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Mechanism of Fuzheng Jiedu Huayu Decoction in the Treatment of Sepsis based on Network Pharmacology and Molecular Docking

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Abstract: ***Objective:*** ***Using network pharmacology and molecular docking techniques, we explored the active ingredients in Fuzheng Jiedu Huayu Decoction (FJHD) and predicted its potential mechanisms of action in treating sepsis, providing a theoretical basis for the clinical application of FJHD.*** ***Methods:*** ***Using the TCMSP platform to screen for active ingredients and their targets in FJHD; obtaining sepsis-related target genes using the GeneCards, OMIM, and TTD databases; intersecting drug targets with disease-related targets using the Venny 2.1.0 platform; constructing drug-active ingredient-target networks using Cytoscape 3.10.3 software; analyzing protein-protein interactions using the STRING platform to identify core targets; performing GO function and KEGG pathway enrichment analysis on the intersected targets using the DAVID database; and validating the binding affinity of key active ingredients with core targets through molecular docking using AutoDock Vina software.*** ***Results:*** ***A total of 86 active ingredients were screened out, including quercetin, β-sitosterol, kaempferol, stigmasterol and luteol. There are 122 intersecting targets of drug components and diseases, of which the core targets are TP53, TNF, AKT1, JUN and IL6. GO function and KEGG pathway enrichment analysis showed that the effect of FJHD on sepsis mainly involved in RNA polymerase II-mediated transcription, positive regulation of gene expression, and negative regulation of apoptosis. cellular components such as cytoplasmic matrix, extracellular matrix and extracellular region; Molecular functions such as protein binding, identical protein binding, and enzyme binding; Cancer pathways, lipid and atherosclerosis mechanisms, and AGE-RAGE signaling pathways are the main pathways. Molecular docking technology found that the minimum binding energy of the core active ingredient and the core target protein of the drug was <-5 kcal/mol.*** ***Conclusions:*** ***FJHD may exert its therapeutic effects on sepsis through a mechanism involving multiple components, multiple targets, and multiple pathways. Among these, quercetin, luteolin, stigmasterol, β-sitosterol, and kaempferol may be the primary active ingredients responsible for the therapeutic effects of FJHD. JUN, TP53, and IL6 may be the potential therapeutic targets for the decoction in treating sepsis. The main pathways through which FJHD may exert its effects on sepsis could include pathways in cancer, lipid and atherosclerosis mechanism, and the AGE-RAGE signaling pathway.***

Keywords: Sepsis, Fuzheng Jiedu Huayu Decoction, Network pharmacology, Molecular docking.

1. Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) caused by infection. It is characterized by immune response disorder and multiple organ dysfunction syndrome (MODS), with high incidence and mortality rates [1-2]. According to epidemiological research, there are over 19 million cases of sepsis worldwide each year, with a mortality rate ranging from 26.7% to 41.9%. Among them, there are approximately 1.8 million patients with severe sepsis, and if secondary septic shock occurs, the mortality rate can increase to 80%, making sepsis an important challenge in the medical field [3-4]. Traditionally, the treatment of sepsis mainly relies on antibiotics and supportive therapy, but this makes it difficult to effectively regulate excessive inflammatory responses, and the therapeutic effect decreases with the increase of widespread bacterial resistance [5]. In recent years, traditional Chinese medicine Decoctions have shown unique advantages in the prevention and treatment of sepsis due to their synergistic effects of "multiple components, multiple targets, and multiple pathways" [6-7].

