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Exploring the Mechanism of Action of Silybum Marianum against Liver Fibrosis Based on Network Pharmacology

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Abstract: *Silybum marianum active ingredients were obtained and their targets of action were predicted using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) and the SwissTargetPrediction. And the disease targets of hepatic fibrosis were predicted through the GeneCards database, the OMIM database, and the DisGeNET database. The intersection of the hepatic fibrosis disease targets and the action targets of the active ingredients was taken after integrating.And a protein-protein interaction (PPI) network was constructed at String12.0, and then the strength of the interaction network of silybum marianum anti-hepatic fibrosis targets was determined using Cytoscape 3.9.1 software; Gene Ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) were performed on the predicted targets of silybum marianum and the targets of hepatic fibrosis diseases using the DAVID database. The final results were visualised and presented through the SRplot website.*

Keywords: *Silybum Marianum, Liver Fibrosis, Network Pharmacology*

1. Introduction

Liver fibrosis often develops due to a variety of etiological factors, but it is most often caused by a com-bination of internal and external attacks. Long-term high-calorie diets and other unhealthy lifestyles can persistently attack the liver, leading to damage and inflammation; at the same time, under the influence of numerous pathogenic factors, cytokine secretion, and disorders of the internal environment, hepatic stellate cells are activated, and the hepatic extracellular matrix is deposited, which leads to excessive regeneration and fibrotic scarring, resulting in a pathologic and histologic change called Hepatic Fibrosis (HF). A pathohistologic change known as Hepatic Fibrosis (HF) occurs [1]. HF can be found in many chronic liver diseases and is an important step in the progression of chronic liver disease towards cirrhosis and the development of chronic liver disease to severe liver disease. A variety of etiologic factors that contribute to chronic liver disease can lead to the development of HF, and common clinical etiologic factors include: heavy alcohol consumption over a long period of time, infection by hepatophagic pathogens (including chronic hepatitis viruses, parasites, etc.), autoimmune hepatitis, medications and chemical toxins, hepatic metabolic disorders, genetic factors, and cholestasis [2]. Predictors of liver status are mainly based on the degree of hepatic fibrosis, which is also an inevitable intermediate step in the progression of chronic liver disease to cirrhosis. The common clinical trilogy: hepatitis-cirrhosis-hepatocellular carcinoma, is a reflection of the gradual aggravation of liver fibrosis. The current treatment of liver fibrosis can be divided into two categories: first, anti-fibrotic drugs, such as: anti-inflammatory and hepatocyte protection, inhibition of activation and proliferation of hepatic stellate cells and promotion of its apoptosis, the use of antioxidants and inhibition of host immune response and collagen synthesis, etc.; second, inhibition of hepatic fibrosis by treating the primary pathology, such as: antiviral therapy for hepatitis, medication for eradication of Schistosoma haematobium infections, and alcohol cessation in patients with alcoholic liver disease, etc. [3]. At present, antipathogenic treatment is still one of the most important means of treating liver fibrosis, but some diseases such as autoimmune or hereditary liver diseases do not lend themselves to treating the cause of the disease and cannot alter the course of patients with liver fibrosis, but still need effective anti-hepatic fibrosis treatment to reduce or reverse the condition. The pathological process of liver fibrosis manifests as persistent liver injury, and liver fibrosis is also a key factor in elevating the risk of hepatocellular

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carcinoma [4]. So far, there is no more targeted drug therapy for anti-hepatic fibrosis in the clinic, which urgently needs us to propose better treatment to solve this challenge.

Silybum marianum is a genus of Asteraceae, a perennial herb of the genus Silybum marianum with a long history of medicinal use, which was used for medicine 2000 years ago [5]. It mainly exhibits its favorable protective effects on the liver by modulating several signaling pathways thereby inhibiting the production of inflammatory mediators and exerting antioxidant effects [6]. Silymarin is a flavonoid lignan extracted from silymarin seeds. It can exert its antitoxic effect by inhibiting the binding of toxins to receptors on the hepatocyte membrane so that toxic substances cannot penetrate the hepatocytes, and it can also protect the integrity of the hepatocyte membrane. It has a large number of active components, the common ones are silymarin, isosilybin, silydianin, silybin and many others, while silymarin is one of the most abundant and active components among the many components [7].

