

Study on the Mechanism of Yiguan Jian in the Treatment of Liver Fibrosis Based on Network Pharmacology

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Abstract: Through the method of network pharmacology, we discussed the possible pharmacological mechanism of consistent decoction in treating liver fibrosis. We used TCMSP and HERB database and related literature to screen the ingredients of traditional Chinese medicine. The key Target of active ingredients was obtained by Swiss Target Prediction analysis platform, and the disease target information was obtained by GeneCards, OMIM and Drugbank database. The intersection targets of drugs and diseases were obtained using the Draw Venn Diagram platform, and the PPI analysis was performed on the intersection targets in the String database. The intersection targets were uploaded to the DAVID6.8 database for GO function and KEGG path enrichment analysis. The "component-target-signal path" network diagram was constructed using Cytoscape3.9.1 software. Resultly, 25 active ingredients were screened, including quercetin, stigmasterol, β -sitosterol and other core ingredients. There were 621 potential targets for the treatment of liver fibrosis with Yiguan decoction, and 18 key targets were obtained by protein interaction network analysis of intersection targets. GO and KEGG enrichment analysis showed that the key targets exert the functions of protein binding, ATP binding and protein kinase activity through biological processes such as signal transduction, apoptosis, cell proliferation and RNA transcription regulation. It regulated liver fibrosis by participating in hepatitis B signaling pathway, cancer pathway, pancreatic cancer signaling pathway, tumor PD-1 checkpoint pathway, etc. In conclusion, the core components of lucobo saponin, saponin and 2'-hydroxymethylololic acid may be involved in signaling pathways such as PD-L1 expression and PD-1 checkpoint in hepatitis B pathway, cancer pathway, pancreatic cancer and tumor, and act on gene targets such as STAT3, SRC and HSP90AA1 to play an anti-fibrosis role.

1. Introduction

Hepatic fibrosis is a process of liver tissue degeneration, inflammatory infiltration and necrosis after various chronic inflammation leads to liver damage. It is a compensatory response to the continuous repair of liver collagen and extracellular matrix. It is a bridge from chronic hepatitis to liver cirrhosis and even liver cancer [1,2]. Timely intervention and treatment in the early stage of liver

fibrosis can slow down or prevent the development of liver fibrosis into liver cirrhosis and even liver cancer. At present, the chemical drugs selected in the clinical treatment of liver fibrosis have great side effects, and the effect is not good. Then, according to the rich clinical application, it shows that traditional Chinese medicine and traditional Chinese medicine prescription can systematically inhibit the progress and transformation of liver fibrosis [3]. And traditional Chinese medicine has the characteristics of multi-components, multi-links and multi-targets, which can give full play to the comprehensive advantages of special diseases with complex pathology and achieve the best therapeutic effect.

It is a famous prescription for nourishing yin and soothing the liver, which is composed of Radix Rehmanniae, Radix angelicae Sinensis, Radix Ophiopogonis, Radix Rehmanniae, Fructus Lycii, and neem, with strict compatibility and accurate medication [4]. This prescription reuses Rehmannia glutinosa, nourishes the liver and regulates qi gently, and mainly treats the syndrome of yin deficiency of liver and kidney and discomfort of liver qi. Evidence of epigastric pain, swallow acid spitting bitterness, dry pharynx and mouth, red tongue, weak pulse or weak string [5]. The classic famous prescription has always been in use since the Qing Dynasty, with full safety and effectiveness. According to the literature, its modern pharmacological research shows that the Yiguan decoction contains saponins, triterpenes, lactones and some free amino acids and trace elements needed by the human body. There are liver protection, inhibition of liver fibrosis, improve the body immunity and other effects [6,7]. Although Yiguan decoction is effective in the treatment of liver fibrosis, the mechanism is not clear, which needs to be further confirmed by network pharmacology or systematic network pharmacology. Therefore, it is necessary to use suitable technical methods to study the complex mechanism of traditional Chinese medicine compound prescription.