Fuzheng Jiedu Huayu Decoction (FJHD) is a compound composed of eight traditional Chinese medicines: Herba Patriniae, Radix Paeoniae Rubra, Trichosanthes Kirilowii Maxim, Scutellariae Radix, Forsythiae Fructus, Rhapontici Radix, Panacis Quinquefolii Radix, and Coicis Semen. It has the effects of clearing heat and detoxifying, promoting blood circulation and removing blood stasis, and nourishing qi and yin [8]. This Decoction has been shown to improve immune inflammatory damage in patients in clinical practice [9]. However, its molecular mechanism of action has not been fully elucidated. With the development of network pharmacology and molecular docking technology, researchers can use these two techniques to systematically screen active ingredients in traditional Chinese medicine Decoctions, predict targets and signaling pathways, thereby breaking through the limitations of traditional single component research and clarifying the specific mechanisms of action of traditional Chinese medicine Decoctions in treating diseases [10-11].

This study integrated the active ingredients of FJHD based on the TCMSP database, combined with disease target databases such as GeneCards and OMIM to screen intersecting targets. By constructing a drug component target network and a protein-protein interaction (PPI) network, core components and key targets were identified. GO/KEGG enrichment analysis was used to reveal the biological processes and pathways that may be regulated by them, and molecular docking was further used to verify binding activity. The aim is to systematically analyze the potential mechanism of FJHD in treating sepsis, and provide scientific basis for clinical application.

2. Materials and Methods

2.1 Screening of Active Ingredients and Targets of FJHD

Using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), (https://old.tcmsp-e.com/tcmsp.php) Retrieve various traditional Chinese medicines from FJHD, set oral bioavailability (OB) ≥ 30% and drug similarity (DL) ≥ 0.18 as screening conditions, and screen for effective active ingredients and targets in FJHD. Use the obtained protein targets through the Uniprot database (https://www.uniprot.org/) Perform calibration to obtain the gene name corresponding to the target.

2.2 Screening of Sepsis Related Targets

Search for the keyword 'sepsis' using the GeneCards database (https://www.genecards.org/) OMIM database (https://omim.org/) TTD database (https://db.idrblab.net/ttd/) Collect and screen target genes, set a relevance score of ≥ 1, and remove duplicates to ultimately obtain sepsis related target genes.

2.3 Prediction of Potential Targets of FJHD on Sepsis

Using Venny 2.1.0 platform (https://bioinfogp.cnb.csic.es/tools/venny/) Draw a Venny diagram of the active ingredients of FJHD and the targets of sepsis, and obtain the intersection targets, which are potential targets for the treatment of sepsis with FJHD.

2.4 Constructing a Drug Active Ingredient Target Network to Predict Key Active Ingredients

Import the drugs, active ingredients, and potential targets of FJHD into Cytoscape 3.10.3 software, construct a drug active ingredient target network, and visualize it. Use the Analyze Network plugin to perform network topology analysis on the obtained data, and predict the key active ingredients of the drug based on the degree values of the connections between each element in the network.

2.5 Constructing a Protein-protein Interaction Network to Predict Core Functional Targets

Upload the intersection targets between the active ingredients of FJHD and sepsis to the String platform (https://cn.string-db.org/). Perform protein interaction analysis, limit the research species to "Homo sapiens", set the lowest interaction score as "highest confidence" (0.900), and maintain the default settings for other parameters. Hide free targets to obtain the protein-protein interaction (PPI) network of the drug target protein disease target protein of FJHD for sepsis. Download the PPI network file, use Cytoscape 3.10.3 to construct a core target network, obtain network graph related data through topological analysis, and predict the core target based on the degree values of the connections between the targets.

2.6 GO Functional Enrichment Analysis and KEGG Pathway Enrichment Analysis

By importing the active ingredients of FJHD and the intersection targets of sepsis into the DAVID database (https://davidbioinformatics.nih.gov/). The study species is limited to "humans" with a Pvalue value less than 0.01, and GO (gene ontology) functional enrichment analysis and KEGG (Kyoto Encyclopedia of genes and genomes) pathway enrichment analysis are conducted. GO functional enrichment analysis includes biological processes (BP), cellular components (CC), and molecular functions (MF). The GO functional enrichment analysis and KEGG pathway enrichment analysis data obtained will be analyzed using a bioinformatics data analysis platform (https://www.bioinformatics.com.cn/). Visualize to reveal the potential molecular mechanisms of FJHD in treating sepsis.