In Chinese medicine, liver fibrosis is often categorized as “hypochondriac pain” and “aggregation-accumulation” according to the clinical symptoms and characteristics of the patient. Liver fibrosis is caused by a variety of factors, but can be broadly divided into two kinds of external evils and internal injuries. Most of the external evil is the feeling of evil poison, that is, the common western medicine, hepatitis B, C, or contact with parasites, toxic substances caused by liver injury. Internal injuries are caused by poor mood, improper diet, such as like to eat fatty, sweet, oil and salt heavy food, like overeating, alcoholism, etc. often lead to fatty liver, alcoholic liver and other diseases. Or congenital endowment is insufficient, easy to suffer from Western medicine called immune liver disease, hereditary liver disease. In Chinese medicine, the understanding of liver fibrosis is based on the function of the liver. The fact that the liver is the main regulator means that liver has the physiological function of ensuring the proper functioning of qi and blood and ensuring that qi functions smoothly and regularly; the liver has the function of storing blood and regulating the amount of blood in the body and plays an important role in regulating the functioning and distribution of qi and blood throughout the body. When internal and external evils come to the liver, blocking the operation of qi and blood, resulting in qi and blood imbalance, and causing tangible evils to accumulate in the liver, the disease develops [8]. Western medicine still does not have target drugs for the treatment of liver fibrosis, so exploring effective TCM treatment is a necessary means to further prevent and treat liver fibrosis. Many traditional Chinese medicines have good advantages in the treatment of liver diseases, and they are also effective in inhibiting or even reversing the pathological process of liver fibrosis. Therefore, in this paper, we would like to understand the relationship between this drug, silymarin, and the HF disease targets and pathways through a network pharmacology approach, and to investigate the rationality and scientific validity of the use of the Chinese medicine herb silymarin marianum in the treatment of hepatic fibrosis.

2. Information and Methods

2.1 Constituent Acquisition and Screening of Silybum Marianum in Chinese Herbal Medicine

The active ingredients of silybum marianum were obtained by using “silybum marianum” as the search term in TCMS(http//tcmspw.com/tcm-sp. php), and screened in accordance with the requirements of Oral Bioavailability (OB) ≥ 30%, Drug Like index (DL) ≥ 0.18, etc.The active ingredients of Cynanchum sativum were obtained by using "Cynanchum sativum" as the search term. The active ingredients of Cynanchum sativum were obtained after screening according to the requirements of Oral Bioavailability (OB) ≥30% and Drug Like index (DL) ≥0.18.

2.2 Prediction of Active Ingredient Targets in Traditional Chinese Medicine

Firstly, the CAS number of each active ingredient of traditional Chinese medicine was obtained from the TCMSP website, and then the SMILES structure of the active ingredient was obtained by searching according to the CAS number on the organic small molecule bioactivity data website (pubchem, https://pubchem.ncbi.nl-m.nih.gov/) and the SMILES structure of the active ingredient was obtained through the SwissADME platform (http://www.swissadme.ch/) to predict the results of reference data such as gastrointestinal absorption and drug-like properties, and set the criteria for the active ingredient based on the data. The active ingredient was considered to be active if the following two conditions were met: (1) the GI absorption was "High"; (2) two or more of the five pharmacokinetic predictions (Lipinski, Ghose, Veber, Egan, Muegge) were "Yes"; (3) the GI absorption was "High"; (4) the GI absorption was "High"; (5) the GI absorption was "High"; (6) the GI absorption was "High"; and (7) the GI absorption was "High". "Yes". The active ingredients obtained based on the screening will be predicted with the

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help of SwissTargetPredi-ction platform (http://www.swiss-targetprediction.ch/) to predict the target associated with the active ingredient, and the results obtained from the final prediction will be screened again based on (Probability > 0) [9].

2.3 Collecting Liver Fibrosis Targets and Predicting Drug Action Targets

In this study, GeneCards (https://www.gene-cards.org), OMIM (https://www.omim.org) and DisGeNET (https:// www.disgenet.org) databases were mainly used. Then, using "hepatic fibrosis" or "liver fibrosis" as the search terms, we searched the three databases and collected the relevant disease targets of HF, and then summarized the target results and deleted the duplicates to obtain the final data results and save them. The results were then summarized and duplicates were removed to obtain the final data and saved. Intersections of silymarin active ingredient targets with high-frequency related targets were plotted in a Wayne diagram using VENNY 2.1 (https://bioinfogp.cnb.csic.es/ tools/venny/ index.html), and the intersection in the diagram was the target of silymarin in the treatment of HF.

