ISSN 2618-1584 Vol. 5, Issue 8: 85-92, DOI: 10.25236/FMSR.2023.050812

The Mechanism of the Poria Cocos for Preventing and Treating Ascites in Cirrhosis Based on Network Pharmacology

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Abstract: *The research aims to utilize network pharmacology to identify the common gene targets of Poria cocos and cirrhosis ascites and subsequently explore the potential components, key targets, and pathways involved. The ultimate goal is to summarize the mechanism by which Poria cocos treats ascites in cirrhosis. To achieve this, a variety of methods were employed .Firstly, the composition and targets of Poria cocos were queried in the TCMSP TCM system pharmacology database and the "uniprot" general protein database. Next, the ascites disease gene targets of liver cirrhosis were extracted from the "GeneCards" database. The venny2.1 online platform was used to obtain the common genes shared between Poria cocos and cirrhosis ascites, resulting in the discovery of 31 intersection genes, including AKT1, TNF, IL6, CXCL8, EP300, and PTGS2.Subsequently, the STRING online database was utilized to build a potential protein interaction network map (PPI). Furthermore, GO analysis was conducted using the DAVID online platform to analyze the enrichment of potential genetic biological processes (BP), cellular components (CC), and molecular functions (MF). Additionally, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were examined to understand the underlying pathways involved in the treatment of cirrhosis ascites by Poria cocos. The data obtained were then visualized using Cytoscape 3.10 software to create a comprehensive network map representing the relationships among the disease, target, component, and pathway of Poria cocos in treating cirrhosis ascites. As a result of these analyses, a total of 34 components, 56 protein targets, and 12 active components were selected from the TCMSP database. Moreover, 156 potential gene biological processes (BP), 16 cell components (CC), 16 molecular functions (MF), and 89 Kyoto Gene and Genome Encyclopedia (KEGG) signaling pathways were identified. In conclusion, Poria cocos emerges as an important drug for preventing and treating cirrhosis ascites, primarily due to its multi-component, multi-target, and multi-pathway advantages.*

Keywords: *network pharmacology; poria cocos; liver cirrhosis ascites*

Cirrhosis ascites refers to the accumulation or retention of fluid in the abdominal cavity due to liver cirrhosis, which occurs as a consequence of liver function decline, portal hypertension, imbalances in the renin-angiotensin-aldosterone system (RAAS), hypoproteinemia, lymphatic reflux blockage, and enhanced secretion of vascular active substances. It is a critical indicator of liver function decompensation and is associated with a 1-year mortality rate of approximately 15% and a 5-year mortality rate of about 44%-85%[1]. Currently, western medicine treatments for cirrhosis ascites primarily involve addressing the underlying cause, salt restriction, diuretics, ascites drainage, concentration and infusion of ascites, as well as interventional and surgical procedures like abdominal α-drainage pump, abdominal venous shunt, and liver transplantation [2]. In contrast, Traditional Chinese Medicine (TCM) has a rich history and early understanding of cirrhosis and ascites. It first analyzed the syndrome and pathogenesis, proposing the concept of "swelling" in *Huangdi Neijing* over 2,000 years ago, accumulating valuable experience since then. In order to preserve and expand the unique characteristics of TCM in treating cirrhosis ascites, this research focuses on studying the mechanism of Poria cocos in treating cirrhosis ascites using network pharmacology. Network pharmacology is an interdisciplinary approach that integrates computer information technology, pharmacology, molecular biology, genetics, and network analysis. It establishes a systematic framework to reveal the relationships between drugs, ingredients, targets, and diseases. By analyzing potential targets and pathways, network pharmacology provides valuable insights for disease treatment and drug innovation, which is well-suited for the complexity of traditional Chinese medicine with its multi-component, multi-target, and multi-pathway

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nature [3].

1. Data and methods

1.1 Query the composition of Poria cocos

In TCMSP Chinese Medicine System Pharmacology Database (https://old.tcmsp-e.com/tcmsp.php), "Database-tcmsp" column input Poria cocos, with pharmaclike (drug likeness, DL) and oral bioavailability (oral bioavailability, OB) as the conditions of screening active ingredients, OB 30%, DL 0.18. The queried drug components and protein targets were exported.

1.2 Construct a Poria cocos gene target database

Enter protein targets in the "UniProtK" column of "uniprot" General Protein database (https://www.uniprot.org). "Popular organisms" is set to "Human". After conversion, the corresponding gene targets are exported.