2.7 Molecular Docking between Main Active Ingredients and Key Targets

In the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) Search for high scoring active substances in the drug active ingredient target network, download and save the 2D structure file of the active substance. The 2D structures were converted to 3D structures using ChemBio3D Ultra 14 software, and adjust the 3D structure of the compound to the lowest energy state. Limit the species to "human" in the Uniprot database, search for the core target predicted by the PPI network, find the Entry ID corresponding to the core target, and search for it in the RCSB PDB database (https://www.rcsb). Search for Entry ID and download the structural file of the core target protein. Use PyMol 3.1.3 software to remove water molecules and ligands from the core target protein, then use AutoDockTools 1.5.7 software for hydrogenation and charge balancing treatment, and convert the core target protein file to PDBQT format. Finally, AutoDock Vina software was used to perform molecular docking analysis between the key active ingredients and the core target, verifying their binding ability. PyMol 3.1.3 software was used to visualize the docking of the key active ingredients of FJHD with good molecular docking scores and the core target protein of sepsis.

3. Results

3.1 Effective Active Ingredients and Targets of FJHD

Table 1: Number of Active Ingredients and Corresponding Targets for Each Herb in FJHD

TCM Name	Number of active ingredients	Number of corresponding targets
Herba Patriniae	13	218
Radix Paeoniae Rubra	29	102
Trichosanthes Kirilowii Maxim	11	15
Scutellariae Radix	36	124
Forsythiae Fructus	23	229
Rhapontici Radix	5	44
Panacis Quinquefolii Radix	11	59
Coicis Semen	9	32

Eight traditional Chinese medicines in FJHD were screened in the TCMSP database using the steps outlined in section 1.1, with OB ≥ 30% and DL ≥ 0.18 as the conditions. A total of 137 active ingredients and 823 corresponding targets were obtained. The effective active ingredients and their corresponding targets were integrated and deduplicated, resulting in 86 active ingredients and 268 corresponding targets in FJHD, as shown in Table 1.

3.2 Collection Results of Sepsis Related Targets

Following the steps in section 1.2, 4181 sepsis related targets

were obtained from the GeneCards database; Obtain one sepsis related target from the OMIM database; 35 sepsis related targets were obtained from the TTD database. After integrating the obtained targets and setting a relevance score of ≥ 1 for screening, duplicate items were removed, resulting in a total of 1830 sepsis related targets.

3.3 Screening of Common Targets for Drugs and Diseases

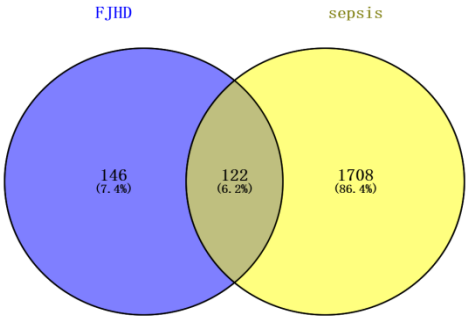


Figure 1: Venny diagram of FJHD and sepsis targets

According to the steps in section 1.3, the effective active ingredients of FJHD obtained in sections 2.1 and 2.2 were intersected with sepsis related targets using the Venny 2.1.0 platform, resulting in 122 intersecting targets. Venny diagrams were then created, as shown in Figure 1. These 122 targets are potential targets for the treatment of sepsis with FJHD.

3.4 Drug Active Ingredient Intersection Target Correlation Network Diagram

Draw a Drug-Ingredient-Target network diagram using Cytoscape 3.10.3 software, following the steps in section 1.4, to identify the active ingredients and potential therapeutic targets of FJHD for treating sepsis, as shown in Figure 2. The network comprises 216 nodes: 8 drug nodes (red), 86 active ingredient nodes (purple for unique components, green for shared components), and 122 target nodes (cyan). There are a total of 913 edges, which demonstrate the relationship between the active ingredients and their targets in FJHD.