2.4 Construction of Protein-Protein Interaction (PPI) Network and Screening of Core Targets

The above targets were submitted to the String12.0 database (https://cn.stringdb.org/) to construct the PPI network, the biological species was set as "homo sapiens", the confidence level of target association was 0.40, and the Clusters were selected as "kmeans cluster-ing" and "kmeans cluster-ing". Set the biological species as "homo sapiens", the confidence level of target association as 0.40, choose "kmeans cluster-ing" for clusters, set 3 clusters, remove the nodes that are not connected with each other, and default the rest of the parameters, so that we can get the PPI network. Export the .tsv file related to the target information, and then import it into Cytoscape 3.9.1 software, measure the node centrality according to degree centrality, construct the PPI network by plug-in CytoNCA and analyze it.

2.5 GO and KEGG Enrichment Analysis

The intersection targets of silymarin active ingredient targets and liver fibrosis disease targets were imported into the Database for Annotated Biological Information website (DAVID, https://david.ncifcrf.gov/), species selector, and then Gene Ontolo-gy (GO) and Kyoto Encyclopedia of Genes and Genomes (Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses, and the data were saved and imported into the Microbiome website (https://www.bioinformatics.com.cn/) for visualization and display.

3. Results

3.1 Screening Results of the Active Ingredients of Silybum Marianum

The TCMSP database was used to obtain the active ingredients of silybum marianum, and 11 active ingredients were obtained according to the conditions of OB≥30% and DL≥0.18. (Table 1).

Table 1: Active ingredients of silymarin marianum.

Mol ID	Molecule Name	OB (%)	DL
MOL000098	quercetin	46.43	0.28
MOL000449	Stigmasterol	43.83	0.76
MOL000953	CLR	37.87	0.68
MOL001439	arachidonic acid	45.57	0.2
MOL001736	(-)-taxifolin	60.51	0.27
MOL007180	vitamin-e	32.29	0.7
MOL007449	24-methylidenelophenol	44.19	0.75
MOL007451	silydianin	59.65	0.76
MOL007454	silymonin	81.81	0.8
MOL007455	silandrin	64.14	0.94
MOL007457	isosilychristin	30.32	0.4

3.2 Prediction of Target Points of Active Ingredients and Disease Targets of Silybum Marianum

The SMILES structures of the active ingredients were obtained from PubChem website, and then the

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active ingredients of silybum marianum were further screened in SwissADME platform according to the parameter settings of gastrointestinal absorption and drug-like properties, i.e., quercetin, (-)-taxifolin, and silymarin. Prediction was performed on the SwissTargetPrediction platform, and 152 predicted active targets were obtained for the two components, quercetin and silandrin;(-)-taxifolin was not successfully retrieved as a predicted target in SwissTargetPrediction platform, so 4 predicted targets were obtained by getting the Target name in TCMSP website and then converted to gene name through UniProt website (https://www.un-iprot.org/). The predicted targets of all the above active ingredients were combined and the duplicates were deleted, and the intersection was taken with 2457 HF disease targets obtained from GeneCards, OMIM and DisGeNET to obtain 62 intersecting targets, and the Wayne plots were plotted through the VENNY 2.1 platform. (Fig. 1)

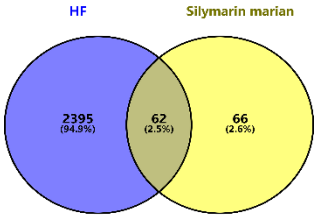

Figure 1: Venn diagrams of intersecting targets of liver fibrosis and silymarin marianum.