1.3 Query of the ascites gene targets in liver cirrhosis

In the "GeneCards" database (https://www.genecards.org), "cirrhosis ascites" and "ascites due to cirrhosis" were used as the search terms to search for the query gene, and then obtain the gene target of cirrhosis ascites disease.

1.4 Construct a latent gene database

The poria cocos gene target and the ascites gene target of liver cirrhosis were uploaded to the venny2.1 online platform (https://bioinfogp.cnb.csic.es/tools/venny/index.html) to obtain the intersection genes, and make a Venn diagram (Venn diagram).

1.5 Construct the protein interaction network diagram

The STRING (https: / / string-db. org) online database was used to construct the potential gene protein interaction network map (Protein-protein Interaction, PPI). Organisms was selected as Homo sapiens, default parameters and confidence score of 0.4.

1.6 The Gene Ontology (Gene Ontology, go) analysis was performed for the potential genes

Using the DAVID Bioinformatics Resources Laboratory of Human Retrovirology and Immunoinformatics (LHRI) online platform (https): / / david.ncifcrf.gov to analyze potential genetic biological processes (BP), cell components (CC) and the molecular function (MF), and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment. Select "Homo sapiens" and download BP, CP and MF data in "Gene Ontology" and KEGG_PATHWAY data in "PATHWAY". The top 10 bars were selected according to the high value of Count, and BP, CP and MF bar charts, and KEGG_PATHWAY bubble charts were made by the online platform (https://www. bioinformatics. com.cn).

1.7 Build a network diagram

According to the potential gene targets, the corresponding components were searched in reverse, the component-target-disease-pathway database was constructed, and Cytoscape 3.10. software was used to make the disease, target, components and pathway network map of Poria-cirrhosis ascites, show the relationship between each other, and analyze the core targets and key components.

2. Results

2.1 Poria cocos components and gene targets

A total of 34 components and 56 protein targets were carefully selected from the TCMSP database.

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Among them, 15 components met the criteria for active ingredient screening. However, during the querying process, 3 components did not yield corresponding protein targets, leaving us with 12 active components that have been listed in Table 1. To ensure consistency and stability, the 56 protein targets were meticulously converted into gene targets, acquiring unique and stable entry identifiers from the "uniprot" universal protein database.

Table 1: The effective active ingredient of Poria cocoss.

Number	MOL ID	Molecule	OB%	DL
1	MOL000300	dehydroeburicoic acid	44.17	0.83
2	MOL000282	ergosta-7,22E-dien-3beta-ol	43.51	0.72
3	MOL000283	Ergosterol peroxide	40.36	0.81
4	MOL000275	trametenolic acid	38.71	0.8
5	MOL000287	3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid	38.7	0.81
6	MOL000292	poricoic acid C	38.15	0.75
7	MOL000279	Cerevisterol	37.96	0.77
8	MOL000296	hederagenin	36.91	0.75
9	MOL000276	7,9(11)-dehydropachymic acid	35.11	0.81
10	MOL000289	pachymic acid	33.63	0.81
11	MOL000290	Poricoic acid A	30.61	0.76
12	MOL000291	Poricoic acid B	30.52	0.75

2.2 Potential gene targets

In the "GeneCards" database, an initial search yielded 2470 gene targets related to cirrhosis ascites disease. After removing 445 targets that lacked "UniProt ID," left with 2025 targets for further analysis. The intersection of 56 poria cocos gene targets and 2025 gene targets of cirrhosis ascites disease were obtained through the "Venny2.1" online platform, and 31 intersection gene targets were identified. Namely, CD40, TNF, RELA, CD86, CD80, TK1, RXRA, AKT 1, PTGS2, PTGS 1, PGR, PLA2G1B, PTEN, PPARA, NR 3 C 2, CXCL 8, IL 6, IL 10, EP300, NR3C1, FABP1, DUOX2, TOP2A, COL1A1, BCHE, CTD, CA2, BCL 2, AR, MAOA, ADH1B,shown in Figure 1.

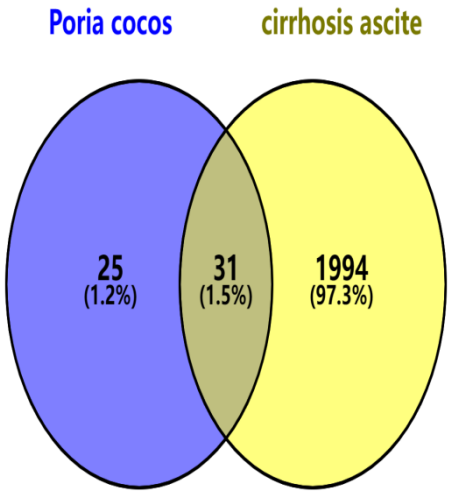

Figure 1: Potential gene target map of Poria cocos and cirrhosis ascites.

