Regular article

Study on the mechanism of *Euphorbia fischeriana* Steud.-Jujubae Fructus in the treatment of hepatocirrhosis based on network pharmacology

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Abstract

The active components, targets, and pathways of *Euphorbia fischeriana* Steud.-Jujubae Fructus in treating hepatocirrhosis and the mechanism of action were explored by means of network pharmacology. Firstly, the active components and related targets of Jujubae Fructus were screened by TCMSP database and standardized by Uniprot database. The compounds of *Euphorbia fischeriana* Steud. were obtained by searching the literature and finally screened by PubChem database, Swiss ADME, and SwissTargetPrediction. Hepatocirrhosis targets were obtained through Genecards database, PPI network analysis was conducted on common targets of *Euphorbia fischeriana* Steud.-Jujubae Fructus and hepatocirrhosis by using String database, GO enrichment analysis and KEGG pathway enrichment analysis was conducted through Metascape database by using intersection targets of *Euphorbia fischeriana* Steud.-Jujubae Fructus and hepatocirrhosis, and the results were drawn by using Weishengxin online drawing platform. Then, the network of drug-compound-target-pathway was constructed by the software of Cytoscape3.8.0. Finally, the above results were verified by molecular docking. 47 active compounds from *Euphorbia fischeriana* Steud.-Jujubae Fructus were screened out, which had 38 common targets, 162 intersection targets, and 340 signal pathways with hepatocirrhosis, mainly involving hepatitis C, JAK-STAT signal pathway and AGE-RAGE signal pathway. Targets, such as MAPK1, AKT1, TNF, JUN, IL6 and PTGS2, play important roles in the treatment. The findings suggested that the main active ingredients of *Euphorbia fischeriana* Steud.-Jujubae Fructus in treating hepatocirrhosis are quercetin, scopolamine, physcion, 7-deoxyrangduin, 17-Hydroxyjolkinolide A, etc. Molecular docking results showed that the main active components and core targets might have a good binding capacity. This study preliminarily explored the potential mechanism of *Euphorbia fischeriana* Steud.-Jujubae Fructus in treating hepatocirrhosis and provided a theoretical basis for the clinical application of *Euphorbia fischeriana* Steud.-Jujubae Fructus.

Keywords: *Euphorbia fischeriana* Steud.; Jujubae Fructus; hepatocirrhosis; network pharmacology

1 Introduction

Hepatocirrhosis is the end-stage of various chronic liver diseases, especially progressive liver fibrosis, and is an increasingly serious public health problem worldwide, affecting an estimated 1%-2% of the global population and causing more than 1 million deaths annually [1,2]. Pathologically, hepatocirrhosis is characterized by chronic progressive hepatocyte degeneration and excessive fibrosis. This leads to a variety of

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serious complications, such as functional liver failure, hepatic encephalopathy, ascites and even hepatocellular carcinoma, and the prognosis is really poor [3-5]. At present, the application of integrated traditional Chinese and Western medicine in the treatment of hepatocirrhosis is becoming increasingly widespread. Therefore, it is urgent to study the application of traditional Chinese medicine in disease treatment.

Euphorbia fischeriana Steud., first recorded in Shennong Materia Medica Classic, is the dried root of the perennial herbaceous plant of the Euphorbiaceae family and the genus Euphorbia. It is also known as "wolf poison" and is mainly distributed in northeast China [6,7]. *Euphorbia fischeriana* Steud. contains terpenoids, phenols, steroids, etc. Because of its efficacy in expelling water and promoting drinking, dispelling accumulation, and dispersing nodules, it is widely used to treat edema, cancer, and ascites. However, the root of *Euphorbia fischeriana* Steud. is highly toxic and has fierce medicinal properties, making it unsuitable for heavy use [8-10]. Jujubae Fructus, the fruit of the Rhamnaceae family, has been used as food and medicine in China for thousands of years because of its functions of invigorating the spleen and stomach, nourishing blood and calming the mind. Modern research has shown that Jujube Fructus has anti-inflammatory, anti-cancer, antioxidant and immunomodulatory activities, and the protective effect of liver and gastrointestinal tract [11-14]. *Euphorbia fischeriana* Steud. combined with Jujube Fructus has been used in ancient prescriptions to treat pulmonary tuberculosis and lung cancer. Terpenoids in *Euphorbia fischeriana* Steud. are the main active ingredients, but they are also toxic components. Combined with Jujube Fructus can enhance, its therapeutic effects can be enhanced, the irritating effect on the gastrointestinal tract can be reduced, and its toxicity can be alleviated. Therefore, the combination of *Euphorbia fischeriana* Steud. with Jujube Fructus has high research value in the treatment of hepatocirrhosis.

However, the molecular mechanism of *Euphorbia fischeriana* Steud. - Jujubae Fructus for the treatment of hepatocirrhosis has yet to be