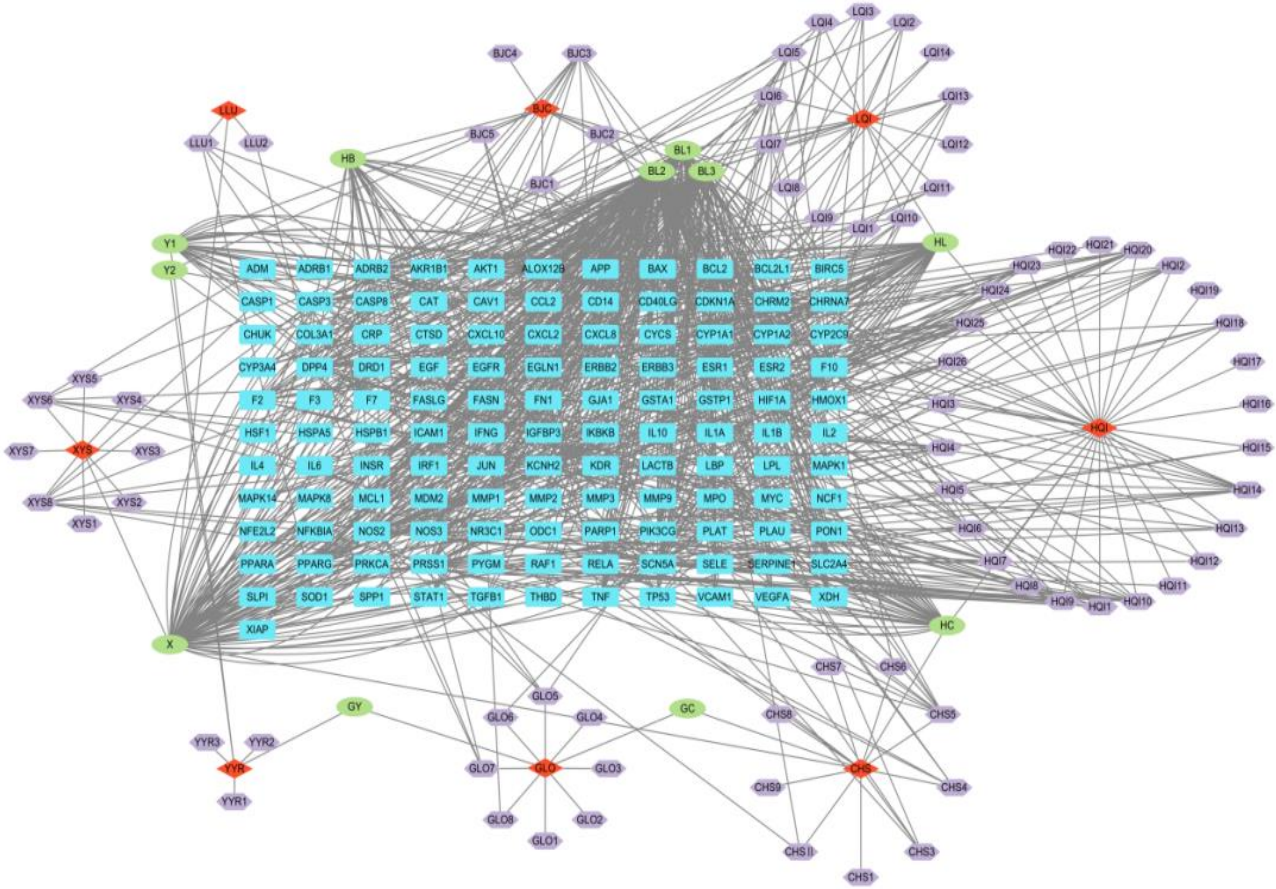


Figure 2: Drug-Ingredient-Target network diagram

Table 2: Core active ingredients of FJHD (top 10)