2.3 Key potential gene targets

PPI network graph analysis of 31 potential gene targets is: nodes 31; edges 147; average node degree:9.48;avg.local cluster coefficient:0.67; expected edges:55;PPIenrichment p-value: <1.0e-16. Download the string_interactions _ short. tsv file, import into Cytoscape 3.10 Further analyze the key targets, and export the numerical values. The median Degree value of the network node is 8. According to the value of 2 times the median Degree value, 6 key targets are selected, namely AKT1, TNF, IL6,

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PTGS2, EP300, CXCL8, shown in Table 2, Figure 2, Figure 3. Six key gene targets: number of nodes 6, number of edges 15, average node degree 5, avg.local cluster coefficient 1, expected number of edges 9, PPIenrichment p-value: 0.0151.

Table 2: Key potential gene targets.

Name	Degree	Betweenness Centrality	Closeness Centrality
AKT1	22	0.12153292	0.783783784
TNF	22	0.124869772	0.783783784
IL6	21	0.113441456	0.763157895
PTGS2	19	0.055085116	0.725
EP300	16	0.053226912	0.659090909
CXCL8	16	0.021083343	0.659090909

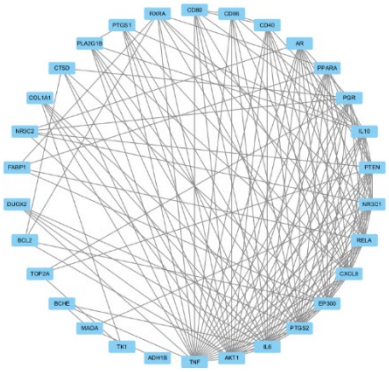

Figure 2: Network diagram of the 31 potential gene targets.

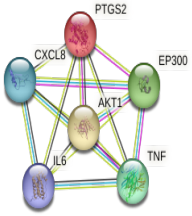

Figure 3: PPI network map of the six key potential gene targets.

2.4 GO analysis of potential genes and KEGG pathway enrichment

There are 156 BP, 16 CC and 16 CF. The "three-in-one" bar shows the top 10 enrichment results of BP, CC and MF, shown in Figure 4. There are 89 KEGG signaling pathways, and the enrichment results of the top 10 count values are shown in the bubble diagram, shown in Figure 5.

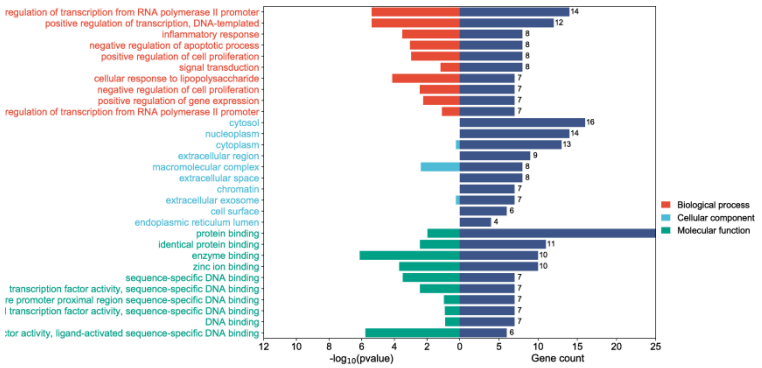

Figure 4: Three in one bar chart of BP, CC and FM.