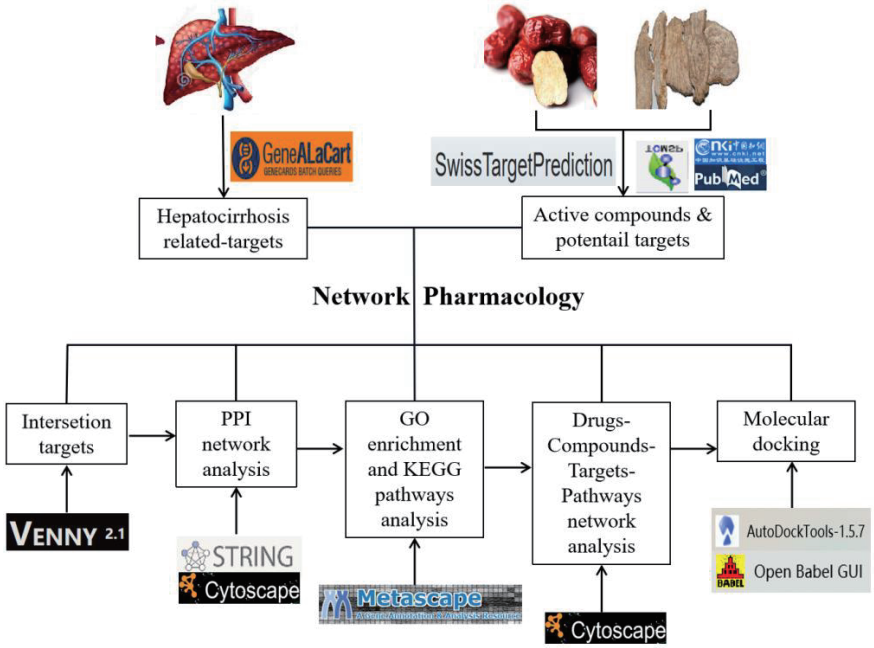

Fig. 1 Flow chart of network pharmacology

clarified. In this study, the active ingredients, action targets, and potential molecular mechanisms of *Euphorbia fischeriana* Steud. combined with Jujube Fructus in the treatment of hepatocirrhosis were discussed based on network pharmacology in order to provide ideas and basis for the clinical treatment of hepatocirrhosis with *Euphorbia fischeriana* Steud. and Jujube Fructus.

2 Materials and methods

2.1 Identification of chemical ingredients in Euphorbia fischeriana Steud. and Jujube Fructus and compound-related targets

The active compounds in Jujube Fructus were screened according to the oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 in the Traditional Chinese Medicine Systematic Pharmacology Data and Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php). The targets corresponding to the screened active compounds were exported and imported into the Uniprot (http://www.uniprot.org/uploadlists/) database for gene name alignment. Because *Euphorbia fischeriana* Steud. can not be found in TCMSP, the active ingredients of *Euphorbia fischeriana* Steud. were searched based on literature. SMILES information of relevant components was queried in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and imported into Swiss ADME (http://www.swissadme.ch/) [15,16]. In pharmacokinetics study, compounds that meet gastrointestinal absorption (GI absorption) were classified as high and those whose DL are two or more Yes were classified as active compounds in the treatment of hepatocirrhosis by *Euphorbia fischeriana* Steud.. Subsequently, the screened compounds of *Euphorbia fischeriana* Steud. were imported into SwissTargetPrediction (http://www.swisstargetprediction.ch/) to predict the corresponding targets [17,18].

2.2 Screening of targets for hepatocirrhosis

With “hepatocirrhosis” as the keyword, we retrieved potential targets and information of hepatocirrhosis from the Genecards database (https://www.genecards.org/).

2.3 Protein-protein interaction network (PPI) analysis

The targets of *Euphorbia fischeriana* Steud. and Jujube Fructus were combined and deduplicated to obtain the common targets. The intersection targets of *Euphorbia fischeriana* Steud. and Jujube Fructus and the targets of hepatocirrhosis were mapped by Venny to obtain the drug-disease intersecting targets. The intersection targets were imported into the String database (https://www.string-db.org/), and the protein interaction network was analyzed by selecting multiple proteins and setting the species as human. Non-interacting targets in the network were hidden.

2.4 GO and KEGG pathway enrichment analysis

The intersection targets were imported into the Metascape database (https://metascape.org/gp/index.html), the species was set as human, and custom analysis was selected to perform KEGG, BP, CC and MF analysis, respectively. The top ten paths were visualized and analyzed by using the online mapping platform (http://www.bioinformatics.com.cn/).

2.5 Construction of Drugs - Components - Targets - Pathways network

The intersection targets, drugs, active ingredients, and KEGG pathways were introduced into Cytoscape3.8.0 to construct the Drugs - Components - Targets - Pathways network.

2.6 Molecular docking

The protein 3D crystal structures of the core targets were downloaded from the PDB database, and the 3D structures of the active ingredients were downloaded from the Pubchem database. After dehydration and ligand removal of the protein by PyMol software, the protein and active ingredients were imported into Auto Dock software for hydrogenation, charge calculation and rigid structure determination, and the results were saved as a pdbqt file. Finally, molecular docking of components with the proteins was performed to obtain the corresponding binding energy.

3 Results

3.1 Active compounds and potential targets of Euphorbia fischeriana Steud. and Jujube Fructus

A total of 29 compounds of Jujube Fructus that met the criteria were retrieved from TCMSP, and a total of 186 targets were obtained after deduplication. 32 compounds were obtained from *Euphorbia fischeriana* Steud., with a total of 680 targets after deduplication. The results were shown in Table 1 and Table 2.

Table 1 Part of the active ingredients of Jujube Fructus

Source	No.	Name	Molecular Formula	PubChem CID	CAS
Jujube Fructus	1	stepharine	$C_{18}H_{19}NO_3$	98455	2810-21-1
Jujube Fructus	2	(*S*)-Coclaurine	$C_{17}H_{19}NO_3$	160487	486-39-5
Jujube Fructus	3	Stigmasterol	$C_{29}H_{48}O$	5280794	83-48-7
Jujube Fructus	4	berberine	$C_{20}H_{18}NO_4^+$	2353	2086-83-1
Jujube Fructus	5	*β*-sitosterol	$C_{29}H_{50}O$	222284	83-46-5
Jujube Fructus	6	Stepholidine	$C_{19}H_{21}NO_4$	6917970	16562-13-3
Jujube Fructus	7	Nuciferin	$C_{19}H_{21}NO_2$	10146	475-83-2
Jujube Fructus	8	Fumarine	$C_{20}H_{19}NO_5$	4970	130-86-9
Jujube Fructus	9	*β*-carotene	$C_{40}H_{56}$	5280489	7235-40-7
Jujube Fructus	10	quercetin	$C_{15}H_{10}O_7$	5280343	117-39-5

Table 2 Part of the active ingredients of *Euphorbia fischeriana* Steud.