Compound Name	Source	MOL ID	degree
quercetin	Herba Patriniae, Forsythiae Fructus	MOL000098	310
beta-sitosterol	Herba Patriniae, Radix Paeoniae Rubra, Scutellariae Radix, Forsythiae Fructus, Rhapontici Radix, Panacis Quinquefolii Radix	MOL000358	234
kaempferol	Herba Patriniae, Forsythiae Fructus	MOL000422	128
stigmasterol	Herba Patriniae, Radix Paeoniae Rubra, Scutellariae Radix, Coicis Semen	MOL000449	128
luteolin	Herba Patriniae, Forsythiae Fructus	MOL000006	116
wogonin	Scutellariae Radix, Forsythiae Fructus	MOL000173	92
baicalein	Scutellariae Radix, Radix Paeoniae Rubra	MOL002714	76
acacetin	Scutellariae Radix, Herba Patriniae	MOL001689	54
bicuculline	Scutellariae Radix	MOL000791	28
oroxylin a	Scutellariae Radix	MOL002928	27

According to the degree values of active ingredients in the network diagram, the active ingredients in FJHD are ranked, as shown in Table 2. The top 5 core active ingredients are quercetin, β-sitosterol, kaempferol, stigmasterol, and luteolin.

3.5 PPI Network Construction and Core Target Screening

The 122 intersection targets of FJHD and sepsis were imported into the string platform according to the steps of "1.5", and the lowest interaction score was 0.9. The free points were removed and the PPI network was constructed, as shown in Figure 3. A total of 109 nodes and 377 edges were obtained, and the average local clustering coefficient was 0.544.

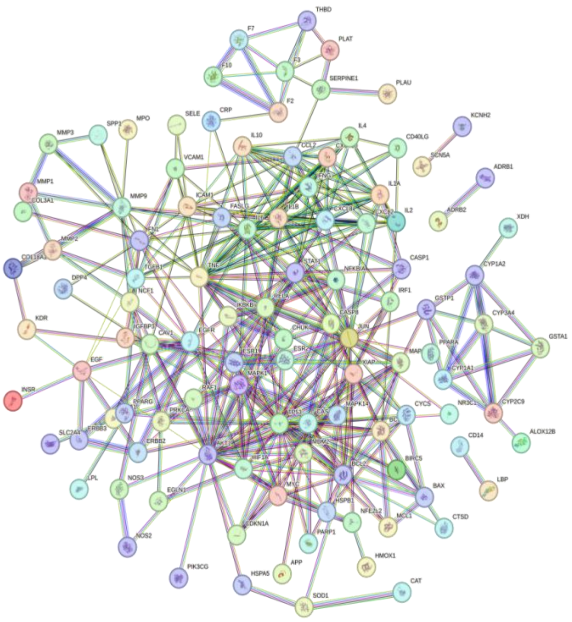


Figure 3: PPI network diagram

Import the PPI network data obtained from the string platform into Cytoscape 3.10.3 software for topology analysis and visualization, as shown in Figure 4. Rank according to the degree value, as shown in Table 3. The larger the area, the darker the color, and the denser the connecting lines, the more likely it is to be the core target of FJHD in the treatment of sepsis. The top five core targets are TP53, TNF, AKT1, Jun, and IL6.