2. Materials and methods

2.1. Screening and target prediction of active components of Yiguan decoction

We used "Beishen", "Angelica sinensis", "Chinese wolfberry" and "toosendan seed" as the search words, all the chemical constituents of the four medicines were found by using the comprehensive data base of traditional Chinese medicine TCMSP (<https://old.tcmsp-e.com/tcmsp.php>). According to the screening criteria of bioavailability (Oral-bioavailability $OB \geq 30\%$) and drug-like drugs (Drug-likeness $DL \geq 0.18$), all the chemical constituents of the four medicines were screened, and finally their effective components were obtained. Since the chemical composition information of Radix Rehmanniae and Radix Ophiopogonis was not found in TCMSP database, all the chemical components of Radix Rehmanniae and Radix Ophiopogonis were found by using HERB (<http://herb.ac.cn/>), and the SMILES format of Radix Rehmanniae and Radix Ophiopogonis was found directly or their SMILES format was found by Pubchem ID. Then the chemical constituents of birthplace and Ophiopogon japonicus were screened by Swiss ADME (<http://www.swissadme.ch/>) database, that is, the SMILES format of input birthplace and Ophiopogon japonicus was used to find the composition information of these two drugs. When GI absorption was high and when two of the five items of Druglikeness (Lipinski, Ghose, Veber, Egan, Muegge, etc.) met "Yes", Swiss Target Prediction (<http://www.swisstargetprediction.ch/>) database was used for drug target prediction. We input the Canonical SMILES format of the compound into the Swiss Target Prediction database analysis platform, selected the species as "Homo sapiens". And we predicted the corresponding target of the compound, and screened the target according to the standard of "probabilistic value > 0 ". The result was the action target of the active components of the two drugs.

2.2. Collection of hepatic fibrosis targets and intersection targets

This study was mainly based on the three databases of GeneCards, OMIM and Drugbank, and used "liverfibrosis" as the search word to search and collect the protein genes related to liver fibrosis. The median of continuous screening in GeneCards was to select the target information of GO functional enrichment analysis and KEGG pathway analysis. After summarizing the liver fibrosis target results of the three databases, the duplicate genes were removed, which was the related target information of liver fibrosis. Then through the DrawVennDiagram platform (<http://bioinformatics.psb.ugent.be/webtools/Venn/>), the active components of traditional Chinese medicine and liver fibrosis related targets were summarized, and the Wayne diagram was drawn. The intersection of the two targets was the potential target of Yiguan decoction in the treatment of liver fibrosis.

2.3. Construction of traditional Chinese Medicine-active ingredient-intersection Target Network

The active components and targets of the above six traditional Chinese medicines and compounds were sorted out, and the network diagram of traditional Chinese medicine-active components-intersection target was constructed by Cytoscape3.9.1 software. The degree centrality of the network diagram was analyzed by "nalyzerNetwork" module. The higher the value, the more important the node was in the network.

2.4. Construction of intersection protein interaction (PPI) network

The intersection proteins of active active components and key targets of liver fibrosis were uploaded to string (<https://cn.string-db.org/>) database, and the interaction network map between them was constructed.

2.5. GO functional enrichment analysis and KEGG pathway analysis

Through the above-mentioned PPI network topological parameter analysis, the key targets for the treatment of hepatic fibrosis were obtained, and the gene list "List" in metascape database was introduced, and the species and background were set to "Homo sapiens". GO functional enrichment analysis and KEGG pathway enrichment analysis were carried out respectively. GO analysis includes [8]: biological processes (biological process, BP), molecular functions (molecular function, MF) and cellular components (cellular component, CC). The top gene functions and pathways are selected and plotted with <http://www.bioinformatics.com.cn/> platform.

2.6. Construction of component-target-signal pathway network

The interaction information of active components, overlapping proteins and signal pathway was introduced into Cytoscape3.9.1 software to build a component-target-signal pathway network for the treatment of liver fibrosis.

3. Results

3.1. Screening results of active components of Yiguan decoction

The four traditional Chinese medicines "Radix Scutellariae, Radix angelicae Sinensis", "Fructus Lycii" and "toosendan seed" were screened by TCMSp database with $OB \geq 30\%$ and $DL \geq 0.18$, and

56 active components were obtained, of which 44 active components had no related target information, so 6 were common components and were also eliminated. finally, the remaining 6 active components were included in this study. There are 104 active components in HERB of "Shengdi" and "Ophiopogon japonicus". After SwissTargetPrediction prediction, the effective drug components and effective target information of birthplace and Ophiopogon japonicus were selected by median screening according to the value of Probability (binding probability). Finally, 19 active components were included in this study. Therefore, there are 25 kinds of active ingredients in Yiguan decoction. See Table 1 and Table 2 for details.