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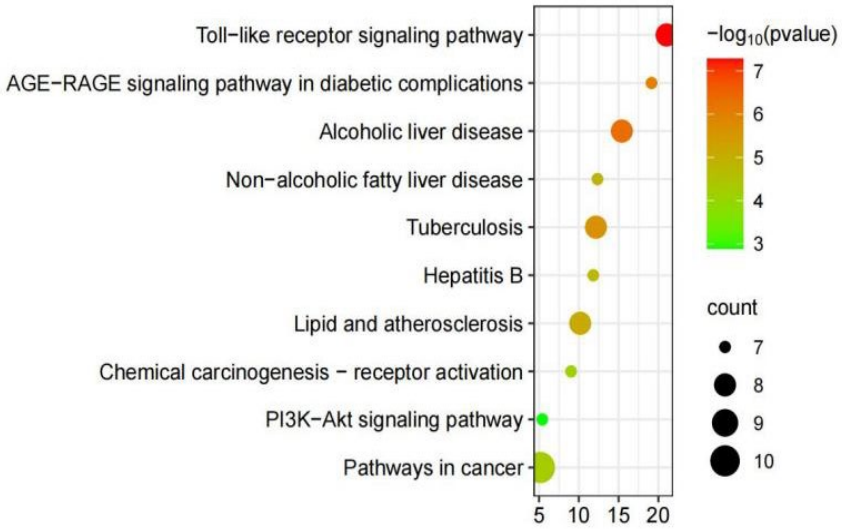

Figure 5: Bubble diagram of the KEGG signaling pathway.

2.5 Topological map of component, target, and pathway Cytoscape networks

The corresponding 11 potential components were reversed according to the 31 potential gene targets. With 31 potential gene targets, 11 potential components, and 10 pathways make the Cytoscape network topology of ascites diseases, targets, components and pathways, shown in Figure 6. Poria cocos has 11 potential components, shown in Table 3. Pathways and potential genes, shown in Table 4.

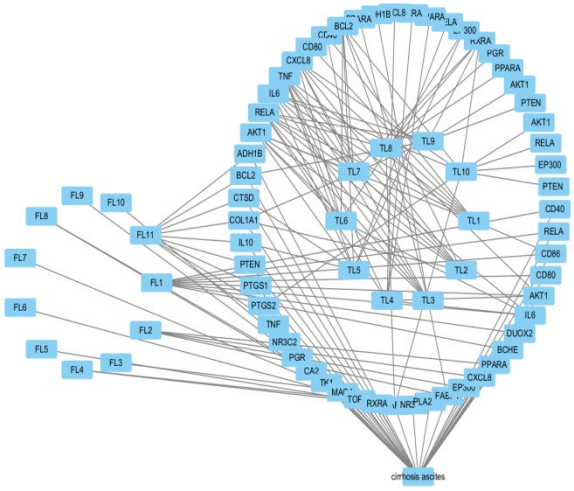

Figure 6: Topology maps of diseases, targets, components, and pathway networks.

Table 3: 11 potential components of poria cocos.

Component number	MOL ID	Molecule name
FL1	MOL000305	lauric acid
FL2	MOL000303	caprylic acid
FL3	MOL000301	2-lauroleic acid
FL4	MOL000298	ergosterol
FL5	MOL000296	hederagenin
FL6	MOL000295	alexandrin
FL7	MOL000286	β-amyrin acetate
FL8	MOL000284	L-uridine
FL9	MOL000283	Ergosterol peroxide
FL10	MOL000279	Cerevisterol
FL11	MOL000069	palmitic acid

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Table 4: Pathways and potential genes table.

Component number	The pathway name	Gene
TL1	Toll-like receptor signaling pathway	CD86, IL6, CD40, CXCL8, CD80, AKT1, TNF, RELA
TL2	AGE-RAGE signaling pathway in diabetic complications	COL1A1, IL6, CXCL8, BCL2, AKT1, TNF, RELA
TL3	Alcoholic liver disease	FABP1, IL6, CXCL8, ADH1B, AKT1, PPARA, TNF, RELA
TL4	Non-alcoholic fatty liver disease	IL6, RXRA, CXCL8, AKT1, PPARA, TNF, RELA
TL5	Tuberculosis	IL10, IL6, BCL2, EP300, AKT1, TNF, CTSD, RELA
TL6	Hepatitis B	IL6, CXCL8, BCL2, EP300, AKT1, TNF, RELA
TL7	Lipid and atherosclerosis	IL6, CD40, RXRA, CXCL8, BCL2, AKT1, TNF, RELA
TL8	Chemical carcinogenesis - receptor activation	AR, RXRA, BCL2, AKT1, PGR, PPARA, RELA
TL9	PI3K-Akt signaling pathway	COL1A1, IL6, RXRA, PTEN, BCL2, AKT1, RELA
TL10	Pathways in cancer	AR, IL6, RXRA, CXCL8, PTEN, BCL2, EP300, AKT1, PTGS2, RELA