Source	No.	Name	Molecular Formula	PubChem CID	CAS
Euphorbia fischeriana Steud.	1	17-Hydroxyjolkinolide A	$C_{20}H_{26}O_4$	6712606	65388-16-1
Euphorbia fischeriana Steud.	2	Physcion	$C_{16}H_{12}O_5$	10639	521-61-9
Euphorbia fischeriana Steud.	3	Gallic acid	$C_7H_6O_5$	370	149-91-7
Euphorbia fischeriana Steud.	4	Scopoletin	$C_{10}H_8O_4$	5280460	92-61-5
Euphorbia fischeriana Steud.	5	Jolkinolide A	$C_{20}H_{26}O_3$	161953	37905-07-0
Euphorbia fischeriana Steud.	6	Jolkinolide B	$C_{20}H_{26}O_4$	161954	37905-08-1
Euphorbia fischeriana Steud.	7	antiquorin	$C_{20}H_{28}O_3$	14262777	125356-08-3
Euphorbia fischeriana Steud.	8	12-deoxyphorbol-13-decanoate	$C_{30}H_{46}O_6$	56841004	70278-05-6
Euphorbia fischeriana Steud.	9	Fischeria A	$C_{19}H_{28}O_2$	15403260	221456-63-9
Euphorbia fischeriana Steud.	10	2,4-dihydroxy-6-methoxyacetophenone	$C_9H_{14}O_4$	10965145	3602-54-8

3.2 Targets for hepatocirrhosis

With "hepatocirrhosis" as the keyword, 4017 hepatocirrhosis targets were obtained in Genecards database, and 772 hepatocirrhosis targets with a score > 10 were obtained.

3.3 Construction of intersection targets and PPI network

The mapping results of the intersection targets of *Euphorbia fischeriana* Steud. and Jujube Fructus and the targets of hepatocirrhosis were shown in Fig. 2, and 38 core target genes were obtained, which proves that *Euphorbia fischeriana* Steud. and Jujube Fructus may play a synergistic therapeutic effect on hepatocirrhosis through multiple targets. The 38 core target genes were imported into the String database, and the interaction score was set to the highest 0.9. There are 38 nodes and 77 edges in the PPI network diagram, and the average node degree is 4.05, as shown in Fig. 3. Topological analysis of Cytoscape3.8.0 showed that the top five targets were MAPK1, AKT1, TNF, JUN, and IL6, which had more interactions with other proteins in PPI network and played an important role in the treatment of hepatocirrhosis, as shown in Table 3 and Fig. 3.

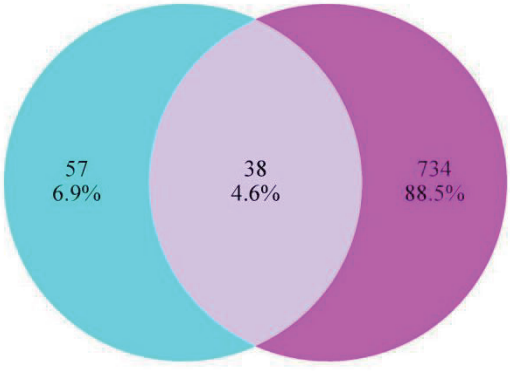

Fig. 2 Interaction targets of drug and disease

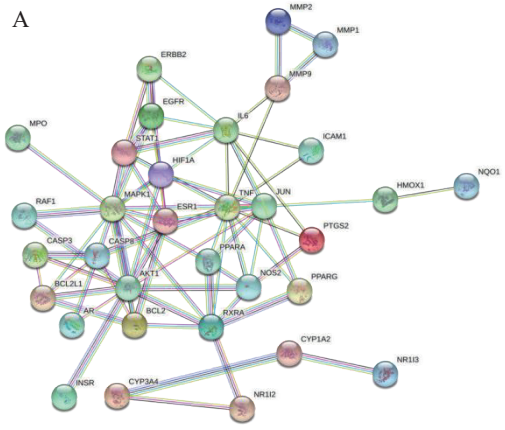

Fig. 3 A: PPI network diagram of interaction targets; B: Visualization of the results of the PPI network; C: Hub genes of PPI network

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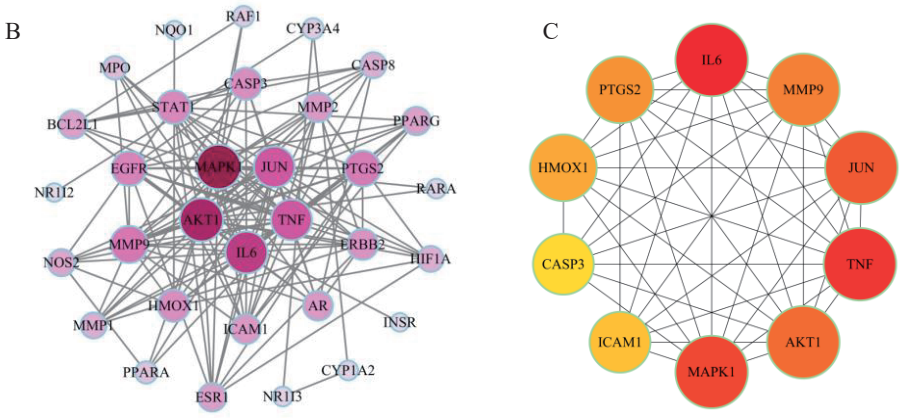

Continued fig. 3

Table 3 Topology parameter analysis of protein interaction (Top 20)