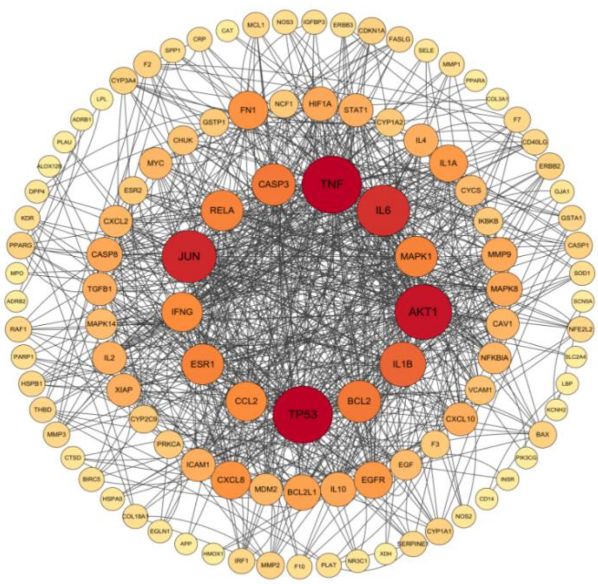


Figure 4: Schematic diagram of core targets

Table 3: The core targets of FJHD in the treatment of sepsis (top 10)

Target Gene	Protein Name	Uniprot ID	degree
TP53	Cellular tumor antigen p53	P04637	58
TNF	Tumor necrosis factor	P01375	58
AKT1	RAC-alpha serine/threonine-protein kinase	P31749	54
JUN	Transcription factor AP-1	P05412	50
IL6	Interleukin-6	P05231	48
IL1B	Interleukin-1 beta	P01584	38
CASP3	Caspase-3	P42574	34
BCL2	Apoptosis regulator Bcl-2	P10415	34
MAPK1	Mitogen-activated protein kinase 1	P28482	32
ESR1	Estrogen receptor	P03372	32

3.6 GO Function Enrichment Analysis and KEGG Pathway Enrichment Analysis

The 122 intersection targets of FJHD and sepsis were imported into David database according to the steps of "1.6", and the research species were limited to "human" with P < 0.01 for analysis. 479 GO functional enrichment entries were obtained, including 360 BP entries, 35 CC entries, and 84 CC entries. According to the order of P value from small to large, take the top 10 items of BP, CC and MF and draw a histogram with count value, as shown in Figure 5. It is suggested that FJHD in the treatment of sepsis involves RNA polymerase II (RNA Pol II)-mediated positive regulation of transcription and gene expression and negative regulation of apoptosis process in BP; CC involves cytoplasmic matrix, extracellular matrix and extracellular region; In MF, protein binding, same protein binding and enzyme binding are involved.

KEGG pathway enrichment analysis yielded 143 signal pathways (P < 0.01), and the top 15 were selected based on the p value to visualize the data, as shown in Figure 6. The larger the dot, the more genes associated with the pathway, and the darker the color, the higher the enrichment. The top pathways are mainly pathways in cancer, lipid and atherosclerosis, and AGE-RAGE signaling pathway in diabetic complications.

Through GO function and KEGG pathway enrichment analysis, the potential molecular mechanism of FJHD in the treatment of sepsis can be revealed.

