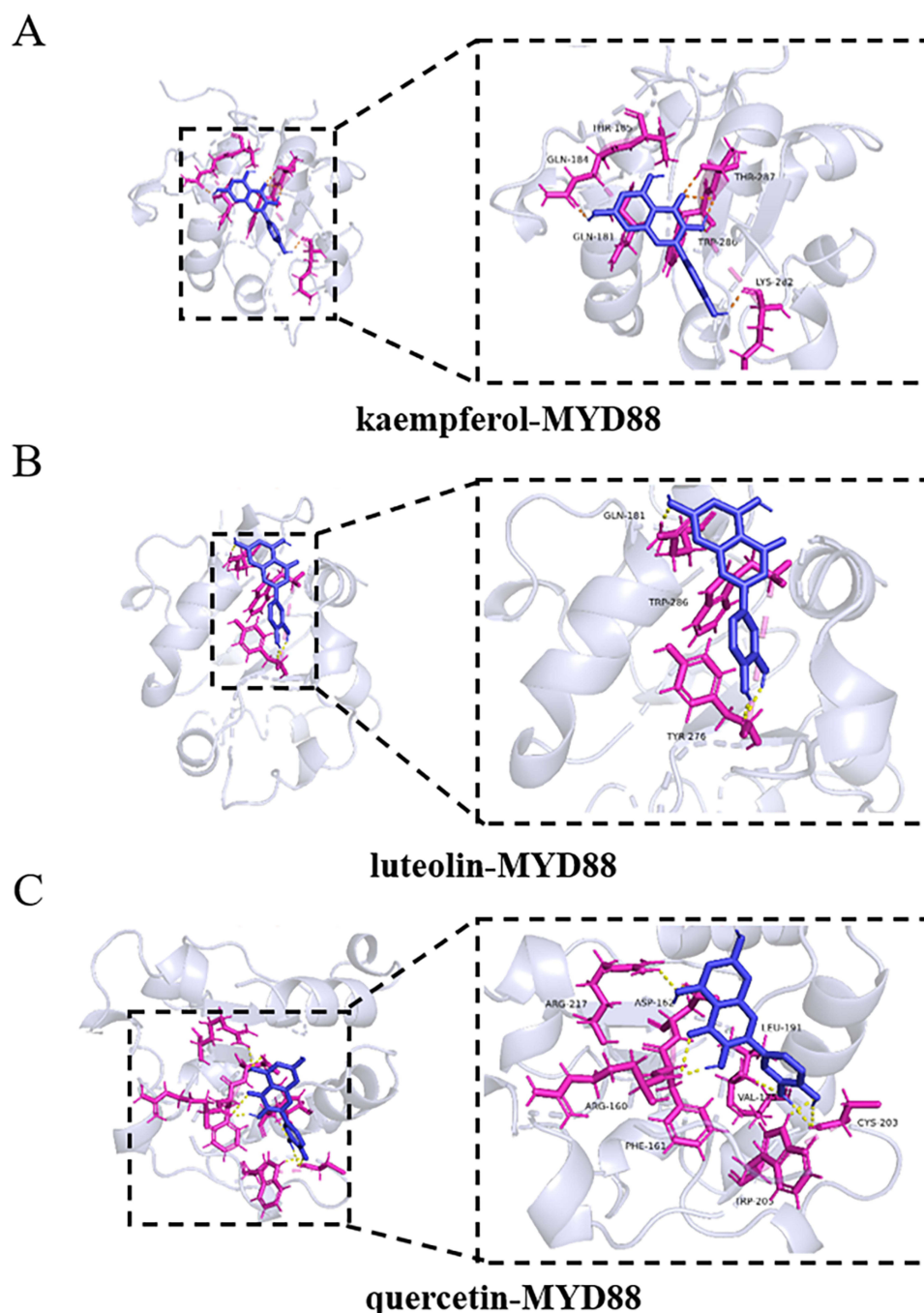


Figure 12 Molecular docking analysis of active compounds with MYD88. (A) kaempferol-MYD88; (B) luteolin-MYD88; (C) quercetin-MYD88.

The study indicates that honeysuckle's active components alleviate LPS-induced sepsis by inhibiting the TLR4/MYD88 signaling pathways, supporting conclusions from molecular docking and network pharmacology analyses.