Gene name	Targets name	Degree	Connectivity	Intermediate centrality	Closeness centrality	Topological parameter
MAPK1	Mitogen-activated protein kinase 1	22	11.09	0.14447476	0.84375000	0.41077441
AKT1	RAC-alpha serine/threonine-protein kinase	21	11.19	0.17342397	0.81818182	0.42857143
IL6	Interleukin-6	20	12.55	0.05672597	0.79411765	0.46481482
JUN	Transcription factor Jun	19	12.58	0.05503013	0.77142857	0.46588694
TNF	Tumor necrosis factor	19	12.26	0.06527287	0.77142857	0.45419103
MMP9	Matrix metalloproteinase-9	16	13.50	0.02893915	0.71052632	0.50000000
PTGS2	Prostaglandin G/H synthase 2	15	14.20	0.01805528	0.69230769	0.52592593
EGFR	Epidermal growth factor receptor	14	13.50	0.01917009	0.64285714	0.54000000
STAT1	Signal transducer and activator of transcription 1-alpha/beta	13	14.46	0.01334764	0.64285714	0.55621302
CASP3	Caspase-3	12	15.17	0.00929622	0.642857143	0.56172839
HMOX1	Heme oxygenase 1	12	14.08	0.08245995	0.64285714	0.53846154
ERBB2	Receptor tyrosine-protein kinase erbB-2	11	14.00	0.00812722	0.61363636	0.53846154
AR	Androgen receptor	10	15.10	0.00541173	0.60000000	0.58076923
ICAM1	Intercellular adhesion molecule 1	10	15.60	0.00606484	0.60000000	0.60000000
MMP2	72 kDa type IV collagenase	10	14.80	0.00674161	0.60000000	0.56923077
BCL2L1	Bcl-2-like protein 1	9	14.11	0.00767987	0.58695652	0.54273504
ESR1	Estrogen receptor	9	15.78	0.00265091	0.58695652	0.60683761
PPARG	Peroxisome proliferator-activated receptor gamma	9	15.33	0.00307738	0.56250000	0.63888889
NOS2	Nitric oxide synthase	8	15.38	0.00561887	0.58695652	0.56944444
CASP8	Caspase-8	7	15.29	0.00116186	0.56250000	0.58791209

3.4 GO and KEGG pathways enrichment analysis

A total of 2549 biological processes (BP), 85 Cellular Components (CC), and 174 Molecular Functions (MF) were obtained by GO enrichment analysis. Bubble charts were drawn for the top

ten enrichment rankings, respectively, as shown in Fig. 4. The larger the bubble in the figure, the more enriched the number of targets in this entry; the darker the bubble color, the higher the degree of enriched targets in this entry. Among them, the top three biological processes with a large number of enriched targets and high degree values were the response to toxic substances, the response to injury, and the response to inorganic substances. The top three cellular components were membrane valve, membrane side, and receptor complex. The top three molecular functions were protein kinase activity, kinase binding, and transcription factor binding. In addition, the top-ranked KEGG pathways include the cancer pathway, hepatitis C, AGE-RAGE signaling pathway and JAK-STAT signaling pathway, which might be the key signaling pathways for the treatment of hepatocirrhosis with *Euphorbia fischeriana* Steud. and Jujube Fructus, as shown in Fig. 5.

3.5 Construction of Drugs - Compounds - Targets - Pathways network

The network consists of 221 nodes (162 targets, 10 KEGG pathways, 47 active compounds, and 2 medicinal herbs) and 1161 edges, as shown in Fig. 6. In this network, the dark blue diamond represents the targets, the light pink octagon represents the compounds of *Euphorbia fischeriana* Steud., the purple octagon represents the compounds of Jujubae Fructus, the blue circle represents *Euphorbia fischeriana* Steud., the red circle represents Jujubae Fructus, and the green V-shape represents the most relevant KEGG pathway. Among them, the degree of a node represents the number of edges connected with other nodes in the network. The larger the node, the more critical it is in the network. Quercetin acted on the most targets, with 71 targets. The number of potential targets for antiquinolin, physion, 7-deoxylangduin and 17-hydroxyjolkinide A is 27,