Table 1: Active components of Radix Glehniae, Angelica sinensis, Fructus Lycii and Fructus Toosendan

Drugs	Serial number	Compound name	OB	DL
Radix Glehniae	BSS1	Alloisoimperatorin	34.8	0.22
Radix Glehniae	BSS2	isoimperatorin	45.46	0.23
Radix Glehniae	BSS3	Bergaptin	41.73	0.42
Radix Glehniae, Angelica sinensis, Fructus Lycii	A	beta-sitosterol	36.91	0.75
Radix Glehniae, Angelica sinensis, Fructus Lycii	B	Stigmasterol	43.83	0.76
Radix Glehniae, Fructus Toosendan, Fructus Lycii	C	quercetin	46.43	0.28

Table 2: Active components of Radix Ophiopogonis and Radix Ophiopogonis

Drugs	Serial number	Compound name	Absorption	Druglikeness
Birth place	SD1	3-indolecarboxylic acid	high	yes
Birth place	SD2	7-isoquinoli-nol	high	yes
Birth place	SD3	adenine	high	yes
Birth place	SD4	coniferin	high	yes
Birth place	SD5	diincarvilone A	high	yes
Birth place	SD6	Rehmaglutin A	high	yes
Birth place	SD7	rehmapicrogenin	high	yes
Birth place	SD8	salidroside	high	yes
Ophiopogon japonicus	MD1	5, 7-dihydroxy-6, 8-dime thyl-3-(4'-hydroxy-3'-methoxybenzyl)chroman-4-one	high	yes
Ophiopogon japonicus	MD2	6-aldehydoisoophiopogone a	high	yes
Ophiopogon japonicus	MD3	diosgenin	high	yes
Ophiopogon japonicus	MD4	methyl ophiopogonanone b	high	yes
Ophiopogon japonicus	MD5	n-trans-feruloyltyramine	high	yes
Ophiopogon japonicus	MD6	ophiopogonanone a	high	yes
Ophiopogon japonicus	MD7	ophiopogonanone b	high	yes
Ophiopogon japonicus	MD8	ophiopogonanone c	high	yes
Ophiopogon japonicus	MD9	orchinol	high	yes
Ophiopogon japonicus	MD10	ruscogenin	high	yes
Ophiopogon japonicus	MD11	Stigmasterol-beta-D-glucoside	high	yes

3.2. Target prediction

Through the SwissTargetPrediction platform, the target prediction of 160 kinds of Yiguan decoction active components showed that there were no corresponding targets. The target prediction results of the remaining 47 active components were screened with probabilistic values > 0 , including 9 repetitive values, and then the repeated 6 active components were removed. After searching all the traditional Chinese medicines in uniprot, the targets obtained by some traditional Chinese medicines have not been verified in humans. Therefore, in the process of screening, 2 active components corresponding to unverified Radix Glehniae and 2 active components corresponding to raw targets were removed, 12 active components corresponding to Ophiopogon japonicus were removed, and finally 25 active components were left, and a total of 621 Yiguan decoction targets were obtained. 1222 liver fibrosis related target genes were obtained by GeneCards database, OMIM database and Drugbank database. Through the HERB platform, the two groups of genes were intersected to obtain 193 potential targets for the treatment of liver fibrosis. See Figure 1.

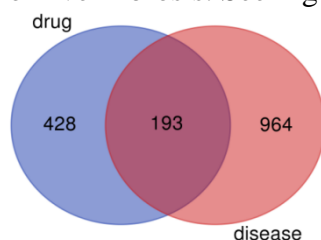


Figure 1: Venn diagram of the intersection target of Yiguan decoction and liver fibrosis

3.3. Construction and Analysis of traditional Chinese Medicine-active components-intersection Target Network

There are 621 decoction targets, 1222 liver fibrosis targets and 193 intersection targets. Then the network diagram of "traditional Chinese medicine-active ingredient-intersection target" is constructed, as shown in figure 2. The network consists of 224 nodes and 221 edges, which may play an important role in the treatment of liver fibrosis.