Discussion

Honeysuckle, a traditional tonic medicine, demonstrates anti-inflammatory, antiviral, antioxidative, and antibacterial properties.^{38,39} This research employed molecular docking and network pharmacology to explore the mechanisms by which honeysuckle combats sepsis. Our findings suggest that kaempferol, luteolin, and quercetin are the principal bioactive compounds responsible for honeysuckle's therapeutic effects, particularly through their interaction with key

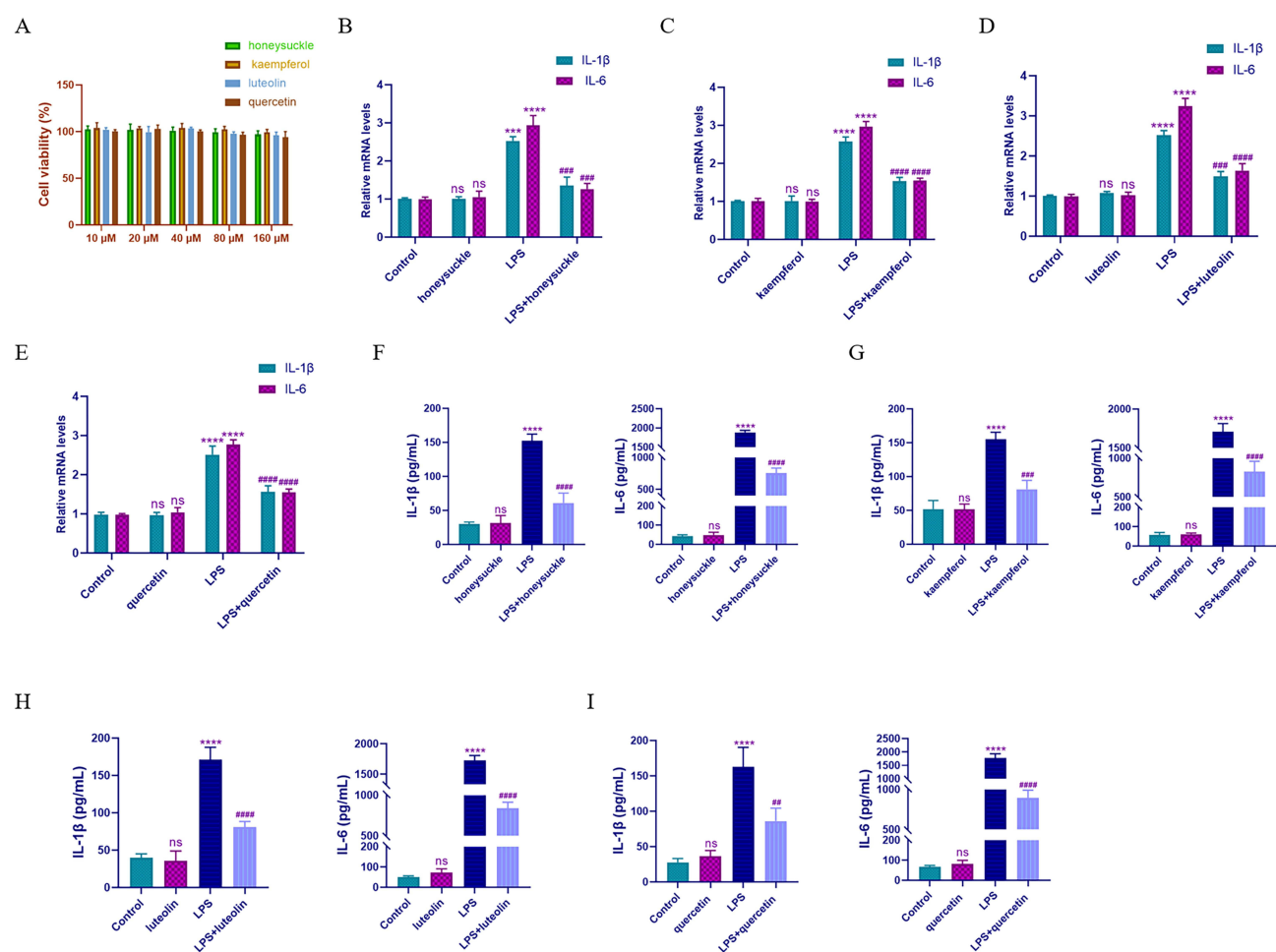


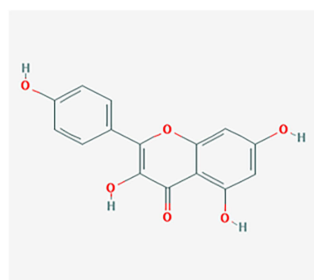
Figure 13 Effect of honeysuckle on the production of proinflammatory cytokines in macrophages. **(A)** The MTT assay indicated that treatment with 160 μ M of honeysuckle, kaempferol, luteolin, and quercetin did not cause cytotoxic effects in RAW 264.7 cells ($n = 3$). **(B–E)** IL-1 β and IL-6 mRNA levels in macrophages were measured by qRT-PCR ($n = 5$). The data are presented as mean $\pm$ standard deviation (SD). *** $P < 0.001$, **** $P < 0.0001$. **(F–I)** The secretion of IL-1 β and IL-6 in macrophages was detected by ELISA ($n = 5$). The data are presented as mean $\pm$ standard deviation (SD), determined using a two-tailed Student's t -test or one-way analysis of variance (ANOVA). *** $P < 0.001$, **** $P < 0.0001$ vs control, ##### $P < 0.0001$, #### $P < 0.001$, ### $P < 0.01$ vs LPS. ns: no significance vs control.

proteins TP53, TLR4, and MYD88. These compounds play crucial roles in modulating inflammation-related pathways, as confirmed by both computational docking and experimental validation.

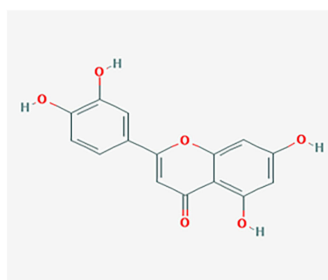