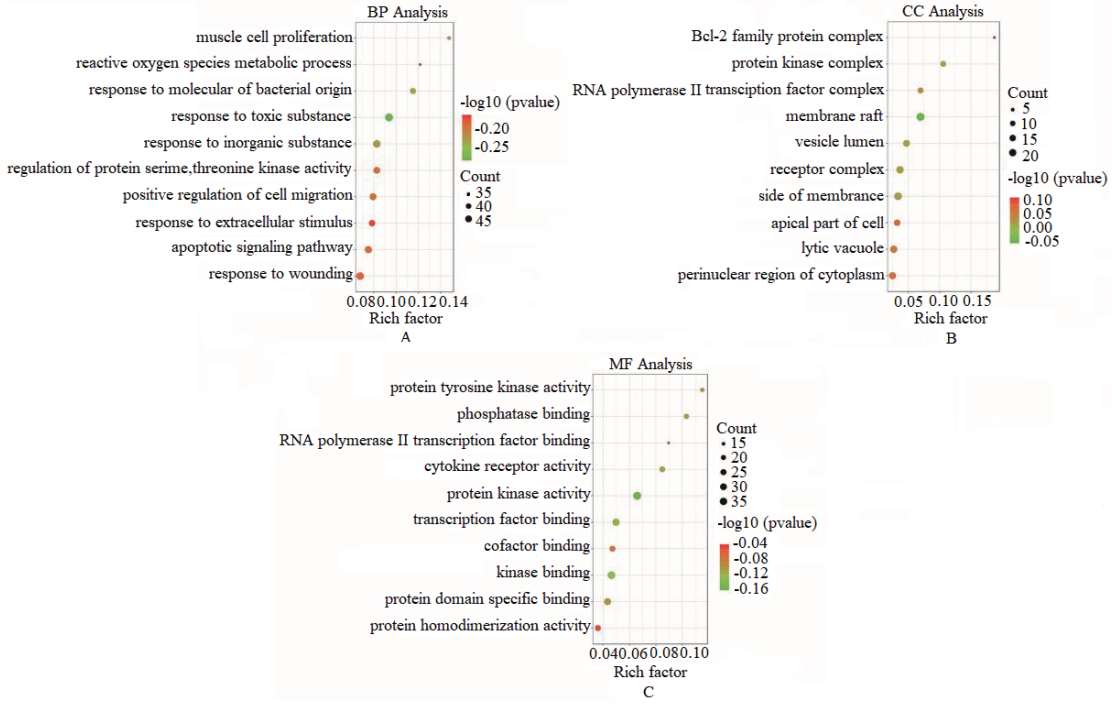

Fig. 4 GO enrichment analysis

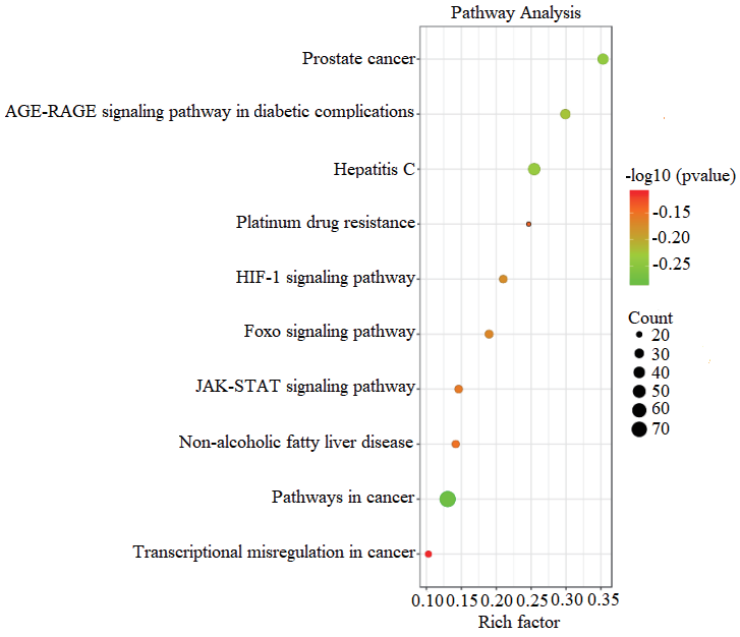

Fig. 5 KEGG pathways enrichment analysis

26, 24 and 24, respectively. The top three targets are AR, PTGS2 and JAK1, and the top five pathways are cancer pathway, prostate cancer pathway, hepatitis C, AGE-RAGE signaling pathway and JAK-STAT signaling pathway. These components, targets, and pathways might be important components, targets and pathways for the treatment of hepatocirrhosis by *Euphorbia fischeriana* Steud. and Jujube Fructus, suggesting that *Euphorbia fischeriana* Steud. and Jujube Fructus might treat hepatocirrhosis through a "multi-component multi-target multi pathway" approach.

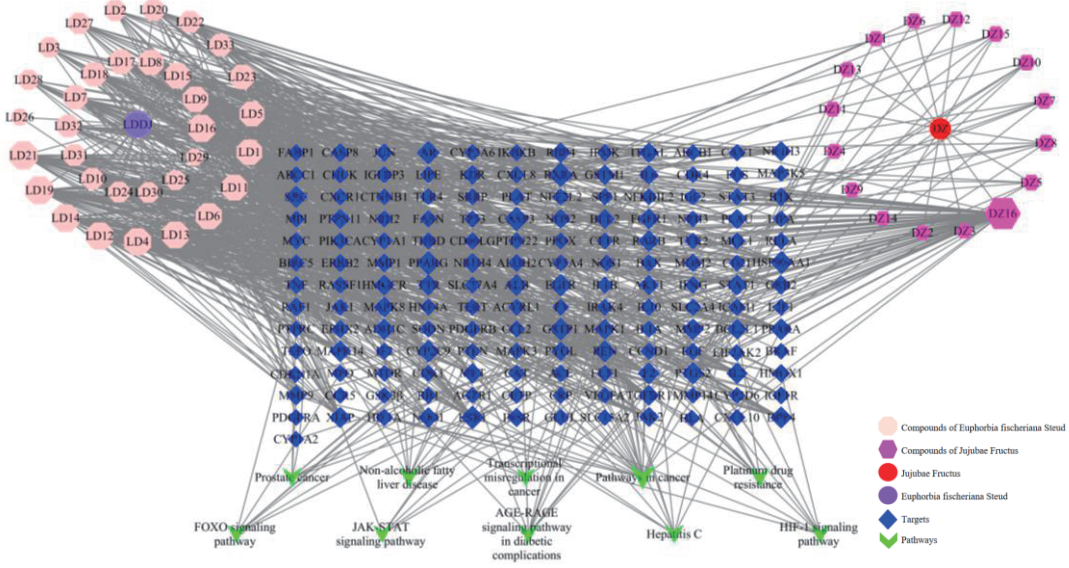

Fig. 6 Drugs -Compounds - Targets - Pathways network

3.6 Molecular docking results

The molecular docking of quercetin, hyopolamine, emodin and antiquorin with MAPK1, IL6, AKT1, JUN, TNF and MMP9 showed that a total of 17 out of 24 sets of receptor-ligand results had binding energies less than -5 kcal/mol, indicating that the components and target proteins might have good binding capacity [19]. The results suggested that *Euphorbia fischeriana* Steud. and Jujube Fructus played a role in the treatment of hepatocirrhosis through the above-mentioned components and targets, as shown in Table 4 and Fig. 7.