3.3 Core Target Screening and PPI Construction

The 62 targets were uploaded using the STRING website to obtain the PPI graph (as in Figure 2) and the .tsv file.The file was imported into Cytoscape 3.9.1 software, and then the size of the nodes was set based on the degree, which was used to construct the interactions network strength relationship graph of the potential targets of the action of silybum marianum in liver fibrosis (as in Figure 3). The target proteins are represented by nodes in the graph, while two proteins connected are represented by edges. After String screening, a total of 60 target proteins and 434 edges were obtained in Figure 3. The higher the degree centrality, the larger the node is, meaning the more important position it occupies in the network. Accordingly, the top 10 key targets of silybum marianum for the treatment of liver fibrosis can be observed, including: AKT serine/threonine kinase 1 (AKT1), Estrogen Receptor (ESR1), B-cell lymphoma-2 (BCL2), Prostaglandin-endoperoxide synthase 2 (PTGS2), Epidermal Growth Factor Receptor (EGFR), Matrix metallopro-teinase 9 (MMT9), Matrix Metallopeptidase 2 (MMP2), Glycogen synthase kinase3β (GSK-3β, GSK3B), SRC proto-oncogene/non-receptor tyrosine kinase (SRC), poly(ADP-ribose) polymerase 1 Gene (PARP1). (Figure 3)

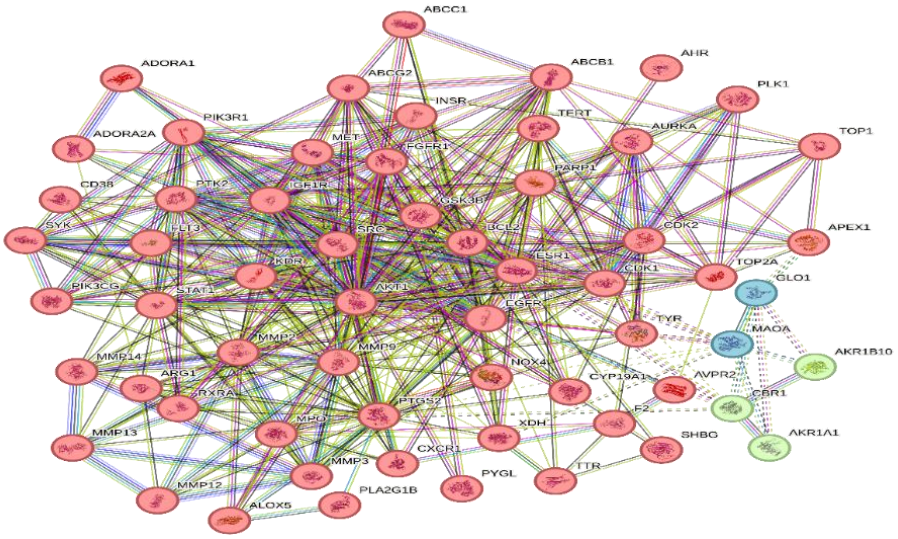

Figure 2: PPI network of anti-fibrotic targets of silymarin marianum in liver fibrosis.

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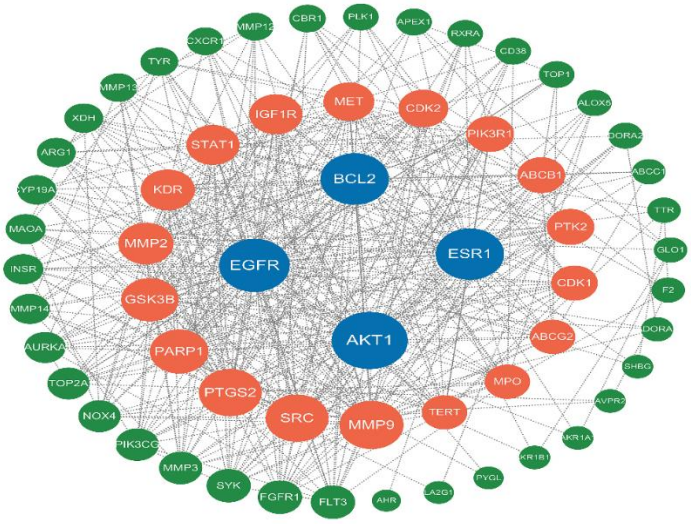

Figure 3: Interaction network strengths of potential targets of action of silymarin marianum in the treat-ment of liver fibrosis.