In this study, we collected 23 chemical components from the TCMS database, with kaempferol, luteolin, and quercetin identified as the principal ones. These compounds target multiple nodes within the network alongside other active components. Kaempferol, luteolin, and quercetin, among the identified active ingredients, have demonstrated significant therapeutic efficacy against sepsis. A functional enrichment analysis involving 78 core targets was executed with the help of the GO and KEGG databases. Protein binding was highlighted as the most enriched GO term by the results, suggesting that honeysuckle could modulate sepsis progression by influencing protein-protein interactions. Furthermore, analysis of 172 KEGG pathways revealed enrichment of sepsis-related genes primarily within inflammatory pathways, indicating that honeysuckle's intervention in sepsis could involve modulation of inflammation-associated signaling pathways.

We explored the molecular mechanisms by which honeysuckle may treat sepsis using network pharmacology, focusing on active ingredient and target screening within the PPI network. We identified three primary bioactive ingredients and their corresponding representative targets. Specifically, kaempferol, luteolin, and quercetin were molecularly docked with TP53, TLR4, and MYD88 proteins to validate our network pharmacology predictions. The docking results confirmed that these ingredients bind effectively to the proteins. Additionally, our findings demonstrated that honeysuckle mitigates LPS-induced sepsis in macrophages and mice by reducing proinflammatory cytokine production. Kaempferol, luteolin, and quercetin, the