Table 4 Results of molecular docking

Target	Binding energy/(kcal/mol)			
	Quercetin	Scopolamine	Physcion	Antiquorin
IL6	-4.09	-4.35	-5.15	-7.17
MAPK1	-6.35	-5.22	-5.09	-7.59
AKT1	-5.36	-4.72	-5.2	-7.05
JUN	-4.31	-3.82	-4.88	-6.13
TNF	-4.64	-5.38	-5.26	-7.31
MMP9	-5.66	-6.44	-6.1	-8.43

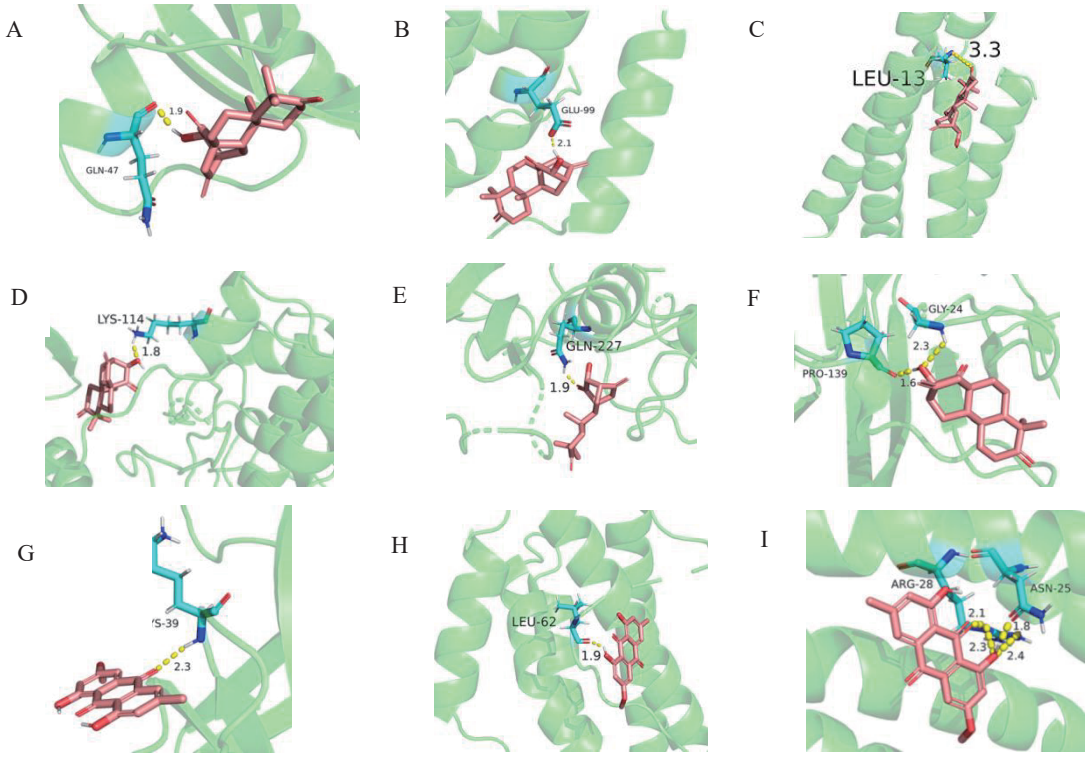

Fig. 7 Diagram of molecular docking

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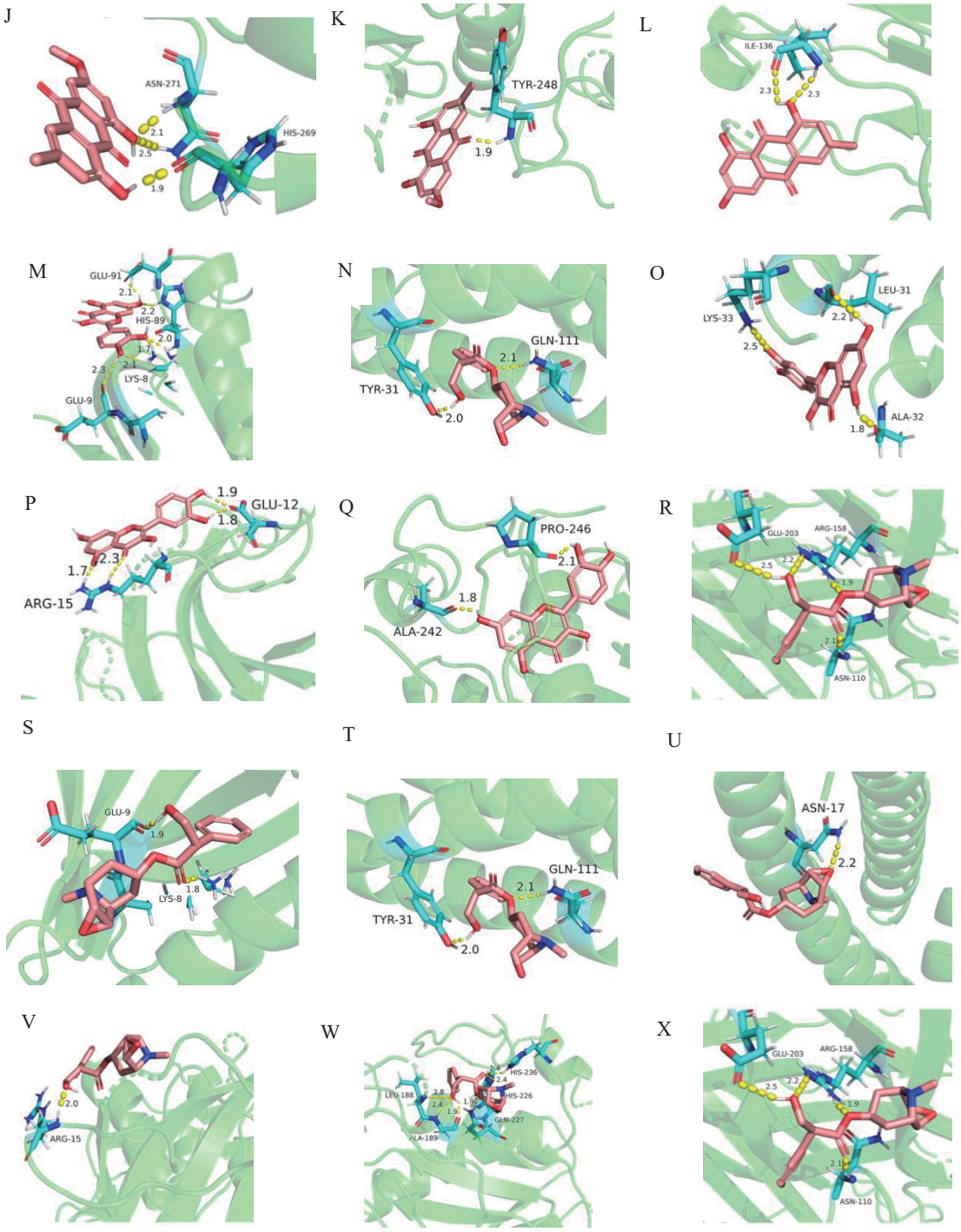