3.4 GO and KEGG enrichment analysis

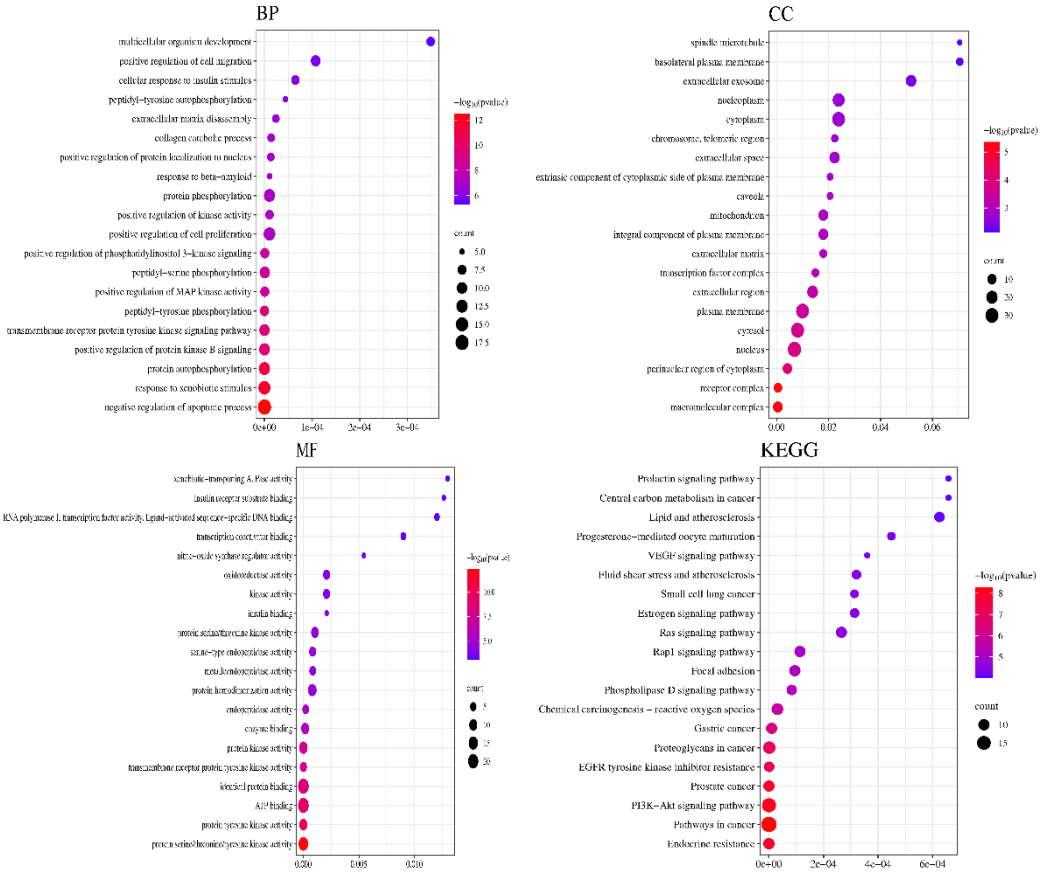

Figure 4: Data analysis of GO enrichment visualization for key targets of silymarin marianum against liver fibrosis

The Gene Ontology of key targets of silymarin marianum treatment for liver fibrosis was performed using the DAVID website.The GO was divided into three categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC). Visualize and analyze the data according to the top 20 entries in BP, CC and MF results. (Figure 4) The target enrichment of silymarin marianum for the treatment of liver fibrosis mainly involves biological processes including response to xenobiotic substance stimulation, negative regulation of apoptotic process, autophosphorylation, positive regulation

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of protein kinase B signaling, and transmembrane receptor protein tyrosine kinase signaling pathway related to it. The results of molecular functional analysis showed that the functions of key targets for the treatment of liver fibrosis were mainly involved in protein tyrosine kinase, identical protein binding, ATP binding cassette protein, transmembrane receptor protein tyrosine kinase activity, and so on. The key targets of cellular component analysis, on the other hand, were related to macromolecular complexes, receptor complexes, cytoplasmic perinuclear region, and nucleus. According to the KEGG pathway enrichment analysis, the targets of silymarin to improve liver fibrosis mainly include cancer pathway, endocrine resistance, PI3K-Akt signaling pathway, prostate cancer, epidermal growth factor receptor (EGFR) tyrosine kinase inhibition, etc., which reflects the multi-component, multi-target, and multi-pathway anti-hepatic fibrosis effects of silymarin. pathways, reflecting the multi-component, multi-target, multi-pathway anti-hepatic fibrosis effects of silymarin marianum.