3. Discussion

Liver cirrhosis ascites, known as "bulge" in traditional Chinese medicine, is characterized by imbalances in liver, spleen, kidney Yin and Yang, as well as disharmony in qi and blood, leading to the accumulation of water in the abdomen. One of the commonly used treatments in traditional Chinese medicine is to invigorate the spleen and promote diuresis [4]. Poria cocos that is sweet and light wet has drug effects on lung, spleen, kidney and heart , widely used in diseases caused by phlegm, wet water, which is the holy medicine of dehumidification. Modern pharmacological studies have confirmed that Poria cocos, a member of the Polyporaceae family, contains beneficial components such as polysaccharides, triterpenoids, palmitic acid, and lauric acid. These components contribute to its diuretic, liver-protective, anti-inflammatory, anti-tumor, and immune-enhancing effects. [5].Network pharmacology studies, hederagenin ,Ergosterol peroxide,Cerevisterol with better drug likeness and oral bioavailability are closely linked to the potential genes RXRA, PGR and NR3C2, respectively, While lauric acid, palmitate acid and caprylic acid, with relatively poor drug likeness and oral bioavailability, are widely linked to the potential genes, Laurene acid contacts CD40, RELA, CD86, CD80, AKT1, IL6, DUOX2, BCHE, Palmitic acid linked TNF, PTGS2, PTGS1, PTEN, IL10, COL1A1, CTSD, BCL2, ADH1B, caprylic acid linked PPARA, CXCL8, EP300, FABP1, shown in Figure 6. It shows that in the treatment of cirrhosis ascites, hederagenin, Ergosterol peroxide, Cerevistero are the components with good pharmacological effects, and lauric acid, palmitate acid and caprylic acid are the potential active components, so it is necessary to use biological and chemical technologies to improve the medicinal properties, drug likeness and oral bioavailability. Liu Yu [6] believes that the hederagenin has a negative regulatory effect on NLRP3 / ASC / Caspase1 signaling pathway, which can relieve oxidative stress, inhibit inflammation, and achieve the purpose of liver protection. Ding Tongqing[7]et al believed that lauric acid could bidirectional regulate the secretion of inflammatory factors to reduce fat deposition and inflammation in mice, which can both reduce the pro-inflammatory factor IL6 and increase the anti-inflammatory factor IL4. Hao Lihong[8] et al believe that palmitic acid can enhance the expression of Nrf2 gene, play anti-oxidant effects, prevent liver fibrosis, and effectively prevent and treat liver injury, fatty liver, and liver cancer. Li Huijun [9] believes that regulating gastrointestinal hormones, colon water metabolism protein and gastric tissue water metabolism related pathway (AC-cAMP-AQPs) can effectively play the role of poria cocos water infiltration.

Most patients with cirrhosis ascites have a history of chronic liver disease, and it is estimated that around 50% of individuals with compensated cirrhosis will develop ascites within a span of 10 years. Ascites is a significant and serious complication during the decompensated stage of cirrhosis. [4].Hepatitis liver virus infection, alcoholic liver disease, non-alcoholic fatty liver disease and chemical poisons or drugs can cause cirrhosis[10]. During the enrichment of the KEGG signaling pathway, in the Hepatitis B

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signaling pathway. Alcoholic liver disease signaling pathway, Non-alcoholic fatty liver disease signaling pathway, and Chemical carcinogenesis-receptor activation signaling pathway, The enriched potential genes were all 7 – 8, Top 10 for count values, It indicates that the four signaling pathways and their potential genes link the etiology of cirrhosis, It has a certain significance to the prevention and treatment of liver cirrhosis ascites. The liver plays a crucial role in fat metabolism. When fat metabolism is impaired, it can lead to various liver conditions, including fatty liver and liver fibrosis, and in severe cases, it can progress to cirrhosis. Additionally, this dysfunction can have systemic effects, contributing to the development of other conditions such as diabetes and cardiovascular disease. Therefore, maintaining proper fat metabolism is essential for overall health and the prevention of liver and related systemic diseases. The AGE-RAGE signaling pathway in diabetic complications, Lipid and atherosclerosis signaling pathways, enriched potential genes and count values. Tang Zizhen [11]et al believe that AGE-RAGE signaling pathway can mediate the damage of a variety of cells, and the pathological state of ischemia and hypoxia in diabetic patients further produces oxidative stress, releasing pro-inflammatory cytokines, enhancing inflammatory response, and stimulating the development of liver fibrosis. Zhang Sen [12]et al believe that the liver plays an important role in lipid metabolism, its dysfunction can lead to inflammation, oxidative stress and insulin resistance, as well as the formation of foam cells, thus inducing the development of atherosclerosis (AS).Wen Ai wei[13]et al believe that the activation of the Toll-like receptor signaling pathway produces many inflammatory factors, which cause inflammatory reactions, stimulate the growth and appreciation of hepatic stellate cells (HSC), and lead to liver fibrosis. Li Ying[14]etal believed that phosphatidylinositol 3-kinase / protein kinase B (PI3K / Akt) signaling pathway has an important role in the development of liver fibrosis, cirrhosis and liver cancer, and many studies regard it as an important target for the treatment of chronic liver disease. Tuberculosis and tumor can also cause ascites. Clinically, liver cirrhosis ascites should be distinguished from it. Tuberculosis signaling pathway and Pathways in cancer can further distinguish them from mechanistic aspects.