Note: A: Antiquorin-AKT1; B: Antiquorin-IL6; C: Antiquorin-JUN; D: Antiquorin-MAPK1; E: Antiquorin-MMP9; F: Antiquorin-TNF; G: Physcion-AKT1; H: Physcion-IL6; I: Physcion-JUN; J: Physcion-MAPK1; K: Physcion-MMP9; L: Physcion-TNF; M: Quercetin-AKT1; N: Quercetin-IL-6; O: Quercetin-JUN; P: Quercetin-MAPK1; Q: Quercetin-MMP9; R: Quercetin-TNF; S: Scopolamine-AKT1; T: Scopolamine-IL6; U: Scopolamine-JUN; V: Scopolamine-MAPK1; W: Scopolamine-MMP9; X: Scopolamine-TNF.

Continued fig. 7

4 Discussion

As traditional Chinese medicine, *Euphorbia fischeriana* Steud. and Jujube Fructus are mainly used to treat diseases such as edema, ascites and cancer. With soothing and nourishing effects, Jujube Fructus is often used in combination with other Chinese medicines to improve efficacy and reduce toxic side effects. The combination of *Euphorbia fischeriana* Steud. and Jujube Fructus can not only improve the therapeutic effect of *Euphorbia fischeriana* Steud. in the treatment of hepatocirrhosis but also reduce the toxicity of *Euphorbia fischeriana* Steud.. In this study, the active ingredients and potential targets of *Euphorbia fischeriana* Steud. and Jujube Fructus were screened through a variety of databases based on network pharmacology. On this basis, a series of analyses were conducted, including PPI analysis of intersection targets, GO enrichment analysis, and KEGG pathway enrichment analysis of intersection targets between *Euphorbia fischeriana* Steud.-Jujubae Fructus and hepatocirrhosis. The drugs - active compounds - targets - pathways network was constructed. From the active ingredients, potential targets, pathways and diseases, the possible action mechanism of *Euphorbia fischeriana* Steud. combined with Jujubae Fructus in the treatment of hepatocirrhosis was speculated.

In this study, the components related to targets, including quercetin, wolfsone and 17-Hydroxyjolkinolide A, were screened, which belong to diterpenoids and phenolic acids. The above research was consistent with the pharmacoactive material basis of wolfsone Euphorbia and jujube reported in the references [20,21]. At the same time, 162 targets of *Euphorbia fischeriana* Steud.-Jujubae Fructus were screened, among which 95 targets were shared by the two drugs, which involved multiple inflammation, response to multiple substances and anti-apoptotic processes, indicating that *Euphorbia fischeriana* Steud.-Jujubae Fructus exerts a synergistic and toxic-reducing therapeutic effect through multiple targets and multiple active ingredients.

In our study, the protein interaction network of 38 targets of the intersection of Euphorbia-jujube and cirrhosis was analyzed, and several effective core targets were identified. The top six hub genes were MAPK1, AKT1, TNF, JUN, IL6 and MMP9, which may be the key targets of *Euphorbia fischeriana* Steud.-Jujubae Fructus in the treatment of hepatocirrhosis. Among them, mitogen-activated protein kinases (MAPKs) are enzymes mediated by growth factor receptors, which participate in various growth regulation processes in cells. The MAPK signaling pathways mainly includes extracellular signal-regulated kinase (ERK), protein-regulated kinase p38 (MAPK p38), stress-activated protein kinase (SAPK), and c-jun terminal regulated kinase (JNK) and ERK5/BMK1 [22]. Studies have shown that the MAPKs signaling pathway is closely related to the occurrence and development of liver cirrhosis. MAPK1 (mitogen-activated protein kinase 1) is a subtype of mitogen-activated protein kinase and a downstream target of miR-217. MiR-217 regulates MAPK1, leading to cirrhosis and even liver cancer [23,24].

Akt, also known as protein kinase B, is a serine/threonine protein kinase. AKT1 is a subtype of Akt kinase that participates in many cellular processes and plays a crucial role in regulating cell proliferation and survival [25]. AKT1 can induce protein synthesis pathways and achieve cell survival by inhibiting apoptosis. Therefore, AKT1 plays an important role in the formation and development of hepatocirrhosis. Phosphoinositol 3-kinase (PI3K) can phosphorylate AKT1 and activate AKT1, ultimately regulating cell proliferation and apoptosis [26,27].

Interleukin 6 (IL6), a kind of interleukin cell, is mainly synthesized by lymphoid T cells, monocytes, macrophages and fibroblasts and is one of the main pro-inflammatory factors in the human body. The secretion of IL6 is significantly increased during inflammation caused by injury or infection in the

body. Studies have shown that IL6 is closely related to the development of fibrosis. Therefore, IL6 plays a crucial role in the occurrence and development of hepatocirrhosis and can be used as a critical target in the treatment of hepatocirrhosis [28,29].