4. Discussion

Silybum marianum, also known as milk thistle, is often used as a medicine with its seeds, which are cool and bitter in nature, and is often used to treat liver diseases as well as cardiovascular disorders because of its efficacy in liver alleviation, choleretic effect, and clearing away heat and dampness. Silymarin , a common active ingredient of silymarin marianum, is a class of flavonoid extracts with a high market share worldwide [10]. As a traditional hepatoprotective and enzyme-lowering drug, silymarin has excellent clinical efficacy and very low toxicity, while silibinin is an important active ingredient of silymarin, which provides high value for silymarin to exert its pharmacological effects [11]. In order to improve the bioavailability of silibinin, silibinin phospholipid complexes, i.e. silibinin capsules, were synthesized for the first time in the 1990s. Since then, silibinin has been widely used in the treatment of liver diseases. Silibinin has various pharmacological effects on the liver: on the one hand, it can improve the stability of hepatocyte membranes and promote liver cell regeneration [12]; on the other hand, the abnormal activation or proliferation of hepatic stellate cells is an important causative factor for the occurrence and development of hepatic fibrosis, whereas silibinin can inhibit hepatic stellate cell proliferation and migration, reduce hepatocellular damage, and reverse the process of hepatic fibrosis [13]. Silibinin capsules have also been put into clinical use many years ago, and have played a remarkable therapeutic effect in the treatment of liver diseases, and no serious adverse reactions have been found, and the population is more tolerable, so its safety is self-evident. The above facts prove the safety and reliability of silymarin marianum in the treatment of liver diseases.

In this paper, the core active ingredients of silymarin marianum for the treatment of liver fibrosis were obtained as quercetin,(-)-taxifolin and silandrin. The therapeutic effect of quercetin for liver fibrosis has long been discovered and has been suggested in many studies. Jiang Wei et. [14] experimentally found that quercetin could modulate hepatic stellate cells cultured in vitro thus proving the role of quercetin for anti-hepatic fibrosis. Wang Shaozhan [15] et. found that quercetin inhibits stellate cell activation and exerts anti-hepatic fibrosis effects by inhibiting the activation of TGF-β/TAK1/JNK and TGF-β/Smad signaling pathways. According to experiments such as Li Yaju [16], it is illustrated that (-)-taxifolin may play a role in influencing the factor interaction signaling pathway, porphyrin and chlorophyll metabolism signaling pathway, Hedgehog signaling pathway, and PPARγ signaling pathway by down-regulating the expression of a number of pro-hepatic fibrogenesis genes, such as Plxn-a4, Olr1, Spon1, and Agrn and by up-regulating the expression of antioxidant genes, such as Hmox1. Lingming Lei [17] and others proved that (-)-taxifolin can effectively reduce IL-1β, IL-6 and TNF-α, inhibit the activation of inflammatory pathways and the expression of related inflammatory factors, and inhibit the development of hepatic fibrosis by influencing the main factors. Mingyi Zhao [18] showed that the administration of (-)-taxifolin reduced Alanine Transaminase(ALT)and Aspartate Aminotransferase(AST), prevented histopathological damage of the liver, reduced the expression of pro-inflammatory cytokine mRNA in the liver tissues, and ameliorated cutinin A (ConA)-induced hepatic injury in mice, which slowed down the progression of hepatic fibrosis. According to KEGG enrichment analysis, the targets of silymarin marianum against liver fibrosis included cancer pathway, PI3K-Akt signaling pathway, endocrine drug resistance pathway, etc., and the targets of liver fibrosis disease were most connected to the cancer pathway, which indicated that silymarin marianum could inhibit liver fibrosis and prevent its progression to hepatocellular carcinoma. Another study found that by regulating the PI3K-Akt signaling pathway, silymarin marianum can inhibit hepatic autophagy, protect and reduce hepatocyte apoptosis, reduce hepatic inflammation, and alleviate hepatic pathological damage, thus achieving the purpose of preventing and controlling liver fibrosis [19]. All of the above studies showed the pharmacological mechanism of antifibrotic of silymarin marianum and proved the possibility of silymarin marianum in the treatment of hepatic fibrosis; they provided more ideas and basis for the further development and utilization of silymarin marianum in liver

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diseases.

In summary, this paper is based on the network pharmacology approach to analyze the mechanism of silymarin marianum in the treatment of liver fibrosis based on the characteristics of Chinese traditional medicine with multiple components, multiple targets and multiple pathways, and the data are processed through visual analysis, which makes the complex components of Chinese traditional medicine become clearer and clearer, and provides ideas and inspiration for the research of other Chinese traditional medicine. However, this paper lacks further experimental data to prove that it is still only a theoretical study, and more data are still needed to prove it.