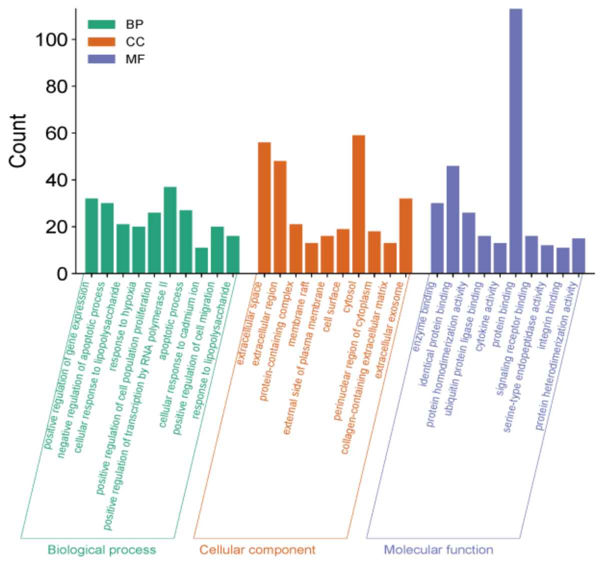


Figure 5: GO function enrichment analysis

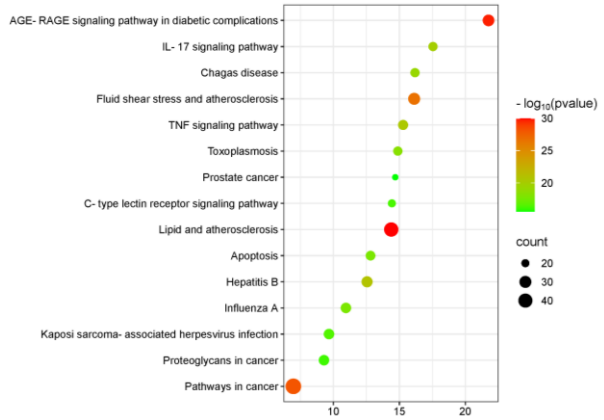


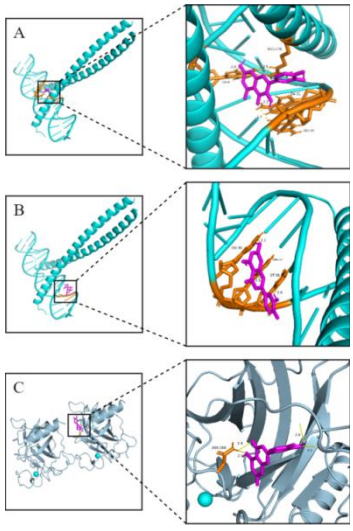
Figure 6: KEGG pathway enrichment analysis

3.7 Molecular Docking

Select the top 5 active ingredients and target proteins in "2.4" and "2.5" to perform molecular docking according to the steps of "1.7", and obtain the binding energy between active ingredients and target proteins, as shown in Table 4. The results showed that the lowest binding energy of the active ingredient and target protein for docking fluctuated between -5.5~-8.8 kcal/mol, which is generally considered to be less than -5 kcal/mol, representing a relatively stable binding conformation. The binding energies of Jun quercetin, Jun luteolin and TP53 luteolin are all less than -8.0 kcal/mol, which are visualized by PyMOL 3.1.3 software, as shown in Figure 7. The molecular docking results showed that the key active ingredients in FJHD had good binding ability with the core target protein, and the docking results were good.

Table 4: Molecular docking results (binding energy < -7.0kcal/mol)

active ingredient	target protein	binding energy(kcal/mol)
quercetin	JUN	-8.8
luteolin	JUN	-8.7
luteolin	TP53	-8.1
quercetin	TP53	-7.7
stigmasterol	JUN	-7.6
quercetin	IL6	-7.5
beta-sitosterol	JUN	-7.4
kaempferol	TP53	-7.4
luteolin	IL6	-7.2
kaempferol	JUN	-7.1



A: JUN-quercetin; B: JUN-luteolin; C: TP53-luteolin

Figure 7: Schematic diagram of docking of some main active ingredients with core target molecules

4. Discussion

Sepsis is a syndrome of physiological, pathological and biochemical abnormalities caused by infection. Its pathological process is complex, involving a variety of pathological factors and mechanisms. Delayed treatment may lead to secondary septic shock and multiple organ failure, which significantly increasing mortality risk. The main pathogenesis is the dysregulation of the body's response in the early stage of sepsis [12]. Therefore, inhibiting the uncontrolled response of immune inflammation is the key to sepsis treatment. Previous studies found that FJHD could reduce the expression of pro-inflammatory factors such as tnf-α, IL-1 β, if n- γ and IL-6, increase the expression level of anti-inflammatory factors such as IL-10, and also reduce the mRNA expression of NLRP3 inflammasome, caspase-1 and ASC, thus significantly reducing the levels of IL-18 and IL-1 β inflammatory response transmitters. Therefore, FJHD has the function of regulating the expression of pro-inflammatory and anti-inflammatory cytokines, maintaining immune homeostasis, and improving the level of inflammation in the early stage of infection [13-15].