The GO enrichment analysis showed that *Euphorbia fischeriana* Steud.-Jujubae Fructus could treat cirrhosis through various biological processes and molecular functions by regulating different cellular components, such as response to toxic substances, response to injury and response to inorganic substances, kinase binding, transcription factor binding and cytokine receptor binding; The top three cellular components were membrane valve, membrane side, receptor complex, etc., indicating that *Euphorbia fischeriana* Steud.-Jujubae Fructus has a therapeutic effect on hepatocirrhosis through the membrane and other cell components, which affect the molecular functions of protein kinases and transcription factors by reacting to different substances.

The Drugs - Components - Targets - Pathways network shows that active ingredients such as quercetin, scopolamine, physcion, 7-deoxyrangduin and 17-Hydroxyjolkinolide A may exert anti-hepatocirrhosis effects through core targets such as PTGS2, JAK1, EGFR, MAPK1, ESR1, AKT1, and BCL2. Studies have shown that both quercetin and scopolamine have anti-inflammatory and antioxidant effects. Quercetin can reduce the expression of inflammatory factors such as PTGS2, TNF and IL6, while quercetin and scopolamine regulate NF- κB. The p38 MAPK signaling pathway inhibits inflammation, and quercetin can also regulate the Bcl-2/Bax signaling pathway to reduce liver cell apoptosis [30-35]. Physcion, 7-deoxylangduin and 17-HydroxyJolkinolide A all have various pharmacological activities, such as anti-inflammatory and antioxidant activities.

The KEGG pathways enrichment analysis in this study shows that the treatment of hepatocirrhosis with *Euphorbia fischeriana* Steud.-Jujubae Fructus is mainly achieved through the cancer pathway, hepatitis C pathway, JAK-STAT signaling pathway and AGE-RAGE signaling pathway. Infected with the hepatitis C virus (HCV), most people suffer from chronic hepatitis C. If left untreated, they may develop into cirrhosis or even liver cancer. In the process of chronic HCV infection, the virus does not directly cause damage to liver cells but rather triggers cellular immunity in the body, leading to immune damage. Hepatitis C can cause imbalance in the network of helper T cell subsets and cytokines, leading to the occurrence of various inflammations. Studies have shown that after infection with chronic hepatitis C, the ratio of Th1 to Th2 in two subtypes of Th decreases, leading to an imbalance of Th1/Th2 and causing inflammation in the body, ultimately leading to cirrhosis [36,37]. Meanwhile, recent studies have found that Th17 and its secretion of IL-17 also play an important role in liver diseases. Hepatitis C virus can induce Th17 to secrete IL-17, while IL-17 can induce the production of NF-κB, promote the expression of IL-6, TNF-α, etc., and then cause inflammation. At the same time, IL-17 can stimulate the proliferation of HSC (hepatic stellate cells), increase ECM (extracellular matrix), and lead to the progression of chronic hepatitis C to cirrhosis [38-41]. At the same time, PTGS2, also known as cyclooxygenase 2 (COX-2), plays a vital role in the process of liver cirrhosis caused by hepatitis C [42,43].

The JAK-STAT signaling pathway is one of the signal transduction pathways of cytokines, involved in multiple biological processes within cells, such as cell proliferation, apoptosis, etc. Several studies have shown a close relationship between the JAK-STAT signaling pathway and fibrosis in various organs [44]. Studies have shown that the JAK-STAT signaling pathway is closely related to various chronic liver diseases. In the process of the development of chronic liver disease, inflammatory factors in patients will activate the JAK-STAT signaling pathway. In the process of the development of chronic liver

disease, inflammatory factors in patients will activate the JAK-STAT signaling pathway, thus causing the proliferation and activation of HSC, and the activated HSC will secrete a large amount of IL6, leading to liver fibrosis and eventually developing into cirrhosis or liver cancer. At the same time, inflammatory factors in patients with chronic liver disease accelerate the phosphorylation process of the JAK2-STAT3 signaling pathway in the JAK-STAT signaling pathway, further expanding inflammation and leading to the occurrence of cirrhosis or liver cancer [45-48]. In addition, the molecular docking results showed good binding capacity between the main active ingredients and targets, which could be used as an auxiliary study to support the network pharmacological prediction results. Therefore, the above reports indicate the feasibility of predicting action mechanisms of *Euphorbia fischeriana* Steud.-Jujubae Fructus in the treatment of cirrhosis by means of network pharmacology.

This study used network pharmacology methods to predict that targets such as MAPK1, AKT1, TNF, JUN, IL6 and PTGS2 play important roles in the treatment of hepatocirrhosis with *Euphorbia fischeriana* Steud.-Jujubae Fructus, providing new methods and ideas for future clinical treatment of hepatocirrhosis. Through the enrichment analysis of the KEGG pathway, pathways other than hepatocirrhosis, such as the prostate cancer pathway, were also obtained, indicating that the mechanisms of action among various diseases in the body influence and interact with each other by targets. In addition, the active ingredients and core targets were preliminarily verified by molecular docking, and the results showed good binding capacity.

5 Conclusion

Taken together, this study demonstrates the active compounds, key targets, and pathways of action of *Euphorbia fischeriana* Steud.-Jujubae Fructus in treating hepatocirrhosis based on network pharmacology and molecular docking. It was found that *Euphorbia fischeriana* Steud.-Jujubae Fructus act on targets such as MAPK1, AKT1, TNF, JUN, IL6, PTGS2, and JAK1 through active compounds such as quercetin, scopolamine, physcion, 7-deoxyrangduin and 17-Hydroxyjolkinolide A, and regulate biological processes such as inflammation, cell proliferation and apoptosis in the body. Furthermore, it regulates signaling pathways such as the hepatitis C pathway, JAK-STAT signaling pathway and AGE-RAGE signaling pathway to exert therapeutic effects on hepatocirrhosis. This study provides a theoretical basis for the treatment of hepatocirrhosis with the combination of *Euphorbia fischeriana* Steud. and Jujubae Fructus and provides ideas and a basis for future clinical development and application.

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