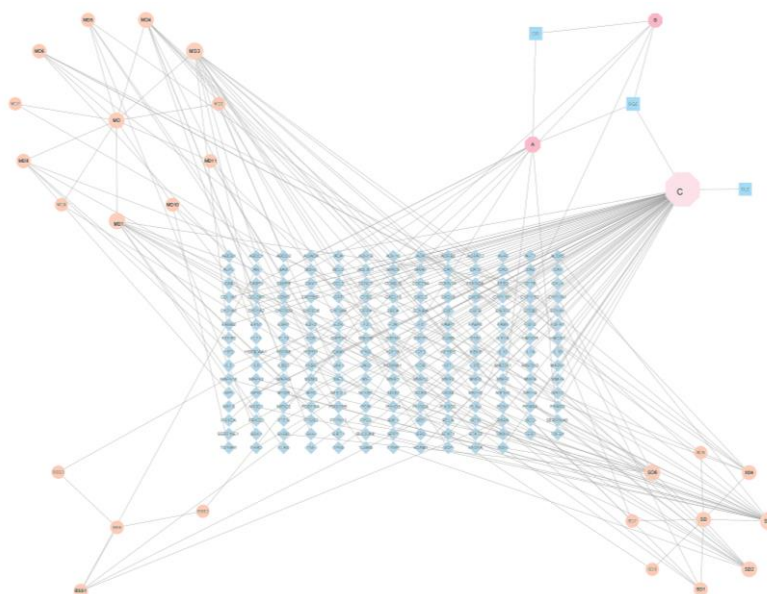


Figure 2: Network diagram of "traditional Chinese medicine-active ingredient-intersection target"

Note: an and B all represent the common active components of Radix Glehniae, Angelica sinensis and Fructus Lycii, while C represents the active components of Radix Glehniae, Fructus Lycii and Toosendan. Among them, the active component of toosendan is C, the active component of Lycium barbarum is A+B+C, the active component of Angelica sinensis is Astragalus Bline MD, which means Ophiopogon japonicus, BSS represents Radix Glehniae, and SD represents raw place.

3.4. Interaction Network between Yiguan decoction and Hepatic Fibrosis intersection protein

The interaction network between intersection proteins is obtained by uploading 193 intersection proteins to string database. The topological attribute parameters of PPI network are analyzed by using the "NetworkAnalyzer" section of Cytoscape3.9.1 software, and the value is taken as the reference index. When the value is larger, the more frequent the target intersection is, the more important it is in the intersection network [9]. There are 70 nodes and 1758 edges, and the size of the target figure is arranged according to the value. According to the value and color, the target protein values such as STAT3, SRC, HSP90AA1, MAPK3, MAPK1, RELA, AKT1, TP53, EP300 and PIK3CA are higher. See Figure 3.

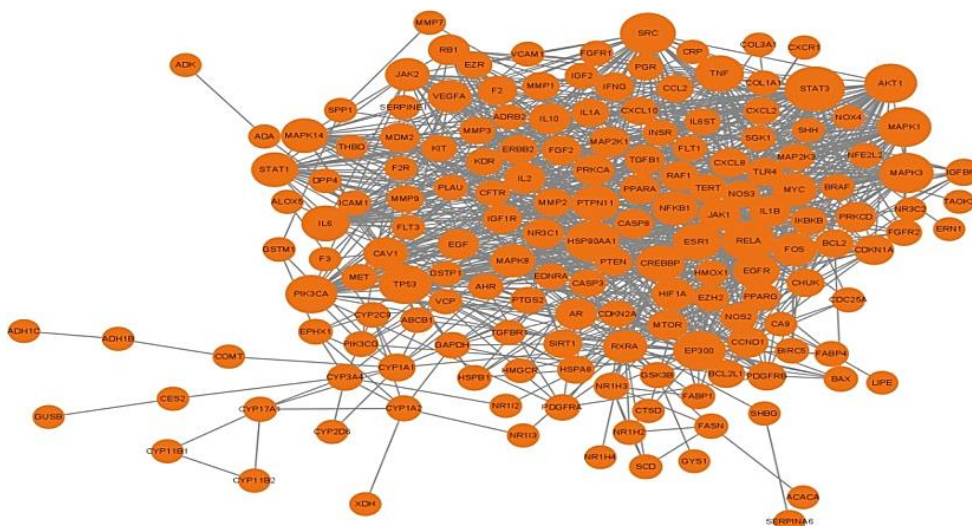


Figure 3: PPI network diagram of potential targets for the treatment of hepatic fibrosis with Yiguan decoction

3.5. GO enrichment analysis and KEGG pathway analysis

Upload the intersection protein to the metaspape database to get the function of the intersection protein in the cell and the signal pathway involved. The key targets selected above were analyzed by GO and KEGG. There are 581 items related to BP. The biological processes mainly include signal transduction, negative regulation of apoptosis, positive regulation of cell proliferation, positive regulation of RNA polymerase II promoter transcription and protein phosphorylation. There are 45 MF related entries, molecular functions including protein binding and AT cytoplasmic phosphorylation, and 33 CC related entries, mainly including nuclear, nuclear, cytoplasmic, plasma membrane and cytoplasmic sites [3] [3]. See Figure 4.