By comprehensively applying network pharmacology and molecular docking technology, this study systematically analyzed the potential mechanism of Zheng Jie Du Hua Yu Fang in the treatment of sepsis through multi-component, multi-target and multi-channel mechanism of action, providing a theoretical basis for subsequent experimental research and clinical application. The study found that FJHD may play the role of anti infection, regulating immune response, regulating oxidative stress injury, inhibiting inflammatory response and apoptosis by combining quercetin, β-sitosterol, kaempferol, stigmasterol and luteolin with key targets such as TP53, TNF, AKT1, Jun and IL6 to regulate cancer pathways, lipid and atherosclerosis mechanisms and AGE-RAGE signaling pathways.

Among the main effective components screened by network pharmacology, quercetin can inhibit oxidative stress-mediated ER stress and mitochondrial dysfunction by inducing sirt1/ampk pathway, thus preventing sepsis induced acute lung injury [16]; β-sitosterol can inhibit the inflammatory response during sepsis by inhibiting nf- κ B signaling pathway [17]; Kaempferol can alleviate sepsis induced acute lung injury by enhancing endothelial barrier and reducing inflammatory response through sphk1/s1p/s1pr1/mlc2 pathway [18]; Stigmasterol can inhibit tgf- β 1/smad2 and IL-17A signaling pathways and reduce the number of inflammatory cytokines such as IL-1 β, IL-5, IL-6 and IL-13 in the alveolar lavage fluid of asthmatic mouse models [19]; Luteolin can affect the inflammatory initiation pathway and reduce the expression of genes that produce inflammatory cytokines, reduce inflammation and oxidative stress during sepsis, while controlling immune responses and preventing organ damage [20]. The above existing research results verify that FJHD contains a variety of effective active ingredients that can improve sepsis.

Through the construction of PPI network, TP53, TNF, AKT1, Jun and IL6 were obtained as the core targets of FJHD in the treatment of sepsis. Among them, TP53 is prone to mutation during inflammatory processes, increasing the probability of a

variety of malignant tumors [21, 22]; Jun activation can reduce the levels of inflammatory cytokines in septic mice [23]; While TNF, AKT1 and IL6 are classical cytokines that play a key role in the inflammatory process [24-26]. At the mechanism level, GO function and KEGG pathway enrichment analysis found that the active ingredients of FJHD were significantly enriched in cancer pathways, lipid and atherosclerosis mechanisms, AGE-RAGE and other signaling pathways, which were highly correlated with advanced glycation end products (AGE) mediated oxidative stress injury and inflammatory mechanisms in the process of sepsis [27].

Through molecular docking, it was found that the core components of FJHD, such as quercetin, luteolin, stigmasterol, β-sitosterol and kaempferol, have strong molecular binding ability with key targets such as Jun, TP53 and IL6, suggesting that the biological components of FJHD may exert curative effect through these targets to regulate the related pathways of inflammation, apoptosis and immune homeostasis, further confirming the synergistic regulation ability of traditional Chinese medicine compound on cytokine network. These findings provide a molecular explanation for FJHD to reduce the expression of inflammatory factors and improve sepsis symptoms in patients with sepsis in the early clinical observation.

This study explored that FJHD may have the potential to treat sepsis through multiple key targets and signaling pathways, but there are still several limitations. First, the prediction results of network pharmacology need to verify the activation and inhibition effects of active ingredients on the target through further in vitro cell experiments; Secondly, tcmsp database does not cover the component transformation products of traditional Chinese medicine decoction process, which may affect the final therapeutic effect of drugs; In addition, this study also did not consider the influence of the intestinal flora and other internal environment on the action of traditional Chinese medicine ingredients. Therefore, future studies need to further verify these prediction results. We can systematically verify the regulatory effect of FJHD on sepsis related signaling pathways and explore its application in clinical treatment by constructing lipopolysaccharide (LPS) induced sepsis animal model [28] and knocking down the core target with RNA interference technology [29].

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