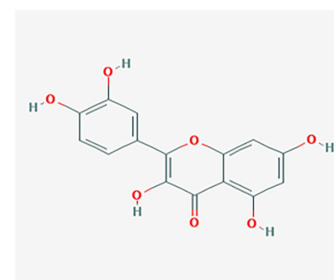
A



kaempferol

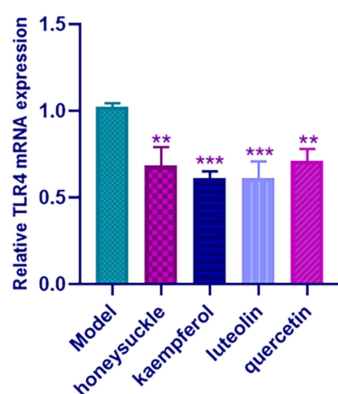


luteolin

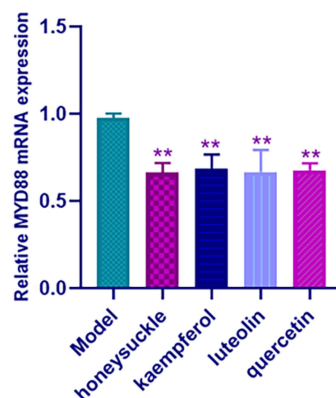


quercetin

B



C



D

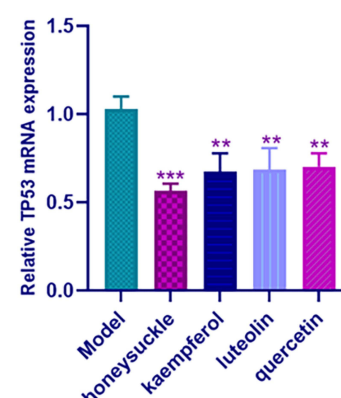


Figure 14 Effect of active constituents of honeysuckle on expression of key target genes and TLR4/MYD88 signaling pathway. LPS-induced RAW 264.7 cells were exposed to 160 μ M concentrations of honeysuckle, kaempferol, luteolin, and quercetin. (A) The planar structures of the in silico kaempferol, luteolin, and quercetin. (B–D) Real-time qRT-PCR was utilized to analyze the mRNA levels of TP53, TLR4, and MYD88 in LPS-induced RAW 264.7 cells treated with these active compounds ($n = 5$). The data are presented as mean $\pm$ SD, determined using a two-tailed Student's t -test or ANOVA. ** $P < 0.01$, *** $P < 0.001$ vs model.

active components of honeysuckle, inhibit LPS-induced activation of the TLR4/MYD88 signaling pathways. TP53, a well-documented tumor suppressor protein, has been increasingly recognized for its role in regulating immune responses. Recent studies have highlighted TP53's involvement in modulating immune response and ferroptosis, which are critical during sepsis.⁴⁰ For example, p53 is closely associated with poor outcomes in sepsis and exerts an immunosuppressive effect by promoting the expansion of functional Tregs during the development of sepsis.⁴¹ Similarly, TLR4 and MYD88, as pivotal components of innate immunity, initiate macrophage proinflammatory cascades and regulate macrophage polarization during sepsis.^{42,43} Suppression of these targets has been shown to alleviate sepsis-related organ dysfunction, consistent with the findings of our study. Kaempferol, luteolin, and quercetin exhibited high docking affinities with TP53, TLR4, and MYD88, suggesting their potential to disrupt the progression of sepsis by modulating these proteins. Comparatively, prior studies have shown that traditional Chinese medicines mitigate sepsis-related multiple organ dysfunction in rats by modulating the inflammatory response and macrophage activation via the TLR4/MYD88 signaling pathways. For instance, Xijiao Dihuang decoction was reported to reduce sepsis-induced cardiac inflammation by inhibiting TLR4/NF- κ B signaling and modulating cytokine expression.⁴⁴ Similarly, Wang et al demonstrated that puerarin attenuates sepsis-induced multiple-organ injury and Inflammatory response via regulation of TLR and MAPK signaling.⁴⁵ In line with these studies, our findings revealed that honeysuckle's active components inhibit the TLR4/MYD88 pathway, a key mediator of proinflammatory cytokine release in sepsis. This consistency reinforces the role of honeysuckle as an anti-sepsis agent targeting inflammatory signaling.

This study has certain limitations. Our research on honeysuckle's effects on sepsis employed modern bioinformatics methods, such as network pharmacology and molecular docking. The existing network information technology necessitates further enhancement, and the precision and promptness of database information require scientific verification. Our

analysis may exclude compounds or targets that are unconfirmed or unrecorded. While luteolin, kaempferol, and quercetin were identified as the main bioactive ingredients of honeysuckle for sepsis treatment, they do not fully encapsulate the plant's therapeutic potential. Therefore, additional pharmacodynamic and molecular biology experiments are necessary to expand our current findings. Furthermore, some of our results have limited precedent in previous studies. The absence of prior explanations and validations regarding the effects and mechanisms of these potential active ingredients on sepsis presents substantial opportunities for future research.

Conclusion

The research utilized network pharmacology to determine the active compounds and crucial targets of honeysuckle in addressing sepsis. Molecular docking analysis demonstrated a high binding affinity between honeysuckle's active compounds and key targets, including TP53, TLR4, and MYD88. In vitro experiment results indicated that honeysuckle has a protective effect against sepsis by reducing proinflammatory cytokine production. Additionally, the active compounds in honeysuckle (kaempferol, luteolin, and quercetin) exhibit therapeutic potential by inhibiting the TLR4/MYD88 signaling pathways. These findings highlight the significance of understanding honeysuckle's mechanisms, providing valuable insights for developing new therapeutic strategies for sepsis management.

Disclosure

The authors report no conflicts of interest in this work.

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