References

[1] Chinese Society Of Hepatology, C.M.A., C.M.A. Chinese Society Of Gastroenterology and C.M.A. Chinese Society Of Infectious Diseases, Consensus on the diagnosis and treatment of liver fibrosis (2019)[J]. Modern Medicine and Health, 2019,35(18): 2928-2938.

[2] Altamirano-Barrera A, Barranco-Fragoso B, Mendez-Sanchez N. Management strategies for liver fibrosis[J]. Ann Hepatol, 2017,16(1): 48-56.

[3] Xu J et al, Exploring the mechanism of action of anti-fibrotic soft liver formula against liver fibrosis based on hepatic sinusoidal capillarization[J]. Journal of Clinical Hepatobiliary Diseases, 2020,36(02): 319-323.

[4] He D et al, Advances in the etiology and mechanism of liver fibrosis[J]. Journal of Kunming Medical University, 2022,43(11): 165-171.

[5] Abenavoli L, Izzo A A, Milic N, et al. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases[J]. Phytother Res, 2018,32(11): 2202-2213.

[6] Federico A, Dallio M, Loguercio C. Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years[J]. Molecules (Basel, Switzerland), 2017,22(2): 191.

[7] Kroll D J, Shaw H S, Oberlies N H. Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies[J]. Integr Cancer Ther, 2007,6(2): 110-119.

[8] Cao Zhengmin et al. Discussion on Chinese medicine treatment of liver fibrosis from the theory of "Yang transforms qi and yin forms"[J]. Journal of Liver Diseases in Chinese and Western Medicine, 2023,33(12): 1130-1131.

[9] Wen, K. S. et al. A network pharmacology and molecular docking based study to explore the prevention of hepatic fibrosis by Chicken Bone Herb[J]. Chinese Journal of Clinical Pharmacology, 2023, 39(16): 2400-2403.

[10] Wang, H. et al. Progress in molecular pharmacological mechanisms of antitumor, antioxidant and immunomodulatory properties of silymarin [J]. Journal of Pharmaceutical Sciences, 2010,45(04): 413-421.

[11] Baeck, C., et al., Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury[J]. Gut, 2012. 61(3): 416-26.

[12] Zhang, T.T. and Lu, X.L., Hepatoprotective drugs in metabolism-related fatty liver disease[J]. World Clinical Drugs, 2021. 42(08): 612-618.

[13] Guo, S. R. et al. Advances in pharmacological studies on the hepatoprotective effects of silymarin capsules [J]. China Hospital Drug Evaluation and Analysis, 2024. 24(01): 116-118+123.

[14] Jiang, W., Deng, Z. L. & Li, F. C., Effect of quercetin on the expression of collagen types I and III in human hepatic stellate cells with its cell cycle study[J]. Chongqing Medicine, 2018. 47(09): 1179-1182.

[15] Wang, Shaozhan et al. Quercetin exerts anti-hepatic fibrosis effects by inhibiting TGF-β/TAK1/JNK and TGF-β/Smad2 signaling pathways[J]. Zhongnan Pharmacology, 2022. 20(05): 965-972.

[16] Li Yaju, Guo Shan & Wei Feili, Activation effect of citrinin on transforming growth factor β1-induced hepatic stellate cells and gene expression profiling[J]. Chinese Journal of Liver Diseases (Electronic Edition), 2023. 15(03): 34-42.

[17] Lei, L., et al., Dihydroquercetin Activates AMPK/Nrf2/HO-1 Signaling in Macrophages and Attenuates Inflammation in LPS-Induced Endotoxemic Mice[J]. Frontiers in Pharmacology, 2020. 11: 662.

[18] Zhao M, Chen J, Zhu P, et al. Dihydroquercetin (DHQ) ameliorated concanavalin A-induced mouse experimental fulminant hepatitis and enhanced HO-1 expression through MAPK/Nrf2 antioxidant pathway in RAW cells[J]. Int Immunopharmacol, 2015,28(2):938-944.

[19] Yang guang and Song, Jianning, PI3K/Akt signaling pathway and endoplasmic reticulum stress in hepatocyte apoptosis in liver fibrosis rats[J]. Basic Medicine and Clinics, 2017. 37(05): 614-618.