The 31 potential gene biological processes mainly include:(1)positive regulation of transcription from RNA polymerase II promoter, (2)positive regulation of transcription DNA-templated, (3)inflammatory response, (4)negative regulation of apoptotic process, (5)positive regulation of cell proliferation, (6)signal transduction, (7)cellular response to lipopolysaccharide, (8)negative regulation of cell proliferation, (9)positive regulation of gene expression, (10)negative regulation of transcription from RNA polymerase II promoter. The cell components are mainly: cytosol, nucleoplasm, cytoplasm, extracellular region, polymer complex, extracellular space, chromatin, extracellular exosome, cell surface, and endoplasmic reticulum lumen. Molecular functions include:(1) protein binding; (2)identical protein binding;(3)enzyme binding;(4)zinc ion binding; (5)sequence-specific DNA binding; (6) transcription factor activity, sequence-specific DNA binding;(7)RNA polymerase II core promoter proximal region sequence-specific DNA binding, (8)RNA polymerase II transcription factor activity, sequence-specific DNA binding;(9)DNA binding;(10)RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding.

Among the six key genes, AKT 1, TNF, IL6, and CXCL8, are closely linked with the top 10 signaling pathways, connecting 10,9,8, and 7 signal pathways, respectively. Chen Xiaolong[15] believed that AkT1 combined with SIRNA and wild-type P53 gene to form a double expression plasmid (Psi-Akt1-P53), which significantly reduced the proliferation and development of Hep-G2 cells and promoted its apoptosis. Chen Jing [16] believes that AKT1 perphosphatidylinositol 3 kinase (PI3K) signaling pathway is abnormally activated in HCC cells. Controlling AKT1 activation can reduce the proliferation and activity of HCC cells. Zhang Feng [17] believes that macrophages will release a large number of TNF- α and IL-6 factors, stimulate hepatic stellate cell activation, and promote the development of liver fibrosis, Astragalus total flavonoids can inhibit the expression of TNF- α, IL-6, IL-8 and NF- κB, reduce hepatocyte apoptosis, and have a better remission effect on cirrhosis. Wang Yan[18] believed that CXCL8 is involved in the inflammatory response, moving neutrophils in an unfavorable direction, and the expression level reflects the degree of hepatocyte injury.

4. Conclusion

The efficacy, properties,taste and channel tropism of Poria cocos are consistent with the TCM pathogenesis of cirrhosis ascites (swelling).In network pharmacology analysis ,there are 31 common gene targets of Poria cocos and cirrhosis ascites, among which :AKT1, TNF, IL 6, PTGS2, EP300 and CXCL 8,6 targets, are widely connected in the common targets and are key targets.Poria cocos has 11 components acting on the common targets, among which: lauric acid, palmitic acid and caprylic acid are the most associated targets.GO analysis of 10 KEGG signaling pathways were more associated with potential genes. Hepatitis B signaling pathway,Alcoholic liver disease signaling pathway, Non-alcoholic

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fatty liver disease signaling pathway, Chemical carcinogenesis-receptor activation signaling pathway are related to the etiology of cirrhosis, and have many enriched gene targets. In conclusion, Poria cocos emerges as a vital therapeutic agent for preventing and treating cirrhosis ascites, primarily due to its advantageous attributes of containing multiple active components, affecting multiple targets, and involving multiple pathways. Based on the findings from network pharmacology research, conducting animal experiments to validate the potential effective ingredients, key targets, and regulatory mechanisms of key pathways holds significant importance. This approach can further enhance our understanding and utilization of Poria cocos in the prevention and management of cirrhosis ascites, contributing to its clinical significance.

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