The results of KEGG showed that the treatment of liver fibrosis by Yiguanjian was mainly related to the following pathways: hepatitis B pathway, Kaposi pathway, cancer pathway, prostate cancer pathway, pancreatic cancer pathway, PD-L1 expression and PD-1 checkpoint pathway, lipid and atherosclerosis pathway, prolactin signal pathway and so on. See Figure 5.

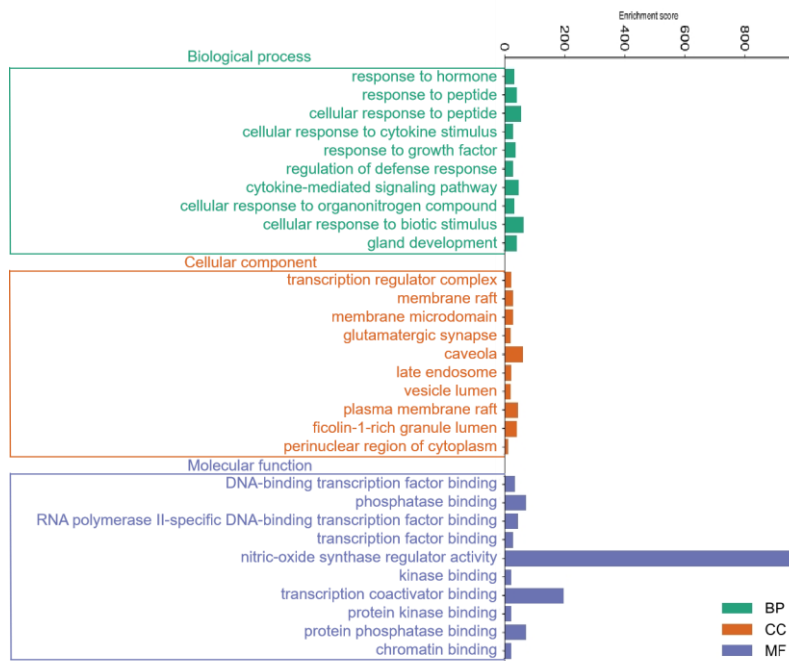


Figure 4: Functional enrichment analysis of GO

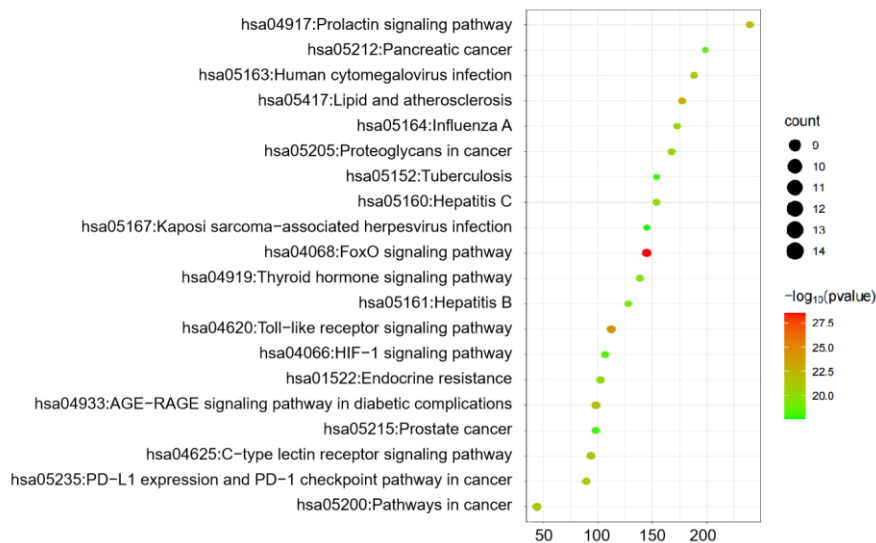


Figure 5: KEGG signal pathway enrichment analysis

3.6. "component-Target-signal Pathway" Network Diagram of Yiguanjian in the treatment of Hepatic Fibrosis

Use Cytoscape3.9.1 software to build a "component-target-signal pathway" network diagram, as shown in Figure 6. The picture includes 25 drug active ingredients, 194 potential targets, involving 20 signal pathways.

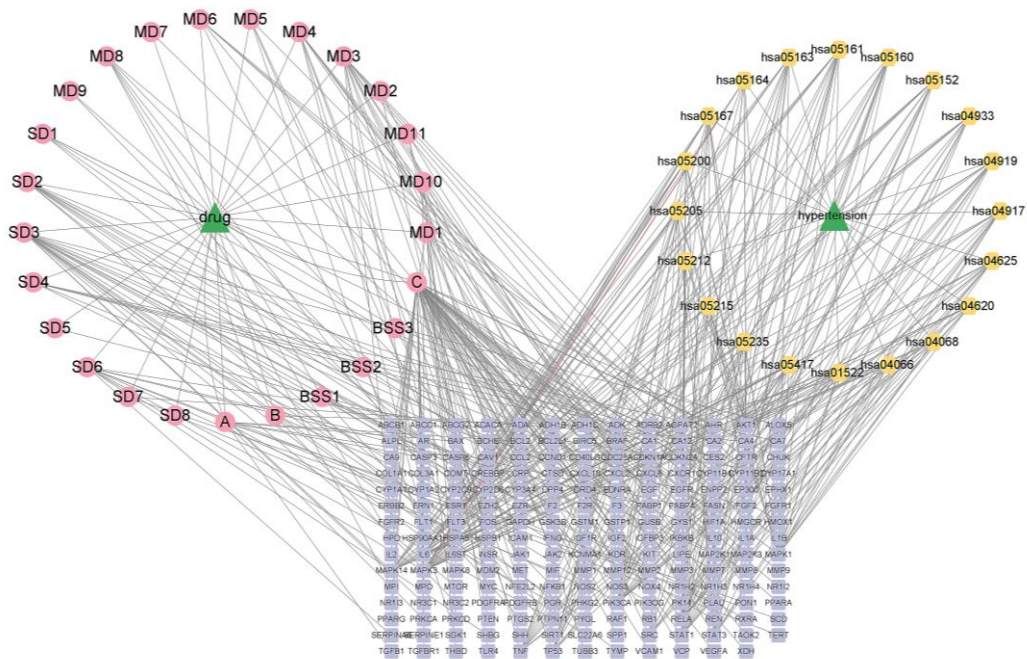


Figure 6: "Component-target-signal pathway" network diagram

4. Discussion

The pathogenesis of hepatic fibrosis is not completely clear, the key link is the activation of hepatic stellate cells and further transformation into myofibroblasts, with the progressive accumulation of extracellular matrix, leading to the destruction of liver structure and the formation of false lobules. Li Manbiao 0 mentioned in the study that liver tissue repair after injury is usually accompanied by liver fibrosis. If the injury factors have not been eliminated, liver fibrosis will further develop into liver cirrhosis. Liver cirrhosis will lead to many serious complications, so it is necessary to reverse liver fibrosis in order to prevent unnecessary complications. Chen Peng 0 and others found that if liver injury is not cured, hepatic stellate cells (hepaticstellatecell, HSC) in the peri-sinusoidal space will activate myofibroblasts, and the main source of extracellular matrix is myofibroblasts, which plays a key role in the pathogenesis of liver fibrosis 0. Li Qingqing and other studies have shown 0 that liver fibrosis is accompanied by serious disorders of a variety of cytokines and oxidative stress response, which involves many important signal transduction pathways in the body. At present, there is no specific drug for the treatment of liver fibrosis, but traditional Chinese medicine has the advantages of multi-targets and multi-components, and has made some progress and achievements in the research and treatment of liver diseases including liver fibrosis. In clinical practice, some traditional Chinese medicine prescriptions show unique effects in the treatment of liver fibrosis, but the specific pharmacological mechanism of their anti-liver fibrosis is not clear.

Yiguan decoction is a famous prescription of traditional Chinese medicine, and its compatible ingredients include neem seed, Radix Scutellariae, Angelica sinensis, Radix Ophiopogonis, Radix Rehmanniae, Fructus Lycii, etc. , which are mostly drugs for nourishing yin and nourishing blood, in which toosendan seed [14,15] is used to soothe liver qi, tonifying liver and soothing liver, which embodies the physiological characteristics of "liver body yin and yang", and has the effect of nourishing yin and soothing liver. Traditional Chinese medicine is commonly used to treat patients with chronic hepatitis, gastric and duodenal ulcers, which belong to yin deficiency and liver depression syndrome. A large number of clinical studies have shown that Yiguan decoction can

improve the symptoms and signs of patients with liver fibrosis and reduce serum hyaluronidase, laminin, type 3 procollagen and type 4 collagen and other indexes of liver fibrosis [16,17]. Liu Wenlan [10] mentioned that the rats with hepatic fibrosis belong to yin deficiency syndrome, and the prescription of nourishing liver and kidney can significantly improve the symptoms of yin deficiency such as dry pharynx and red tongue. In the follow-up pathological analysis, it was found that the liver fibrosis in the liver tissue section of mice was significantly alleviated, indicating that Yiguanjian has a certain antagonistic effect on liver fibrosis in rats. Bai Chen [11] and other studies have found that Yiguan decoction can reduce the serological indexes of rats with hepatic fibrosis, and its main mechanism is to combat hepatic fibrosis by regulating MMP-1/TIMP-1 to degrade collagen fibers. This study suggests that the function of Yiguan decoction of soothing the liver and promoting qi may be related to its degradation of collagen fibers and improvement of organ structure [20,21]. However, the detailed mechanism of Yiguan decoction against liver fibrosis is not clear. This study systematically analyzed the active components and efficacy targets of Yiguan decoction through network pharmacology, and preliminarily explored the molecular mechanism of Yiguan decoction in the treatment of liver fibrosis.

In this study, 25 kinds of active components of Yiguan decoction were included. According to the results of traditional Chinese medicine-active ingredient-intersection target network analysis, the results showed that the active components such as quercetin, methyl hexamethanoic acid, pine cypress, adenine, dixanthine-An and so on were at the core network node. It can be regarded as the main component of Yiguan decoction in the treatment of liver fibrosis. By using the method of network pharmacology, the drug component-target-signal pathway network was constructed, and the main molecular mechanism of Yiguan decoction in the treatment of liver fibrosis was discussed by analyzing the node, value and other related elements. According to the topological structure analysis of PPI protein network, the top ten targets are: STAT3, SRC, HSP90AA1, MAPK3, MAPK1, RELA, AKT1, TP53, EP300, PIK3CA. KEGG signal pathway enrichment analysis showed that the main pathways of YJ in the treatment of liver fibrosis included hepatitis B pathway, Kaposi pathway, prostate cancer pathway, pancreatic cancer pathway, PD-L1 checkpoint pathway, lipid and atherosclerosis pathway and so on.

Zhu Yue et al. [12] found that betulinic acid can inhibit the secretion of inflammatory factors through STAT3 signal pathway, thus block TLR4 signal transduction, and then regulate AMPK/LKB1 phosphorylation, and finally improve liver fibrosis. Feng Yinyi et al. [13] found that total flavonoids of litchi kernel can exert anti-fibrosis effect by regulating pancreatic cancer pathway mediated by HSP90AA1 and MAP2K1 and many signal pathways related to liver fibrosis, such as PI3K-Akt pathway. Ou Shiyu et al. [14] found that total flavonoids of litchi kernel can inhibit the expression of JAK2/STAT3 protein and block the signal transduction of AK2/STAT3 signal pathway, thus play an anti-fibrosis effect. The anti-fibrosis targets and pathways reported in the above literature are consistent with the results of this study.

5. Summary

To sum up, at present, the clinical treatment of liver fibrosis is mainly to remove the etiology, and there is still a lack of specific drugs and methods. Yiguan decoction compound contains a variety of active components, which can act on multiple targets related to hepatic fibrosis, and then inhibit the process of hepatic fibrosis through multiple signal pathways, indicating that Yiguan decoction has the characteristics of multi-components, multi-targets and multi-pathways in the treatment of liver fibrosis. This study not only provides a theoretical basis and reference for the clinical application of Yiguan decoction in the treatment of liver fibrosis, but also provides clues for the further study of the molecular mechanism of liver fibrosis. However, this study is based on big data's bioinformatics

analysis, and its results still need to be verified by further basic research.

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